CLINICAL MEMORY PERFORMANCE COVARIES WITH CORTICAL THINNING OF DEFAULT MODE NETWORK ARCHITECTURE IN ALZHEIMER'S DISEASE

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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]
- Recent structural & functional magnetic resonance imaging (MRI) studies suggest neurodegeneration is spatially associated with intrinsic brain functional network architecture, particularly the default mode network (DMN) [2,3,4,5]
- The DMN is a task-negative or resting-state network that has been spatially mapped to the superior parietal, prefrontal, posterior cingulate cortex (PCC) and medial temporal lobe (MTL) [6]
- CT studies have traditionally used univariate methods, which independently test significance at each element/vertex of a surface mesh
- The multivariate method Partial Least Squares (PLS) is ideal for studying the network degeneration hypothesis in AD, as this technique can map spatial covariance between vertex-wise cortical thickness (CT) and clinical cognitive measures in a single analytical step [7]
- **AIM:** We assessed whether a spatial pattern of covariance between CT and memory performance co-localized to DMN architecture in AD versus normal elderly controls (NC)

DEMOGRAPHICS

Table 2: SDS Demographic Profile

	NC	AD
N	95	144
Age (y) mean (SD)	71 (8)	72 (9)
Sex (N=m)	42	85
Education (y) mean (SD)	16 (3)	14 (4)

METHODS

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

-AD subjects were diagnosed according to NINCDS-ADRDA criteria, had no clinical stroke and had no evidence of a coexistent neurodegenerative disorder

-Composite cognitive scores were computed for the three cognitive domains listed in Table 2, based on z-scores from several neuropsychological tests (Table 2)

Table 1: SDS Neuropsychological Composite Scores

Executive	Verbal Fluency 'FAS' Test	Total words correct
	Wisconsin Card Sorting Test	Total correct
	Wisconsin Card Sorting Test	Perseverative errors to previous response
	Wisconsin Card Sorting Test	Perseverative errors to previous category
Memory	California Verbal Learning Test	Total correct at acquisition
	Wechsler Memory Scale Revised Visual Reproduction	Immediate recall
	Dementia Rating Scale	Memory
Visuospatial	Benton Judgement of Line Orientation Test	Total correct
	Rey-Osterrieth Complex Figure Test	Figure copy

-All subjects had 1.5 Tesla 3D T1-SPGR MRIs (Matrix =256x192; TE/TR =35ms/5ms; flip-angle =35°, in-plane resolution =0.859 × 0.859 x 1.2–1.4mm)

-An in-house modified version of the Freesurfer Cortical Thickness algorithm [8,9] was used to minimize false positive grey matter signal from white matter lesions hypointense on T1 MRI

-Lesion Explorer [10] software was used to delineate WMHs including manual removal of false positives and negatives

-PLS software was adapted in-house for surface-based parametric data [7]. Behavioural PLS with bootstrapping (x1000) and permutation testing (x1000) was applied to detect significant latent variables (LVs) that represent commonalities/differences of the brain behaviour covariance between groups. Analyses were corrected for sex, age and education

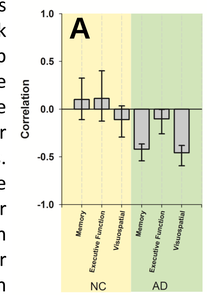
-Figures were rendered using a modified version of the Surfstat Matlab toolbox

RESULTS

- PLS revealed a significant age, sex and education-independent pattern of covariance (Latent Variable or LV) between cognitive performance and cortical thinning in AD but not NC
- The pattern co-localized to the PCC, superior (precuneus) and lateral parietal, prefrontal and MTL bilaterally (p<0.00001) (Figure 1)

RESULTS

Figure 1: (A) Group-wise differences showing a topographical network corresponding to the positive relationship between cortical thinning and cognitive decline (B), which explained 62% of the overall variance in brain-behaviour relationships between NC and AD groups. The colourbar in panel B represents the most reliable regions (>99% CI after bootstrapping) contributing to the pattern observed in panel A, where warmer colours represent stronger associations in AD



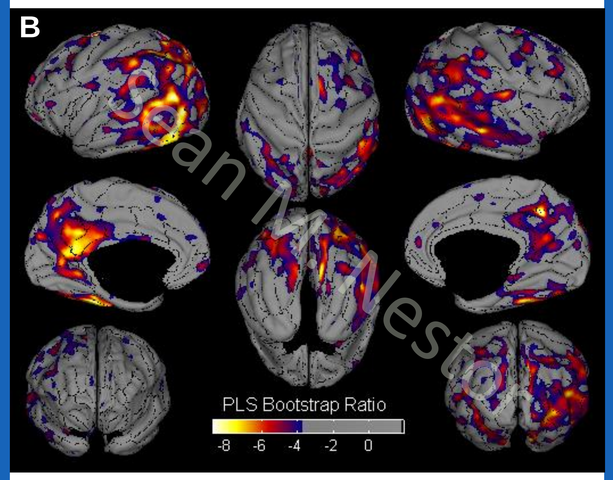
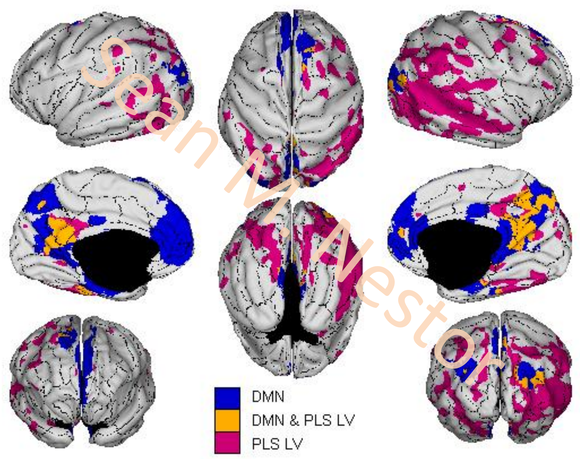


Figure 2: PLS map overlaid with DMN architecture derived from healthy controls (DMN map downloaded from the: http://findlab.stanford.edu/functional_ROIs.html , Shirer et al., 2011)



CONCLUSIONS

1. These data suggest that clinically measured cognitive performance relates to cortical grey matter thinning, which localizes to ventral DMN nodes in AD but not NC
2. The brain-behaviour network pattern was also expressed in a few non-DMN regions (i.e. lateral temporal, parietal and frontal), suggesting that the pattern may be more widespread than just DMN architecture
3. This pattern may relate to degeneration of other networks that share a common set of network nodes with the DMN (e.g. PCC, superior parietal and precuneus)
4. Further longitudinal analyses are warranted to measure whether degenerative changes in the DMN are temporally associated with cognitive decline

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