Event-based modeling of the temporal ordering of regional β-amyloid deposition in the brain

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Background

Amyloid imaging by Positron Emission Tomography (PET) provides a unique opportunity to visualize the spatial distribution of amyloid-β (Aβ) plaques in the brain *in vivo*. Current research efforts place the accumulation of these plaques as the earliest detectable change in the path towards AD[1]. However, recent studies have shown that the standard classification of amyloid PET images (dichotomous) might miss the earliest pathological signs[2].

With the shift in focus of clinical trials towards secondary prevention, identification of subjects at risk of developing AD might require more sensitive staging of Aβ levels. Therefore, unraveling the spatio-temporal trajectory of Aβ brain deposition may not only improve early diagnosis, but also support future secondary prevention trials in AD.

Aim

To determine, in a data-driven manner, the temporal ordering of regional amyloid deposition in the brain using PET imaging and the event-based model (EBM)[3].

Methods

Event-based modeling

The event-based model (EBM) is a probabilistic generative model of disease progression that can learn the ordering of biomarker changes from large cross-sectional data sets, as well as providing insights into the uncertainty of the reconstructed ordering. EBM treats each biomarker as either 'normal', i.e. non-pathological, or 'abnormal', i.e. as seen in Alzheimer's disease, and the switch from normal to abnormal is termed an 'event'. To define the events, no *a priori* abnormality cut-off is set, and instead a mixture of two Gaussian curves provides probabilistic models for normal and abnormal biomarker (Aβ in this case) levels from which one can determine the likelihood of Aβ deposition for each region (biomarker) of each subject.

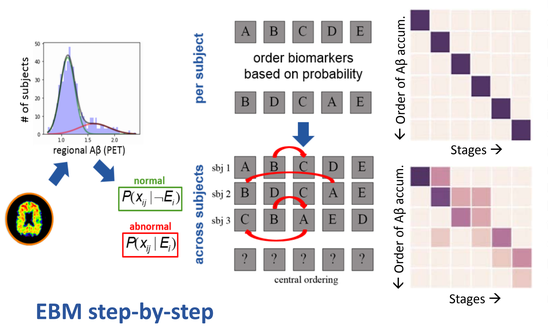


Figure 1. EBM Scheme. First step is the Gaussian Mixture Modeling to calculate the probability of Aβ accumulation, then the probabilities of each biomarker abnormality are ranked per subject to determine individual orderings. Next, a central ordering is computed by averaging the individual orderings such that the distance (probabilistic Kendall's tau distance) is minimized between individual orderings. Finally, the process is cross-validated with a bootstrapping sequence to determine the frequency of orderings. The intensity of each matrix entry corresponds to the proportion of bootstrapped samples where a certain region (y-axis) appears at the respective stage (x-axis).

EBM step-by-step

The main steps of EBM include:

1. Model input = regional values of Aβ deposition (standard uptake value ratio, SUVR, or binding potential, BPnd)
2. Model fitting = see Figure 1
3. Cross-validation = bootstrapping 100x

Methods

Population

For this study, three data sets were included:

Data set	Tracer/metric	N subjects	Negative PET (-)	Positive PET (+)	Anatomical Atlas
VUmc	[18F]FLUT SUVR	Total =335 [HC = 190]	216 (64%)	119 (36%)	Hammers†
OASIS3	[11C]PIB SUVR & BPnd	Total = 572 [HC = 484]	430 (75%)	142 (25%)	FreeSurfer wmparc.mgz‡
OASIS3	[18F]AV45 SUVR	Total = 360 [HC = 301]	240 (67%)	120 (33%)	FreeSurfer wmparc.mgz‡

Table 1. Summary of data sets included in the study.

†Hammers A, et al. Hum Brain Map 2003
‡Fischl B, et al. Neuron 2002.

To define groups for EBM fitting, subjects were classified as "healthy controls" when the PET scan was deemed negative (visually or global cut-off), and "diseased" when the PET scan was deemed positive.

Results

VUmc [18F]FLUT

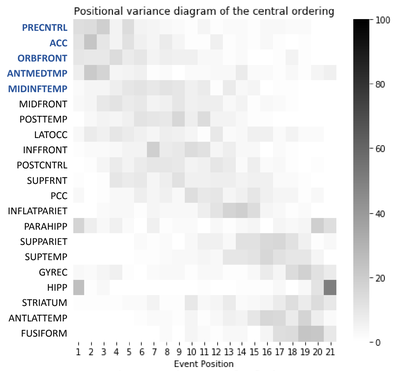


Figure 2. Resulting ordering of Aβ deposition using VUmc [18F]FLUT SUVR data (n=335).

