White matter integrity disruption in early amyloid accumulators

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Background

Amyloid-β accumulation is suggested to be closely followed by white matter (WM) integrity alterations in subjects with preclinical Alzheimer's disease (AD). However, reports on the relationship between the two measures have been conflicting. Generally, a loss of WM tract integrity, i.e. decrease of Fractional Anisotropy (FA) and increase of Mean Diffusivity (MD), has been reported in preclinical AD subjects compared to amyloid negative controls.

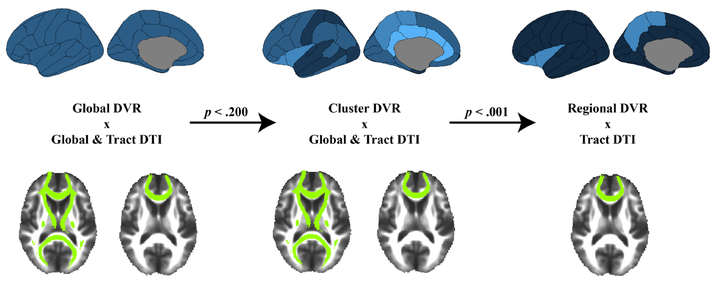
Goal

Investigate the relationship between amyloid burden and WM integrity in preclinical AD on a regional level.

Methods

- **179 subjects** from the EMIF-AD preclinAD study were included.
- Diffusion Tensor MRI (DTI): **global and tract-level** Fractional anisotropy (FA) and mean diffusivity (MD) were determined using the JHU WM atlas.
- Dynamic [^{18}F]flutemetamol PET imaging (Philips Ingenuity PET-MR): **global, cluster, and regional** amyloid burden were determined by the non-displaceable binding potential (BP_{ND}+1 = DVR), with cerebellar grey matter as reference region.
- **Generalized estimating equations** (GEE), correcting for family relatedness, were used to assess the relationship between amyloid burden and WM integrity measures.
- **Linear and quadratic fits** were tested using QIC.
- Analyses were corrected for age, sex, and white matter hyperintensity (WMH) load (significance set at p<0.05, Bonferroni-corrected).

Study design



Left) First, regression analyses were performed between global amyloid (DVR) and global and tract level white matter integrity measures (DTI FA and MD). All associations with a p-value < .200 were selected for further analyses. **Middle)** Then, cluster level amyloid burden was associated with both global and tract level white matter integrity measures. Clusters of amyloid were based on the cortical amyloid staging model as proposed by Collij and colleagues (*under review*). Associations surviving Bonferroni correction were selected for **right)** regional analyses; regional amyloid burden and regional white matter integrity measures.

Regional amyloid burden is associated with WM tract integrity measures in cognitively unimpaired subjects.

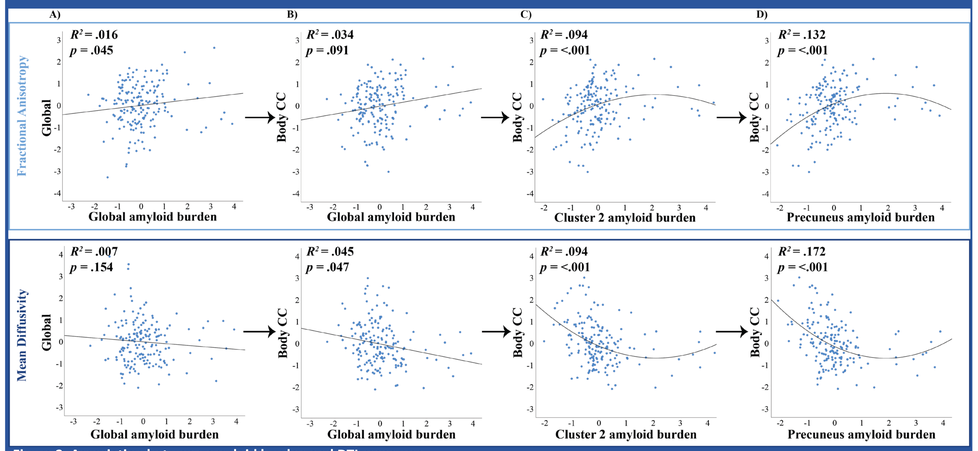


Figure 2. Association between amyloid burden and DTI measures
Scatterplots show the associations between standardized amyloid burden (x-axis) and standardized DTI measures (y-axis), corrected for age, sex, and WMH load.

