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[1,2]. Over the course of aging and neurodegenerative diseases, atrophy occurs in well-known AD-signature regions[3,4], 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=198, mean age: 23 ± 5
- Human Connectome Project (HCP)
  n=270, mean age: 33 ± 2

Cognitviely 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

Cognitivetly impaired older adults

- Early mild cognitive impairment (eMCI) ADNI
  n=65, mean age: 72 ± 7
- Late mild cognitive impairment (lMCI) ADNI
  n=50, mean age: 79 ± 7
- Alzheimer's disease (AD) ADNI
  n=72, mean age: 74 ± 7

STRUCTURAL IMAGE PROCESSING

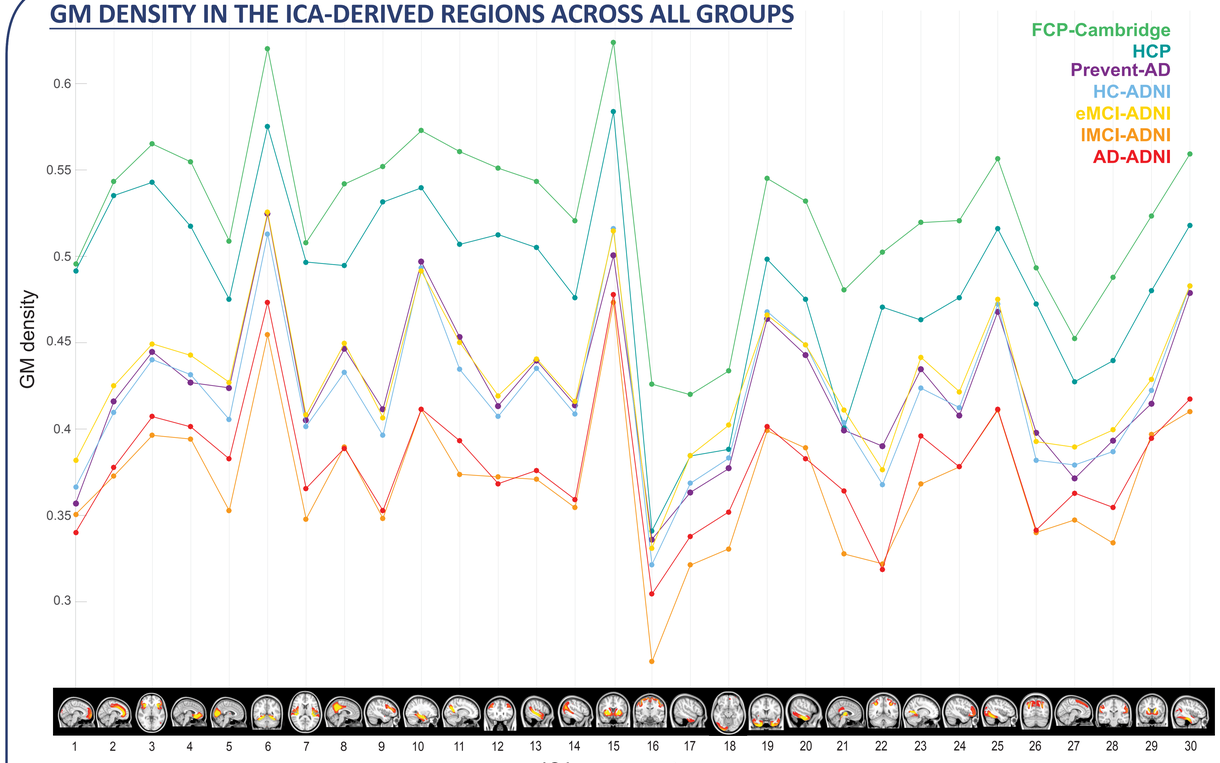
Native T1-weighted MRI
↓
Tissue segmentation
↓
Common DARTEL template created from all group-specific DARTEL templates
↓
Normalized DARTEL warped modulated, smoothed GM maps
↓
Concatenate GM maps from all groups

