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

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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 (Aβ) accumulation have both been linked to neurodegeneration in AD.

Existing studies have sought to establish the independent and interactive effects of AD-associated Aβ burden and WMH on neurodegeneration [2]. However, the independent effects of global WMH and regional Aβ 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 Aβ 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 Aβ;
- Independent contribution of global WMH and regional/composite Aβ on the corresponding regional/composite cortical thickness;
- Any interaction of global WMH with regional/composite Aβ.

RESULTS

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

DISCUSSION

Main Findings
- WMH contributes to regional neurodegeneration in AD dementia disease progression independent of regional Aβ 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 Aβ is, however, muted in preclinical stages before manifesting in temporal regions in MCI individuals;
- Independent associations of global WMH beyond regional Aβ 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 Aβ;
  - Further elucidate potential longitudinal relationships of WMH and regional Aβ on the progression of regional cortical thinning.

REFERENCES