SRIP Team 38: Tai Wen Bin, Toh En Qi, You Hongyang Emmanuel
LKCMedicine, MBBS Programme, Year 3
Supervisor: Prof Balázs Zoltán Gulyás

Differential effects of white matter hyperintensities and regional amyloid deposition on regional cortical thickness

Chin Hong Tan, Justin Chew, Liwen Zhang, Balázs Gulyás, Christopher Chen
Neurobiology of Ageing 115 (2022) 12-19. doi: 10.1016/j.neurobiolaging.2022.03.013

INTRODUCTION

Background
In mixed dementias, Alzheimer's disease (AD) pathology is most often found alongside another neurodegenerative and/or vascular pathology [1]. White matter hyperintensities (WMH) of presumed vascular origins and *β*-amyloid (A*β*) accumulation have both been linked to neurodegeneration in AD.

Existing studies have sought to establish the independent and interactive effects of AD-associated A*β* burden and WMH on neurodegeneration [2]. However, the independent effects of global WMH and regional A*β* on the corresponding regional cortical thickness have not been investigated [3].

Objective
This study investigates the differential and independent effects of global WMH and regional A*β* positron emission tomography (PET) deposition on the corresponding regional cortical thickness in cognitively normal (CN), mild cognitive impairment (MCI) and AD dementia individuals separately. This allows for targeted intervention and better understanding of AD progression.

METHODS

Subjects: Data of 280 CN individuals, 450 MCI individuals and 64 AD dementia individuals was used, obtained from the ADNI database.

Data acquisition: Structural MRI scans were acquired. Cortical reconstruction and volumetric segmentation were performed, and regional cortical thickness, intracranial volume (ICV) and WMH data were derived in 34 cortical regions of interest (ROIs).

Statistical analysis: Testing was performed for:
- Basic relationships between global WMH and regional A*β*;
- Independent contribution of global WMH and regional/composite A*β* on the corresponding regional/composite cortical thickness;
- Any interaction of global WMH with regional/composite A*β*.

RESULTS

Basic relationships between WMH and regional A*β*
- CN: Association between in 22 (out of 34) ROIs, strongest in frontoparietal regions;
- MCI: Association only in superior parietal cortex;
- AD dementia: No association.

Independent effects of WMH and regional A*β* on lower regional cortical thickness
- CN
  - WMH: Associated in 13 ROIs, predominantly in fronto-temporal regions (Fig. 1A);
  - Regional A*β*s: No independent associations (Fig. 1B).
- MCI
  - WMH: Associated in 10 ROIs, in temporal regions and cingulate cortex (Fig. 1C);
  - Regional A*β*s: Associated in 8 ROIs, in temporal (strongest), precuneus and inferior parietal regions (Fig. 1D).
- AD dementia
  - WMH: No independent associations;
  - Regional A*β*s: Associated in 4 ROIs, but not statistically significant.

RESULTS (CONT'D)

Interactions of WMH and regional/composite A*β* on regional/composite cortical thickness
- All diagnostic groups: No significant interactions.

Independent effects of WMH, A*β* and cortical thickness on progression to AD dementia
- 116 non-demented individuals (5 CN and 111 MCI) progressed to AD dementia;
- In these subjects, higher WMH, higher composite A*β* and lower composite cortical thickness were all found to predict progression to AD dementia.

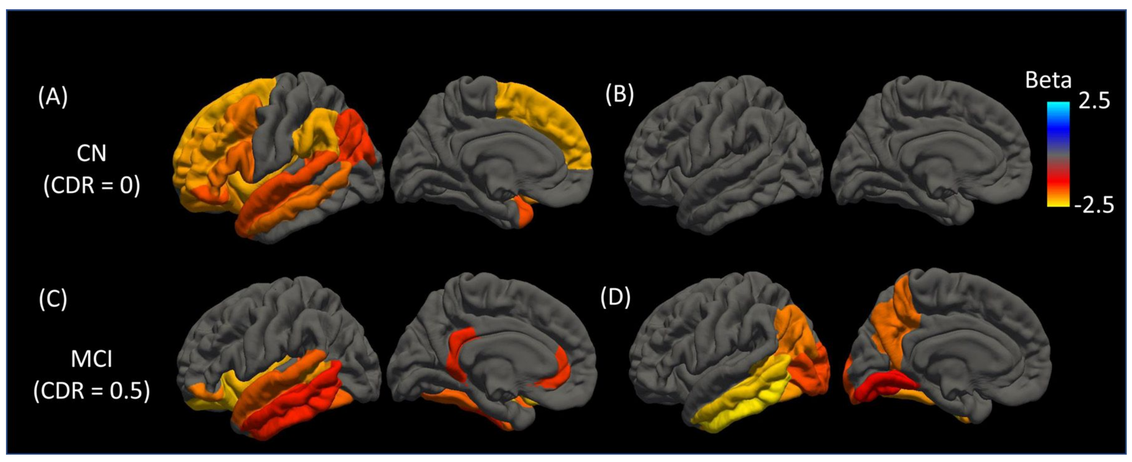

Fig. 1. Independent associations of WMH and regional A*β* with regional cortical thickness in CN (A and B) and MCI (C and D) individuals.

DISCUSSION

Main Findings
- WMH contributes to regional neurodegeneration in AD dementia disease progression independent of regional A*β* accumulation, following different spatial patterns: fronto-temporal in CN individuals; temporal and cingulate regions in MCI individuals;
  - Cingulate involvement in the latter reflects possible cerebrovascular pathology underlying neuropsychiatric symptoms in AD dementia;
- Independent influence of regional A*β* is, however, muted in preclinical stages before manifesting in temporal regions in MCI individuals;
- Independent associations of global WMH beyond regional A*β* and cortical thickness in AD-associated regions on disease progression also support the importance of cerebrovascular disease in the AD process.

Conclusion and Future Directions
- WMH has potential utility as an additional biomarker for AD dementia
  - Vascular dysfunction can be modified through interventions to slow down disease progression;
- Future studies could:
  - Delineate gross regional WMH in the different cerebral lobes, to provide further insights into the regional relationships between regional WMH and A*β*;
  - Further elucidate potential longitudinal relationships of WMH and regional A*β* on the progression of regional cortical thinning.

REFERENCES

1. Boyle, P.A. , Yu, L. , Wilson, R.S. , Leurgans, S.E. , Schneider, J.A. , Bennett, D.A. , 2018. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 83 (1), 74–83.
2. Bos, I. , Verhey, F.R. , Ramakers, I. , Jacobs, H.I.L. , Soininen, H. , Freund-Levi, Y. , Ham- pel, H. , Tsolaki, M. , Wallin, ˚A.K. , van Buchem, M.A. , Oleksik, A. , Verbeek, M.M. , Olde Rikkert, M. , van der Flier, W.M. , Scheltens, P. , Aalten, P. , Visser, P.J. , Vos, S.J.B. , 2017. Cerebrovascular and amyloid pathology in predementia stages: the relationship with neurodegeneration and cognitive decline. Alzheimers Res Ther 9 (1), 101 .
3. De Guio, F. , Duering, M. , Fazekas, F. , De Leeuw, F.E. , Greenberg, S.M. , Pantoni, L. , Aghetti, A. , Smith, E.E. , Wardlaw, J. , Jouvent, E. , 2020. Brain atrophy in cerebral small vessel diseases: Extent, consequences, technical limitations and perspectives: The HARNESS initiative. J Cereb Blood Flow Metab 40 (2), 231–245 .