↓
Independent component analysis (ICA) (FSL Melodic) (n=30)
↓
Threshold components Z>3.5
↓
Extract GM density in all components

ANALYSES

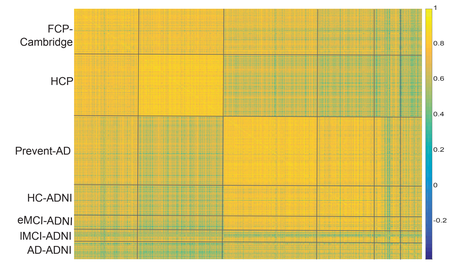
For each subject, GM density in the 30 ICA components was correlated with the GM density in those same regions for every other subject, as a metric of GM pattern correlation.
Using GM density in all regions as inputs, k-mean clustering algorithm was used to classify participants into 3 clusters representing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

GM DENSITY IN THE ICA-DERIVED REGIONS ACROSS ALL GROUPS



Despite atrophy over the course of aging and disease (FCP-Cambridge > HCP > [Prevent-AD = HC =eMCI] > [lMCI = AD]), the overall GM pattern is largely preserved.

CORRELATION BETWEEN GM DENSITY IN THE 30 REGIONS FOR ALL SUBJECTS



Correlation matrix representing GM pattern correlation coefficient between all participants (matrix 1087x1087).

Matrix summarizing mean GM pattern correlation between groups (matrix 7x7).

Despite the overall preserved GM pattern, the similarity is highest in young and old adulthood, and decreases with severe AD pathology.

REGRESSION MODELS OF GM PATTERN AND AD MARKERS

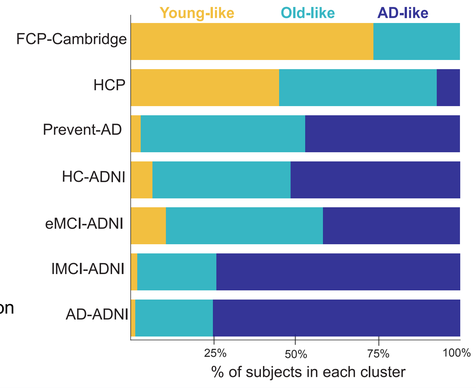
	Similarity to FCP-Cambridge		Similarity to HCP		GM density in ICA10	
	R	p	R	p	R	p
CSF Markers						
$Amyloid_{1-42}$	0.21	**0.035**	0.18	0.074	-0.15	0.141
p-*tau*	0.22	**0.028**	0.18	0.079	-0.20	0.045
Cognitive Index Scores						
Immediate memory	0.10	0.084	0.05	0.376	-0.07	0.250
Language	0.11	0.068	0.07	0.214	-0.11	0.057
Attention	0.14	**0.015**	0.12	0.045	0.03	0.585
Delayed memory	0.09	0.117	0.08	0.171	0.01	0.841
Total RBANS	0.11	0.069	0.08	0.169	0.03	0.612

Bolded values mean that relationships remain significant with age and total GM as covariates.

For each **PREVENT-AD participant**, we assessed whether the GM pattern similarity to the groups of young adults vs.GM density in a given AD region was related to CSF AD markers and cognitive performance using linear regressions.

Having a brain pattern more similar to yound adults is related to lower amyloid burden, higher tau burden, and higher attention scores.

CLUSTERING BASED ON GM DENSITY IN THE 30 REGIONS



Percentage of participants in each of the 3 clusters is depicted.

All groups present heterogeneity in their overall GM density, as participants in every group are classified across multiple clusters.

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 lMCI 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 given 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 robus GM organization similar in young adults and elderly with no cognitive impairment, but that decreases with severe cognitive impairment.

REFERENCES

1. Chen et al., J of Neuroscience, 2008
2. Hafkemeijer et al., Aging Cell, 2014
3. Fjell et al., J of Neuroscience, 2013
4. Dickerson et al., Neurology, 2011