Voxel-based amyloid PET staging along the Alzheimer's disease *continuum*

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AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

efpia imi innovative medicines initiative

Background

Regional staging of amyloid PET scans has advantages to global PET dichotomization because it is able to identify earlier pathology and to assess a more detailed risk for each participant.
However, current relies on atlas-based regions of interest (ROI) approaches and global cut-offs to assess amyloid abnormality [1-3].

Aim

To create a voxel-wise staging model for amyloid burden without a priori bias for regional segmentation nor global cut-offs

Material and Methods

Participants:

A total of 870 amyloid PET scans from four different cohorts: ALFA [4], EMIF-AD [5], ADC [6] and ADNI comprising the whole AD *continuum* and scanned with two amyloid tracers ([^{18}F]flutemetamol, and [^{18}F]florbetapir)

Construction of the model:

The model was constructed by 4 steps (**Figure 1**) by using the scans of 224 cognitively normal (CN) participants from the ALFA cohort

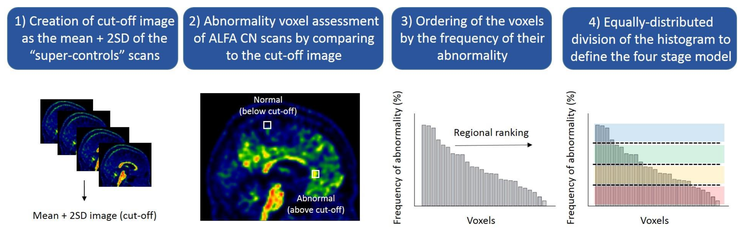


Figure 1: Summary of the model construction

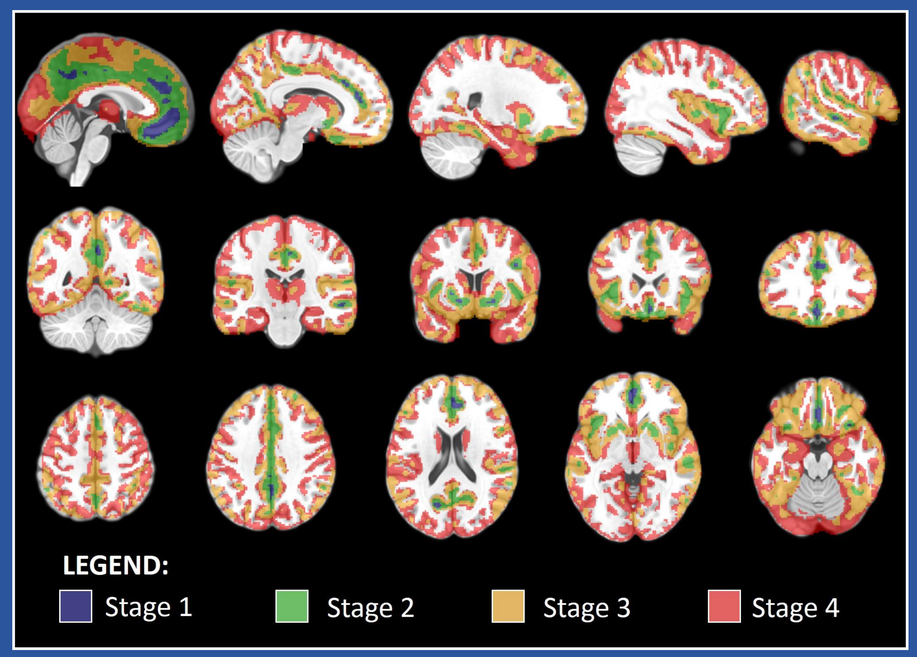
Stage participants:

We applied the model constructed (**central figure**) to all available amyloid PET scans. For each scan, a particular stage was considered if: 1) >50% of the voxels of that stage was abnormal; and 2) the previous stages were also positive. If the second condition was not fulfilled the scan was classified as "unstageable".

