Moving away from single AD-signature ROI: Assessing the relationship between whole-brain gray matter pattern, AD pathology, and cognition in healthy elderly at risk of AD

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BACKGROUND AND OBJECTIVES

The structural and functional brain architecture is highly organized. Studies revealed that gray matter (GM) is organized into stable covariance regions that often recapitulate functional networks. Over the course of aging and neurodegenerative diseases, atrophy occurs in well-known AD-signature regions, with some overlap with "normal" aging. At an individual level, the boundary between "normal" atrophy and AD-related atrophy in the asymptomatic phase of AD is therefore probably more challenging than what we want to admit. Given this we aimed to assess GM covariance networks across lifespan and AD spectrum and characterize GM organization over this wide spectrum, with a focus on elderly in the asymptomatic phase of AD.

PARTICIPANTS

Young adults
- 1000 Functional Connectomes Project (FCP) - Cambridge site
n=72, mean age: 74 ± 7
- Human Connectome Project (HCP)
n=270, mean age: 33 ± 2

Cognitively normal older adults
- PREVENT-AD (well-characterized cohort with a family history of AD, McGill University, Montreal)
n=296, mean age: 64 ± 5
- Healthy Controls (HC) ADNI
n=136, mean age: 74 ± 7

Cognitively impaired older adults
- Early mild cognitive impairment (MCI) ADNI
n=65, mean age: 72 ± 7
- Late mild cognitive impairment (MCI) ADNI
n=150, mean age: 79 ± 7
- Alzheimer’s disease (AD) ADNI
n=72, mean age: 74 ± 7

STRUCTURAL IMAGE PROCESSING

Native T1-weighted MRI

Common DARTEL template created from all group-specific DARTEL templates

Normalized DARTEL warped modulated, smoothed GM maps

Concatenate GM maps from all groups

Independent component analysis (ICA) (FSL Melodic) 

Threshold components Z>3.5

Extract GM density in all components

ANALYSES

For each subject, GM density in the 30 ICA components was correlated with the GM density in those same regions for every other subject, as a metric of GM pattern correlation. Using GM density in all regions as inputs, k-mean clustering algorithm was used to classify participants into 3 clusters representing yound adults, older adults with intact cognition, and older adults with cognitive impairment.

CONCLUSIONS

In a large multi-cohort sample of young adults, cognitively normal older adults and patients along the AD spectrum, whole-brain GM covariance regions recapitulate meaningful anatomical brain regions and are consistent with the literature.

At the group level, the overall GM pattern is largely preserved, albeit extensive GM atrophy in the MCI and AD groups. Those two groups are also the ones exhibiting the least GM pattern similarity compared to other groups.

At the individual level, there is also a lot of heterogeneity in all groups, as participants from each group are classified in different clusters.

In elderly with intact cognition, having a GM pattern more similar to the one of young adults is associated with less amyloid burden, more tau burden, and better cognition.

Overall, our results highlight the intrinsic and robust GM organization similar in young adults and elderly with no cognitive impairment, but that decreases with severe cognitive impairment.