Brain structural alterations in cognitively unimpaired individuals with discordant amyloid-β PET and CSF Aβ42 status: findings using Machine Learning

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ALFA study, ADNI study

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Introduction:

CSF Aβ42 is thought to show AD-related alterations earlier than amyloid-β PET. Therefore, cognitively unimpaired (CU) individuals with abnormal CSF Aβ42 and normal amyloid-β PET are believed to be in the earliest stages of the AD *continuum.* In this work, we sought to detect structural cerebral alterations in CU individuals with discordant status in these amyloid-β biomarkers using Machine Learning techniques.

Methods:

We included 498 CU individuals from the ALFA+ and ADNI studies with available MRI, amyloid-β PET and CSF $A\beta_{42}$ measurements, the latter measured with the exploratory Roche NeuroToolKit assays, a panel of automated robust prototype immunoassays. In addition, we calculated Centiloid (CL) values for the PET measurements. Individuals were categorized as CSF-/PET-, CSF+/PET- and CSF+/PET+ according to established cut-offs (CSF Aβ42<1098pg/mL for ALFA+ and <880pg/mL for ADNI, and CL<17 for PET). We trained XGBoost classifiers to predict amyloid-β positivity using as features age, sex, APOE-ε4 status, brain volumes and cortical thicknesses, obtained with Freesurfer 6.0 and the Desikan-Kiliany atlas. Relevant features for pairwise-group classification were sought (CSF-/PET- vs CSF+/PET-; CSF+/PET- vs CSF+/PET+; CSF-/PET- vs CSF+/PET+), calculating SHAP values to determine the most important features for prediction.

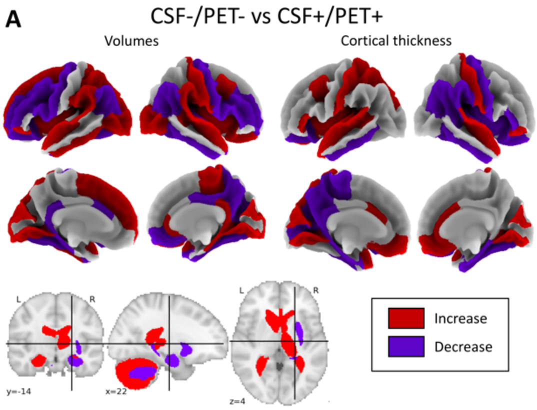
Results:

With respect the CSF-/PET- group, the CSF+/PET- showed decreased gray matter volumes in the anterior and posterior cingulate/precuneus and increases in the lateral ventricles and bilateral parahippocampal gyri, among other regions (Figure 1A). Unexpectedly, the posterior cingulate/precuneus showed the opposite effect in cortical thickness measurements. These patterns were similar but more prominent in the comparison between the CSF-/PET- vs CSF+/PET+ group (Figure 1B). Finally, CSF+/PET- group was characterized, with respect the CSF+/PET+ group by higher volume of the bilateral supramarginal gyri and lower cortical thickness in the posterior cingulate/precuneus (Figure 1C). Regarding the other variables in the model, APOE-ε4 status was the most predictive variable in models with respect the CSF-/PET- group and age in the CSF+/PET- vs CSF+/PET+ comparison.

Conclusion:

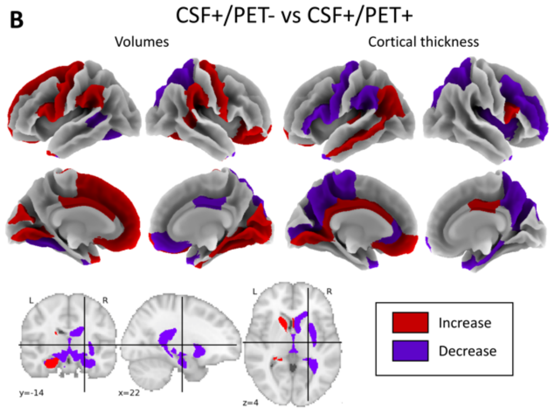
Our results show that model-free machine learning techniques can detect complex brain morphological alterations in the earliest stages of the AD continuum. Interestingly, some regions showed increases in volume and/or cortical thickness which may reflect compensatory or inflammatory effects.

A



Feature	β(A+)	p-value	SHAP direction
Left-Lateral-Ventricle	0,270042	0,0345	+
Right-Inf-Lat-Vent	0,229685	0,07182	+
Left-Accumbens-area	-0,16537	0,1929	-
Left-Caudate	0,239838	0,061865	+
left_inferiorparietal_vol	-0,18416	0,157953	-
left_supramarginal_vol	0,277804	0,035076	+
left_rostralmiddlefrontal_vol	-0,10123	0,435835	-
left_cuneus_vol	0,32753	0,012374	+
Left-Hippocampus	0,133054	0,286796	+

B



Feature	β(A+)	p-value	SHAP direction
Left paracentral thickness	-0,42741	0,013711	-
Left supramarginal vol	0,53325	0,00183	+
left_superiorfrontal_vol	0,243505	0,150613	+
Right supramarginal vol	0,378228	0,021694	+
Left pericalcarine thickness	-0,03846	0,824003	-
Left precuneus thickness	-0,08924	0,602298	-
Right posteriorcingulate vol	0,041829	0,808658	-
Left cuneus vol	0,48669	0,004654	+
Left-Inf-Lat-Vent	-0,11864	0,478087	-