Assessment of the model's performance:

Finally, the model's performance was evaluated by assessing the number of unstageable scans and the correlation between stage classification and CSF biomarkers as well as MMSE scores (by Speaman's rho correlation, p<0.001).

Voxel-wise staging model



The derived model correlated with CSF core AD biomarkers and MMSE

	ALFA (n=224)	EMIF-AD (n=190)	ADC (n=145)	ADNI (n=311)
$A\beta_{42}$	-0.45***	-0.34***	-0.69***	-0.55***
pTau	0.30***	0.37***	0.59***	0.49***
pTau/$A\beta_{42}$ ratio	0.56***	0.41***	0.72***	0.62***
$A\beta_{40}/A\beta_{42}$ ratio	NA	-0.25**	NA	NA
MMSE	0.03	-0.15*	-0.30***	NA

Spearman's rho correlation values between stages and CSF core AD biomarkers and between stages and MMSE. *** p<0.001; ** p<0.005; *p<0.05

Results

	All (n=870)	ALFA "super-controls" (n=35)	ALFA (n=224)	EMIF-AD (n=190)	ADC (n=145)	ADNI (n=311)
Age, years, mean (SD)	68.1 (8.7)	58.6 (4.2)	61.1 (4.8)	70.5 (7.6)	62.2 (5.6)	74.5 (7.1)
Sex, Female, n (%)	476 (54.7)	21 (60.0)	146 (64.6)	112 (58.9)	66 (45.5)	152 (48.9)
APOE-ε4 carriers, n (%)	428 (50.4)*	8 (22.9)	88 (38.9)	74 (38.9)*	87 (63.5)*	179 (57.6)
MMSE, mean (SD)	27.6 (3.1)*	29.1 (1.0)	29.2 (1.0)	29.0 (1.1)	23.4 (3.3)	-
Diagnsosis, n (%)						
CN	468 (53.8)	35 (100.0)	224 (100.0)	190 (100)	3 (2.1)	51 (16.4)
MCI	2247 (28.4)	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.9)	237 (76.2)
AD	107 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	84 (57.9)	23 (7.4)
non AD	48 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	48 (33.1)	0 (0.0)
Amyloid PET tracer	-	[^{18}F]flutemetamol	[^{18}F]flutemetamol	[^{18}F]flutemetamol	[^{18}F]flutemetamol	[^{18}F]florbetapir
Stages, n(%)						
Normal	340 (39.1)	35 (100.0)	190 (84.2)	63 (33.2)	46 (31.7)	41 (13.2)
1	118 (13.6)	0 (0.0)	12 (5.4)	75 (39.5)	9 (6.2)	22(7.1)
2	113 (13.0)	0 (0.0)	14 (6.3)	38 (6.8)	10 (6.9)	51 (16.4)
3	233 (26.8)	0 (0.0)	8 (3.6)	13 (6.8)	53 (36.6)	159 (51.1)
4	66 (7.6)	0 (0.0)	0 (0.0)	1 (0.5)	27 (18.6)	38 (12.2)

Table 1: Demographics and stage classification by cohort

- The model was able to stage all **870 included scans** covering the **whole AD *continuum*** with three different amyloid tracers (**Table 1**)
- First areas to become abnormal: **anterior cingulate, orbitofrontal** and **precuneus** (central figure)
- The staging levels correlated highly with **$A\beta_{42}$** but also with **progression markers** as pTau/$A\beta_{42}$ ratio and cognition by means of MMSE in the cohort including AD patients (central table)

Conclusions

The presented voxel-wise model circumvents the need for pre-established **global cut-offs**. The strong correlation between stages and $A\beta_{42}$ suggests that this model could be used to detect **early amyloid accumulation**. Moreover the significant correlation with pTau/$A\beta_{42}$ ratio also suggests that this model might be **useful to monitor** not only amyloid load, but the whole AD *continuum*.

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