Long-term longitudinal patterns of hypometabolism and atrophy progression from preclinical to dementia stages of Alzheimer's disease

Miguel Labrador-Espinosa[1], Jesús Silva-Rodríguez[1], Michael Schöll[2] *, Michel Grothe[1] *

1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2. University of Gothenburg, Department of Psychiatry and Neurochemistry, Mölndal, Sweden.

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INTRODUCTION

- Structural MRI–derived atrophy and FDG-PET–measured hypometabolism are complementary markers of neurodegeneration in Alzheimer's disease (AD), capturing cumulative tissue loss and synaptic–neuronal dysfunction, respectively.
- However, the temporo-spatial evolution of cortical hypometabolism and atrophy patterns from preclinical stages to AD dementia remains incompletely understood.
- **Aim: In this study, we investigated the temporal evolution of cortical hypometabolism and atrophy using serial FDG-PET and MRI acquisitions in individuals who developed AD dementia.**

METHODS

- **Participants:** 208 nondemented individuals (15% CU, 85% MCI) enrolled in the ADNI study who developed biomarker-confirmed AD dementia over clinical follow-up (Table 1).
  - All participants underwent serial MRI and [18F]FDG-PET acquisitions spanning from −15 years before to +5 years after dementia onset.
- **Neuroimaging:**
  - Cortical thickness on MRI and standardized uptake value ratios on FDG-PET were calculated across 200 cortical regions defined in the Schaefer atlas.
  - Region-wise z-scores were calculated to quantify cortical thickness and hypometabolism relative to healthy elderly controls (N(MRI)=218, N(FDG)=56).
- **Statistical analyses:**
  - Longitudinal atrophy and hypometabolism progression of each brain region was calculated using linear mixed-effects models adjusted for age and sex.
  - Predicted z-scores were generated at 2-year intervals spanning from −10 years before dementia onset to +2 years after.
  - Inter-modality z-score differences quantified the relative predominance of regional hypometabolism versus atrophy over the course of disease progression.

Table 1. Demographic and clinical characteristics.

Variable	Statistical values
N	208
Male (%) / Female (%)	111 (53%) / 97 (47%)
Age at dementia, years	78.2 (7.8)
Education, years	16.0 (2.7)
ApoE4 carrier, N (%)	132 (63.4%)
MMSE at dementia, total score	23.9 (3.4)
Individuals included as CU, N (%)	31 (15%)
Progression time from CU to AD, years	9.3 (3.1)
Individuals included as MCI, N (%)	177 (85%)
Progression time from MCI to AD, years	3.4 (2.8)
PET scans	2 [1, 2]
Years of progression with PET scans	-3.6 (4.3)
Range of years with PET scans	-3 [-6,-1]
MRI scans	4 [3, 5]
Years of progression with MRI scans	-2.5 (3.7)
Range of years with MRI scans	-2 [-4, 0]

The statistical values are mean (SD) for numerical variables, count (%) for categorical variables, and median [interquantile range: p25, p75] for nominal variables. Abbreviations: CU = Cognitively unimpaired; MCI = Mild cognitively impaired.

RESULTS

Figure 1. Temporal trajectories of cortical hypometabolism and atrophy over the course of AD.

