Relationship Between Cortical Thinning And Cortical FDG Hypometabolism In Individuals with Progressive MCI and AD

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Background and Objective

- The prevailing theory of the development and progression of Alzheimer disease (AD) is that functional changes precede structural changes in the brain. Although patterns of cortical atrophy and FDG hypometabolism have been shown to be generally similar in AD, few studies have directly compared them.
- For this purpose, we developed a cortical surface framework that integrated cortical thickness and cortical FDG-PET data analysis in the ADNI-1 cohort.

Methods

Participants (ADNI-1)

- cNC: Controls with no ApoE4, Ab1-42>192, Ab1-42/Tau<0.39
- sMCI: MCI and have not progressed to AD
- pMCI: MCI progressed to AD within 1 year
- AD

Mean (SD)	cNC	sMCI	pMCI	AD	Difference
N (M/F)	23 (11/12)	98 (68/30)	69 (43/26)	89 (56/33)	p = 0.27
Age	77.3 (5.8)	75.4 (7.2)	75.4 (7.3)	75.5 (7.3)	p = 0.69
MMSE	29.3 (1.1)	27.3 (1.9)	26.1 (2.2)	23.4 (2.1)	p <0.0001
Education	15.9 (2.2)	15.2 (3.3)	15.9 (2.9)	14.6 (3.3)	p =0.054

Imaging

- 1.5T MPRAGE and FDG-PET scans
- For pMCI, both scans at 1 year before conversion
- For cNC, sMCI, AD, imaging data at initial FDG-PET scan timepoint

Image Preprocessing

- MPRAGE and FDG-PET scans downloaded from the ADNI website that have been preprocessed as follows:
- MPRAGE scans were preprocessed within the ADNI framework to remove artifacts: geometric distortion of gradient nonlinearity, non-uniformity normalization, and histogram-peak sharpening, resulting in image volumes at 1x1x1 mm^3 uniform resolution.
- FDG-PET scans were preprocessed within the ADNI framework to account for and reduce inter-site differences: co-registration, averaging, intensity normalization, and scanner-specific smoothing to archive 8-mm FWHM and re-slicing, resulting in image volumes at 1.5x1.5x1.5 mm^3 uniform resolution

Methods – MPRAGE

Cortical Thickness

- FreeSurfer 4.3.0, 20-mm FWHM kernel, re-indexed on the fsaverage white surface

Quality Control

- Visual inspection for anatomic accuracy
- 3% fail, 74% pass, 23% partial pass

Methods – FDG-PET

Cortical Metabolism

- Partial volume effect (PVE) correction (Chen, 2011):
  - Estimation of the probabilistic tissue membership functions P_{CSF}, P_{GM}, and P_{WM} in MPRAGE image space using SPM8
  - Down-sampling with a smoothing kernel of FWHM=1.5mm^3 to match the PVE and the resolution of FDG-PET
  - Masking at P_{GM}>0.3 to minimize correction artifacts
- Corrected FDG-PET update values were calculated

$$I_{\text{corrected}} = \frac{I_{\text{uncorrected}}}{P_{\text{GM}} + 0.4\,P_{\text{WM}}}, \text{where } P_{\text{CSF}} + P_{\text{GM}} + P_{\text{WM}} = 1$$

CSF uptake value = 0, WM = 40% GM (Du, 2006)

- Normalized by mean uptake value of the brainstem (FS ROI, as proxy to the pons) (Minoshima, 1995)

Methods – Co-Registration

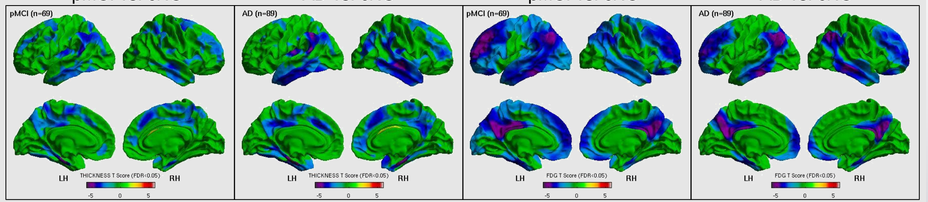
MPRAGE – FDG-PET Image and Surface Co-Registration

