Amyloid predicts longitudinal atrophy in non-demented individuals: Results from the AMYPAD Prognostic & Natural History study

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Background

While the association between tau deposition on PET and brain atrophy on MRI is well documented in the literature, the relation between amyloid deposition and neurodegeneration in the earliest stages of Alzheimer's disease is less studied. We investigated this relationship in a large cohort of non-demented individuals.

Aim

Assess the effect of cortical amyloid presence at baseline, as measured by quantitative PET amyloid imaging, on longitudinal cortical and subcortical atrophy in non-demented individuals.

Materials and Methods

Data. We included 1383 participants from the AMYPAD Prognostic & Natural History study (PNHS) with available MRI and amyloid-PET. Among those, 789 had longitudinal MRI, with a mean follow-up time of 3.47 years (SD=1.55).

Image-Derived Phenotypes. The FreeSurfer 7.0.1 longitudinal pipeline was used to measure gray matter (GM) thickness and volumes in 40 regions (**Figure 1**; Reuter et al., 2012; Desikan et al., 2006). From PET scans, cortical amyloid burden was assessed globally using the Centiloid (CL) method in reference to the cerebellum. Amyloid status at baseline was defined as negative (**A-**; CL < 10), grey-zone (**GZ**; 10 ≤ CL ≥ 30) or positive (**A+**; 30 < CL). MRI-derived regional volumes and thickness were harmonized across sites with neuroCombat while retaining the variance from all investigated covariates (Fortin et al., 2018); all variables were Z-scored.

Analyses. Linear mixed-effect models were used to investigate the effect of amyloid burden at baseline and its interaction with time on regional volume and thickness measurements. Models were corrected for age, sex, CDR and estimated total intracranial volume. *P*-values were FDR-adjusted.

