

00152 Stage-dependent Contributions of Brain Atrophy, Free-water Increases, White Matter Microstructural Abnormalities and Functional Dysconnectivity to Memory Impairment in Alzheimer's Disease Continuum

Ji Fang¹, Pasternak Ofer², Ng Kwun Kei¹, Chen Christopher Li-Hsian³, Zhou Juan¹

¹Duke-NUS Medical School, ²Harvard Medical School, ³National University of Singapore

Aims: Instead of assuming a constant relationship between brain abnormalities and memory impairment, we aimed to examine the stage-dependent contributions of multimodal brain structural and functional deterioration to memory impairment in Alzheimer's disease (AD) continuum.

Methodology: We assessed grey matter volume, white matter (WM) microstructural measures (freewater (FW) and FW-corrected fractional anisotropy), and functional connectivity of the default mode network (DMN) of 100 memory clinic participants (54 amnesic mild cognitive impairment, 46 AD). We employed a novel sparse varying coefficient model to investigate how the associations between abnormal brain measures and memory impairment varied along the disease continuum (clinical dementia rating sum-of-boxes).

Result: Lower functional connectivity in the DMN was related to worse memory across disease continuum. In contrast, widespread WM FW increases and reduced fractional anisotropy in the fornix showed a stronger association with memory impairment in the prodromal stage. Notably, the association between regional atrophy and memory deficit was dependent on disease severity: the effect of the DMN atrophy mainly occurred in the prodromal stage, while the effect of the medial temporal lobe atrophy occurred in the clinical stage.

Conclusion: Our study provided evidence to support the hypothetical progression models underlying memory dysfunction in AD cascade and underscored the importance of FW increase and DMN degeneration in early stage of memory deficit. Our findings highlighted the value of studying stage-dependent multimodal brain-cognition associations and may guide the development of early intervention strategies to slow down memory decline.