- Rigid-motion co-registration matrix between MPRAGE and FDG-PET images was determined (FS *spmregister* command)
- FDG-PET uptake values within the cortical gray matter were projected onto FS white surface (FS *mri_vol2surf* command with *interpolation method = nearest neighbor*)
- Cortical FDG-PET uptake values were re-indexed onto the fsaverage white surface
- Smoothing FDG-PET to achieve the same effective 20-mm FWHM as cortical thickness (Hagler, 2006)

Multimodal vectors of cortical thickness and cortical FDG-PET uptake, with corresponding vertices and smoothed to the same degree

Results – Group Comparison

Cortical Thickness pMCI vs. cNC | AD vs. cNC — **Cortical Metabolism** pMCI vs. cNC | AD vs. cNC

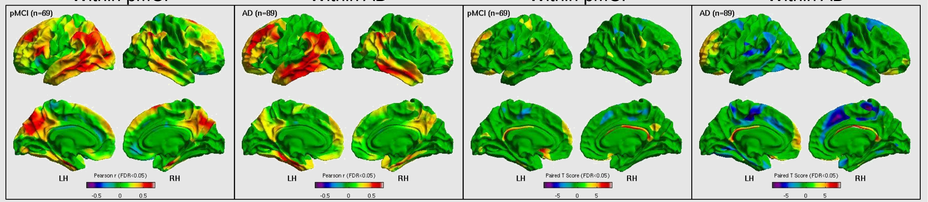


- sMCI did not differ from cNC in any region in any modality

Results – Direct Cortical Thickness / Metabolism Relationship

- Cortical regions showing either thickness and FDG-uptake difference were used to compute z-scores:
  - Multiple linear regression on age, gender and education within the cNC, residuals computed for all subjects
  - Z-score was computed for all subjects residual data using the cNC reference means and standard deviations
- For correlation, we computed Pearson correlation coefficients: Thickness and FDG z-scores
- For difference, we performed paired T-tests: Thickness vs. FDG z-scores
- All analyses were performed at each vertex within each group separately, FDR adjusted (p<0.05)

Pearson Correlation Within pMCI | Within AD — **T scores** (Thickness-FDG) Within pMCI | Within AD



Positive correlation → Cortical thinning is correlated with cortical hypometabolism
Positive T-score → Cortical hypometabolism is more severe than cortical thinning
Negative T-score → Cortical thinning is more severe than cortical hypometabolism

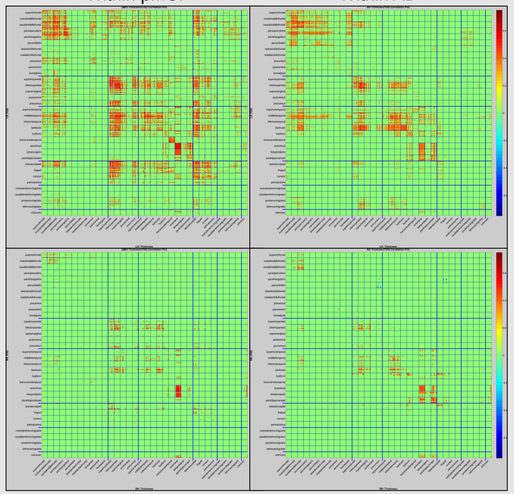
- pMCI and AD – Frontal, temporal and parietal regions show similarly severe cortical thinning and cortical hypometabolism (correlation maps)
- Correlation maps show lateralization toward the left hemisphere
- AD – Many cortical regions show more severe thinning than hypometabolism, while relatively few show more severe hypometabolism than thinning
- pMCI – By contrast, a similar number of cortical regions show more severe hypometabolism than thinning as show more severe thinning than hypometabolism

Results – Inter-Modality Cross-Region Relationship

- Partitioned cortical surface
- Mean value across the partition
- Correlation between thickness and FDG, FDR (p<0.05)

Pearson Correlation

Within pMCI | Within AD



- AD – Hypometabolism is correlated with thinning within and across brain regions; e.g., parietal thickness highly correlated with FDG in frontal, parietal, lateral temporal regions
- pMCI – This pattern is similar, and more extensive
- These patterns are more prominent in the left hemisphere
- sMCI or cNC – no evidence of these relationships

Conclusions

- Cortical hypometabolism-atrophy relationships vary by region
- pMCI – Cortical thinning may be accompanied by functional compensation
- In AD this compensation has resulted in more extensive areas of neuronal loss compared to hypometabolism (see negative T-scores, e.g., right SFG)
- Inter-modality cross-regional relationships may indicate network dysfunction, and can be used to study disease mechanisms and pattern classification