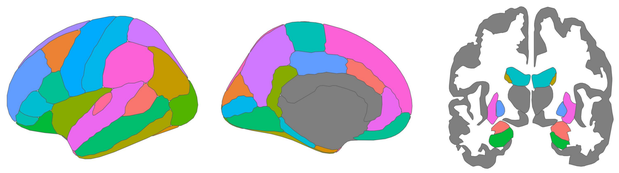

Figure 1. *Illustration of the 34 Cortical ROI's & 6 Subcortical ROI's.*

Cross-Sectional & Longitudinal Effects of Aβ on Volume & Thickness

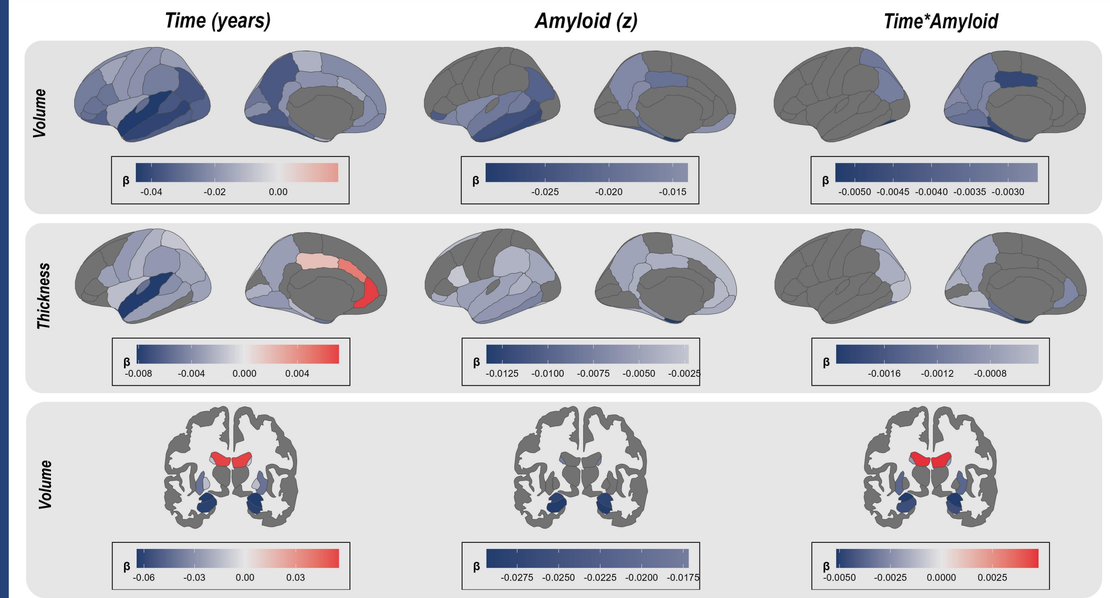

Figure 2. *Regression Coefficients of the Linear Mixed-Effects Models.*

Atrophy Trajectories: Precuneus

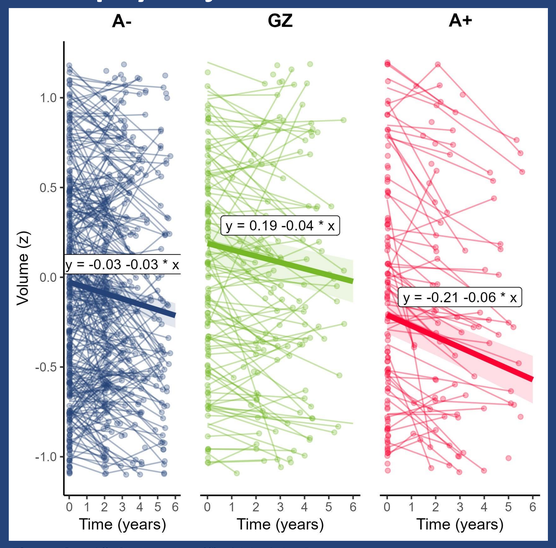

Figure 3a. *Aβ-Status stratified Models: Precuneus.*

Atrophy Trajectories: Hippocampus

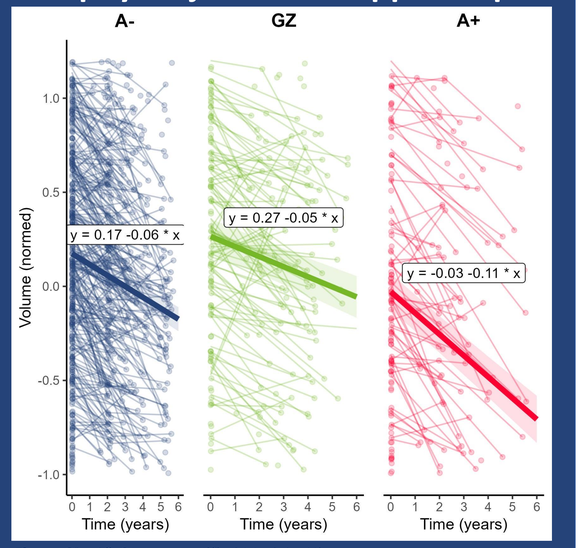

Figure 3b. *Aβ-Status stratified Models: Hippocampus.*

Results

Cohort characteristics are shown in **Table 1**. Decreasing cortical thickness and volumes were observed over time in most regions, apart from a longitudinal increase in cingulate areas. At baseline, higher amyloid burden was related to smaller volumes of the hippocampus and amygdala; and lower volume and thickness especially of temporal regions.

Over time, subjects with higher baseline amyloid burden showed greater loss of volume and thickness in mainly temporal and parietal regions, as well as caudate, putamen, amygdala and hippocampal volume (**Figure 2**). In selected regions such as the hippocampus and precuneus, participants with GZ status had significantly larger volume at baseline in comparison to participants with A- status, while volumes of participants with A+ status declined significantly faster than those of participants with A- or GZ status (**Figure 3**).

Table 1.

Baseline Characteristics of the Included Participants.

	Overall (N=1383)	A- (N=786)	GZ (N=276)	A⁺ (N=321)	*P*-Value
Sex					
Female	778 (56.3%)	463 (58.9%)	144 (52.2%)	171 (53.3%)	0.072
Male	605 (43.7%)	323 (41.1%)	132 (47.8%)	150 (46.7%)	
CDR, global score					
0 - Normal	1070 (77.4%)	660 (84.0%)	231 (83.7%)	179 (55.8%)	**< 0.001**
0.5 - Very mild	259 (18.7%)	97 (12.3%)	37 (13.4%)	125 (38.9%)	
Age, years (mean ± SD)	68.2 (8.74)	66.3 (8.31)	67.6 (7.86)	73.1 (8.69)	**< 0.001**
Follow-up time, years (mean ± SD)	3.73 (1.87)	3.85 (1.97)	3.55 (1.57)	3.45 (1.79)	0.051
MMSE, score (mean ± SD)	28.8 (1.57)	29.0 (1.29)	29.0 (1.35)	28.0 (2.08)	**< 0.001**
Education, years (mean ± SD)	14.6 (3.95)	14.7 (3.85)	14.8 (4.15)	14.1 (3.96)	**0.031**
PET Centiloid (mean ± SD)	19.9 (32.8)	-0.162 (6.66)	17.2 (5.26)	71.2 (29.4)	**< 0.001**
Estimated Total Intracranial Volume, cm³ (mean ± SD)	1.48 (0.178)	1.47 (0.178)	1.50 (0.180)	1.47 (0.174)	**0.023**

Abbreviations: A- = Amyloid negative; GZ = Amyloid grey-zone; A⁺ = Amyloid positive; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; PET = Positron emission tomography.

Conclusion

In the largely asymptomatic AMYPAD PNHS cohort, we show that amyloid burden at baseline is predictive of future neurodegeneration, especially affecting temporal and parietal areas. Cortical thickness was slightly more sensitive towards amyloid burden at baseline, while loss of cortical volume was greater than loss of thickness. Volumetric differences at baseline and of rate of decline between amyloid status groups suggest non-linear rate of atrophy trajectories.

Academic partners

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