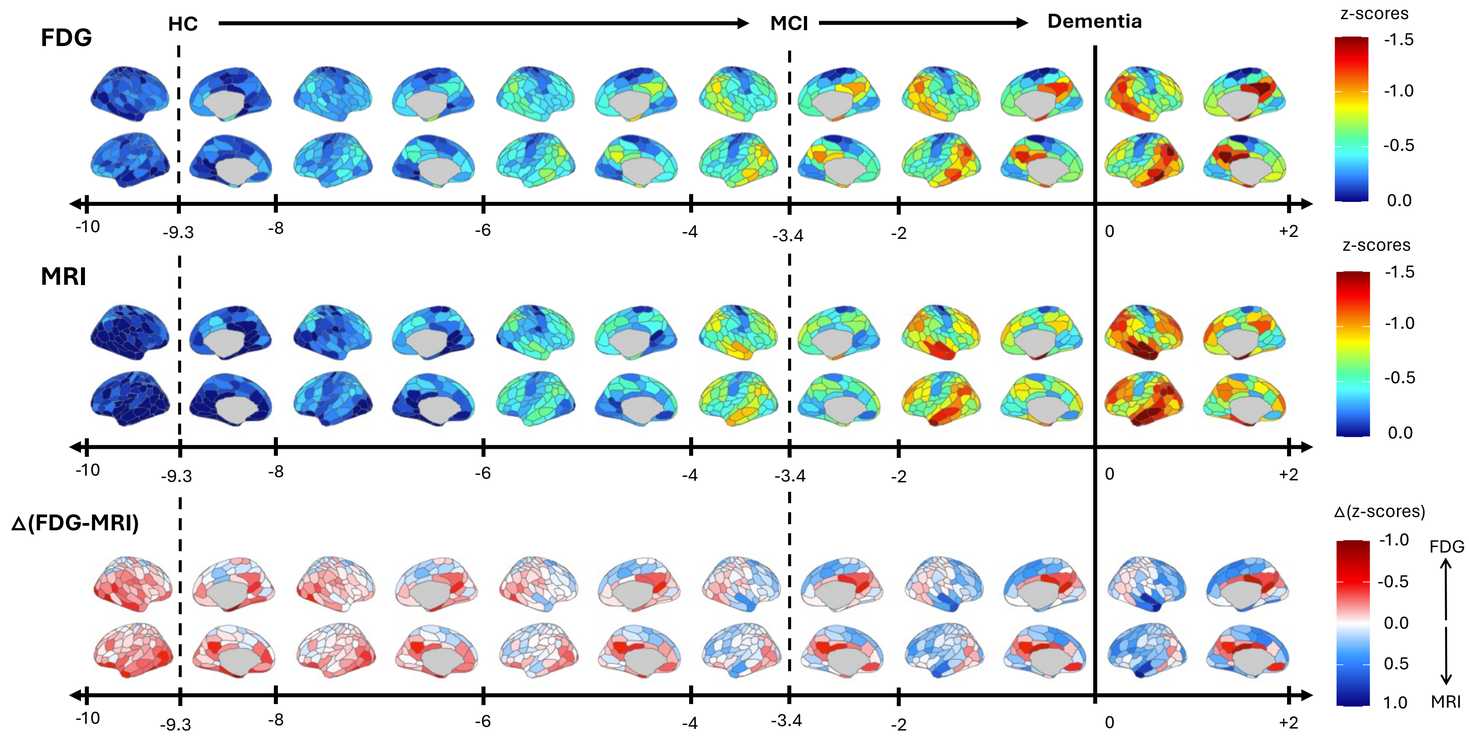


Figure shows predicted z-scores for hypometabolism on FDG-PET (a), cortical thinning on MRI (b) and inter-modality z-score differences (c) at 2-year intervals across a 12-year window spanning 10 years before dementia onset to 2 years after.

- **Hypometabolism on FDG-PET**
  - ✓ First pronounced hypometabolism (z>1) was observed in the posterior cingulate cortex and precuneus approximately 3.5 years before dementia, temporally overlapping with MCI onset.
  - ✓ Over progression to dementia, hypometabolism extended to lateral temporo-parietal areas.
- **Cortical atrophy on MRI**
  - ✓ By contrast, first pronounced cortical thinning was observed in the temporal pole and inferior temporal cortex at a comparable time point, approximately 3.5 years before dementia.
  - ✓ Cortical thinning progressively involved additional fronto-temporo-parietal regions during the progression to dementia.
- **Divergent regional patterns**
  - ✓ A marked predominance of cortical hypometabolism over atrophy was already evident in a widespread cortical pattern at the preclinical stage (−9.3 ± 3.1 years).
  - ✓ As individuals progressed to MCI and dementia, a divergent regional profile emerged, characterized by prominent hypometabolism in medial parietal regions and predominant atrophy in inferior temporal regions.

CONCLUSION

- Cortical atrophy and hypometabolism in AD progression show markedly different origins and temporal trajectories, indicating differential patterns of neurodegenerative phenomena over the course of AD.

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CONTACT

Miguel A. Labrador-Espinosa

mlabrador@fundacioncien.es

X (Twitter): @mlabesp