CORTICAL THICKNESS IN ALZHEIMER'S DISEASE WITH COEXISTENT SMALL VESSEL DISEASE: A PARTIAL LEAST SQUARES ANALYSIS

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BACKGROUND

Cortical thickness (CT) measured from T1-weighted magnetic resonance imaging (MRI) provides a sensitive morphometric measure of Alzheimer's disease (AD) progression [1].

Cerebral small vessel disease (SVD) often coexists with AD [2], and may differentiate cortical thinning across the cortex compared to AD alone.

SVD commonly manifests as cerebral White Matter Hyperintensities (WMH), which can be visualized as regions of hyperintense signal on PD/T2 and FLAIR MRI (Fig 1).

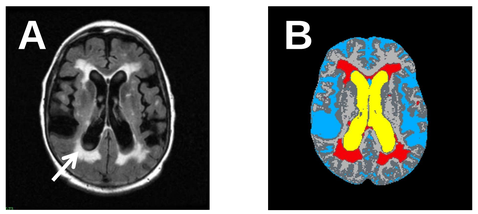


Figure 1: (A) Axial FLAIR MRI showing WMHs (B) T1 Segmented image with tissue class labels.

Previous studies suggest that a threshold-effect of WMH burden >10 cc is related to cognitive deficits [3].

CT studies have traditionally used univariate methods, which independently test significance at each element/vertex of a surface mesh.

Conversely, multivariate models such as Partial Least Squares (PLS) [4] identify significantly distributed patterns of thinning across the entire cortical surface.

PURPOSE & HYPOTHESIS

To examine with PLS, whether a differential pattern of cortical thinning exists based on a threshold of WMH burden in normal elders (NC) and subjects with AD.

METHODS

PLS software was adapted for surface-based parametric data [4].

Cross-sectional data were acquired from the Sunnybrook Dementia Study.

All subjects had 1.5 Tesla T1-SPGR MRIs (Matrix=256x192; TE/TR=35ms/5ms; flip-angle=35°, in-plane resolution=0.859×0.859x1.2–1.4mm).

Participants were dichotomized into groups with >13cc of white matter hyperintensity (-WMH) volume on PD/T2-MRI (+WMH) and those with <13cc of WMH volume. We selected 13cc to ensure WMH+ subjects were above the threshold of 10cc reported in reference 3.

An in-house modified version of the Freesurfer Cortical Thickness algorithm [5, 6] was used to minimize false positive grey matter signal from WMHs.

Lesion Explorer [7] software was used to delineate WMHs including manual removal of false positives and negatives.

ANALYSIS

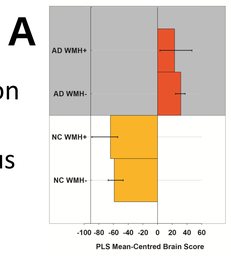
Mean-centred PLS with bootstrapping (x1000) and permutation testing (x1000) was applied to detect significant patterns of cortical thickness differences between groups. Analyses were corrected for sex and age.

	NC WMH-	NC WMH+	AD WMH-	AD WMH+
N	83	11	149	28
Age	69 (8)	79 (6)	71 (10)	77 (6)
CVLT1-5	52 (9)	43 (13)	22 (10)	21 (9)
Mean WMH volume cc (SD)	3.3 (3.2)	27.5 (12.8)	4.7 (4.3)	28.6 (14.1)

RESULTS

Figure 2a, b and c: PLS analysis revealed a significantly different pattern of cortical thinning in NC versus AD-WMH and AD+WMH (p<0.0001), involving:

- Posterior cingulate
- Superior parietal region
- Prefrontal cortex
- Parahippocampal gyrus
- Medial temporal lobe
- Lateral temporal lobe



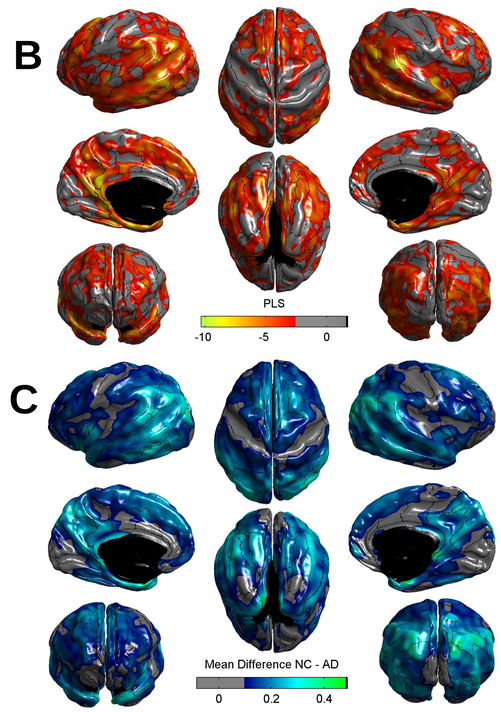


Figure 2: (A) Group-wise differences that related to a topographical network of cortical thinning (B), which explained 83% of the overall variance between NC and AD groups. The colorbar in panel B represents the most reliable regions (>95% CI after bootstrapping) contributing to the pattern observed in panel A, where warmer colours represents a stronger dissociation between AD and NC. Panel C shows the mean difference in cortical thinning between NC and AD.

No significant networks of cortical thinning differentiated subjects who were WMH- versus WMH+ in NC or AD ($p=0.25$). However, the NC WMH+ group had significantly worse performance on the California Verbal Learning Test 1 (CVLT-1).

CONCLUSION

1. Previous studies report cognitive impairment in persons with >10 cc of WMH volume. Our findings reveal no significant networks of cortical thinning that relate to a WMH threshold of 13cc. However, there were only 11 subjects in the NC group with >13 cc of WMH volume. While more subjects with WMH burden >13cc may be required to detect a threshold effect on cortical thinning, other structures may be more affected within our cohort, including WM fasciculi and subcortical structures.
2. Although we did not find any evidence of a WMH threshold effect on cortical thinning, we did find a network of cortical thinning in both AD WMH- and AD WMH+ compared to NC, and this topographical pattern of atrophy co-located with regions implicated in the default mode network.

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