This association is mainly driven by amyloid burden in the *precuneus* and *posterior cingulate cortex.*

Results

Clinical Characteristics (N =179)	
Gender (% females)	102 (57%)
Age	70.1 (7.14)
MMSE score	29.0 (1.15)
WMH	$5.41E^{03}$ ($7.33E^{03}$)
APOE-ε4 positivity (%)	74 (41.3%)
PET metrics	
Global amyloid DVR	1.03 (0.12)
Global amyloid positivity (%)*	20 (11.2%)

Table 1. Demographics of the cohort
Continuous measures are shown as mean (SD) unless otherwise specified.
*Based on predefined cut-off using Gaussian mixture modelling (i.e. DVR > 1.15).

1. Global amyloid and DTI:
Global amyloid burden was associated with global FA (β = 0.068, p = 0.045), but not with global MD (p = 0.154) (**Fig. 2A**). Global amyloid burden was most strongly related to FA and MD in the body of the Corpus Callosum (CC) (**Fig. 2B**).

2. Cluster amyloid and DTI:
Significant associations between FA in the body of the CC and amyloid burden in cluster 1 (β_{linear}=0.227, $\beta_{quadratic}$=-0.061, ΔQIC=2.8) and cluster 2 (β_{linear}=0.262, $\beta_{quadratic}$=-0.071, ΔQIC=4.0) were observed.
Significant associations were found between MD in the body of the CC and amyloid burden in cluster 1 (β_{linear}=-0.385, $\beta_{quadratic}$=0.094, ΔQIC=5.5), cluster 2 (β_{linear}=-0.349, $\beta_{quadratic}$=0.089, ΔQIC=5.6), and cluster 3 (β_{linear}=-0.198, $\beta_{quadratic}$=0.053, ΔQIC=3.0). The quadratic model was preferred for these associations (**Fig 2C**).

3. Regional amyloid and tract DTI:
The association between cluster 2 amyloid burden and FA in the body CC was driven by the precuneus (β_{linear}=0.352, $\beta_{quadratic}$=-0.103, ΔQIC=6.7, **Fig. 2D**).
The association between cluster 1 and MD in the body CC was mainly driven by the posterior cingulate (β_{linear}=-0.393, $\beta_{quadratic}$=0.101, ΔQIC=4.0), to a lesser extent by the anterior cingulate (β_{linear}=-0.277, $\beta_{quadratic}$=0.061, ΔQIC=2.7), and not by the isthmus cingulate (p=0.065). The association with amyloid burden in cluster 2 was driven by the precuneus (β_{linear}=-0.434, $\beta_{quadratic}$=0.128, ΔQIC=8.0, **Fig. 2D**).

Interpretation

An initial increase in amyloid burden corresponded to higher FA and lower MD, followed respectively by a maximum for FA and a minimum for MD, and finally lower FA and higher MD for further increases in amyloid burden. These associations were largely driven by amyloid burden in early accumulating regions.
Our observed quadratic patterns might entail multiple stages of axonal damage, with initial oligodendrocyte proliferation and axonal swelling upon low amyloid burden, and actual axonal degeneration only becoming apparent at a higher amyloid burden.

Conclusion

Regional amyloid burden is associated with WM tracts' integrity measures in cognitively unimpaired subjects. This work highlights the importance of regional investigations in the context of preclinical AD. Taken together, WM tracts' integrity measures of body CC are promising early AD biomarkers and could, together with amyloid burden, support risk-profiling efforts in preclinical AD subjects.

Academic partners **SMEs** **Industrial partners** **Patient Organization**

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