Quantifying AD-related brain amyloid with linearised progression models: model-based vs. data-based

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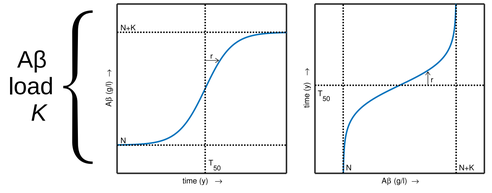
Introduction

Background
- The main biomarker for early AD is brain amyloid (Aβ)
- In a logistic progression model, biomarker curves are sigmoids *see figure*
- If the Aβ time curve has global shape it is a whole-brain regressor / predictor
- For Aβ PET images aligned wrt AD onset a global curve can serve as regressor

Voxelwise maps of these regressors show regional Aβ uptake capacity during AD (NS for baseline, K for capacity, Whittington 2018)
In a spatial regression of an Aβ PET image with NS and K, weights of K can be used to estimate time since AD onset.
But this model uses the biomarker curves twice: *(i)* to order scans by TSO, and *(ii)* to estimate local model values.

We propose a data-driven alternative for load K to quantify SUVR maps of Aβ accumulation from TSDO-synchronised scans and demonstrate its validity in clinical studies.

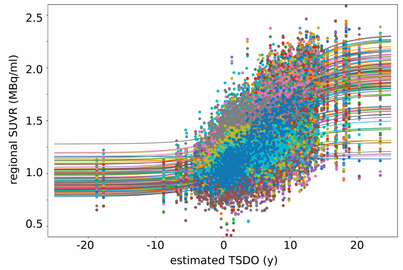


Methods

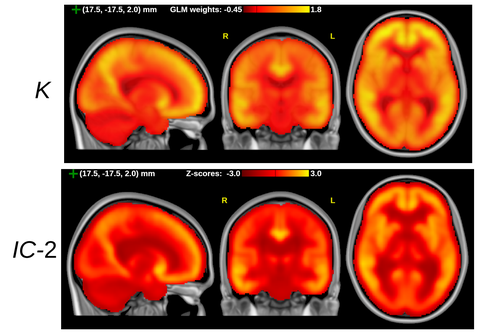
Data sets: cross-sectional
- model estimation:
  ADNI-2*: ^{18}F-florbetapir HC/SCD/MCI/AD
  MCI: e(arly)MCI,MCI,l(ate)MCI *n* = 1071
- cognitive evaluation (see Collij 2021)
  OASIS-3§: ^{12}C-PiB HC *n* = 329

Preprocessing
- SUVR computed; reference: cerebellar grey matter
- SUVR mapped to the MNI space at 2 mm^3 resolution

Verify validity of a global Aβ time curve
- use logit (inverse sigmoid) to obtain time since AD onset from mean cortical SUVR
- compare 16 models with regional sigmoid *K*, *N*, T_{50} and *r,* optimised globally or locally
- best model: global T_{50} and *r*, local *K* and *N* based on Bayesian information criterion using python3 package lmfit†



Data-driven estimation of weight maps
- map of *K* compted as in (Whittington 2018)
- 2-components ICA on aligned SUVR maps
- map *IC*-2: very similar to that of *K* (*r* = 0.86)



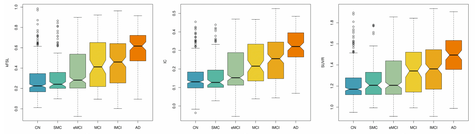
Model comparions
Statistical analyses used R 3.6.2‡.

Effect size in for separating ADNI subgroups
Separations of ADNI groups were computed using weights of *K*, corresponding component *IC*-2 mean SUVR in cortical grey matter.

Correlation with cognitive scores in OASIS
Averages weights within SUVR from OASIS were correlated with cognitive scores: logical memory, category fluency, digit span backwards. Mean SUVR was within the centiloid regions, *K* and *IC*-2 across MNI space.

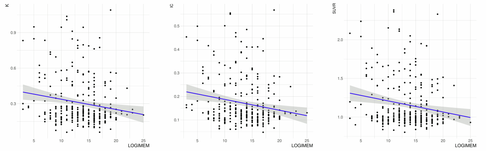
Results

Effect size in separating ADNI subgroups



Effect sizes, computed with Hedges' *g*: 2.25 for *K,* 2.42 for component *IC*-2 and 1.46 for mean cortical SUVR.

Correlation with cognitive scores in OASIS



Hedges' *g*:	Logical Mem.	Mem. Units	Digit-B
K	4.65	4.03	4.11
IC-2	4.70	4.08	4.21
$SUVR_{centiloid}$	4.34	3.75	3.53

Differences in effect sizes were small but consistent, both models outperforming SUVR, maximum *g* for IC-2 over *K*.

References
Whittington 2018: JNM 59(5): 822-827
Collij2021: Alz. Dem. 13(1): e12216

*adni.loni.usc.edu §www.oasis-brains.org
‡www.r-project.org †lmfit.github.io/lmfit-py

Conclusions

We have:
- reproduced the validity of a whole-brain Aβ accumulation time curve
- reproduced the map *K* for Aβ accumulation capacity in AD for PET-based quantification
- presented a data-driven alternative that does not repeatedly use the sigmoid model
- shown that both methods outperform mean cortical SUVR for identifying ADNI groups
- shown that both methods correlate more strongly with cognition in OASIS controls
- found that the effect sizes reported by data-driven weight map IC-2 are higher than K

The findings in OASIS also suggests that the weights maps can be used across tracers. Our future efforts will focus on establishing tracer independence and statistical validation.

Contact

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