OASIS [18F]AV45

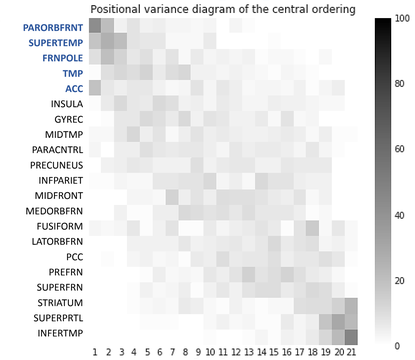


Figure 3. Resulting ordering of Aβ accumulation using OASIS3 [18F]AV45 SUVR data (n=360).

OASIS [11C]PIB

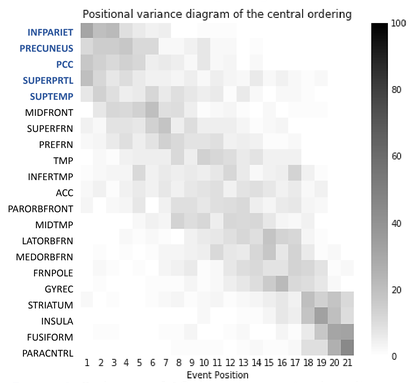


Figure 4. Ordering of Aβ deposition using baseline subjects from OASIS3 ([11C]PIB) SUVR data (n=572).

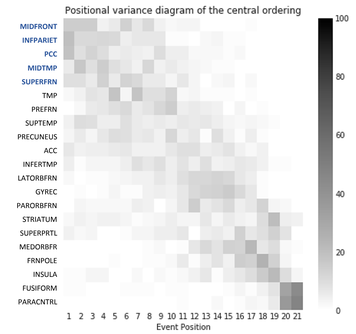
Comparing 3 radiotracers/populations

- [18F]AV45 and [18F]FLUT data show more frontal and temporal involvement in earlier stages
- Distinct regions appearing earlier in [11C]PIB (e.g. precuneus, PCC, parietal)
- Striatum in later stages for all tracers
- [11C]PIB model more certain of the central ordering (smaller off-diagonal variance)

Results

OASIS [11C]PIB split by carriership

APOE ε4 carriers



APOE ε4 NON-carriers

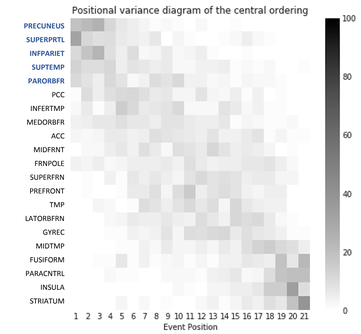
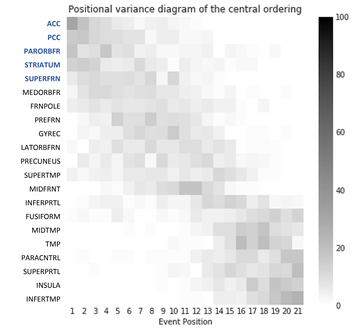


Figure 5. Ordering of Aβ deposition using baseline subjects from OASIS3 ([11C]PIB) SUVR data for APOE ε4 carriers (left, n=211 / 45% +, 55% -) and non-carriers (right, n=361 / 13% +, 87% -).

OASIS [11C]PIB with each metric

BPnd



SUVR

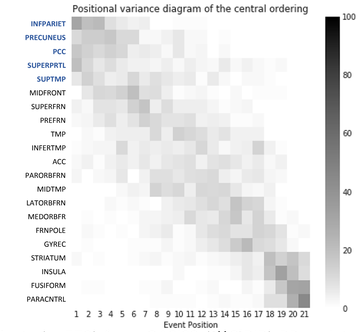


Figure 6. Ordering of Aβ deposition using baseline subjects (n=572) from OASIS3 ([11C]PIB) BPnd data (left) and SUVR data (right).

Conclusion(s)

- Earlier regions in all EBMs generally agree with previous reports (orbitofrontal, ACC, precuneus)
- Most EBMs showed great uncertainty in ordering, with wide variance off-diagonal
  - Possible sub-groups with distinct ordering (future work)
  - Larger sample size may increase certainty

Limitations

- Data processing is not yet fully harmonized across data sets
- Biomarkers are not independent from each other, increasing uncertainty in the model

EBM shows promising results in determining the ordering of amyloid accumulation in a data-driven manner

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Acknowledgement(s): This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. www.imi.europa.eu
Data were provided [in part] by OASIS3: Longitudinal: Principal Investigators: D. Marcus, R, Buckner, J. Csernansky, J. Morris; P50 AG05681, P01 AG03991, P01 AG026276, R01 AG021910, P20 MH071616, U24 RR021382