Retrospective prediction of amyloid accumulation trajectories in a risk-enriched Alzheimer's disease cohort with sequential neural network

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BACKGROUND

- Understanding the **longitudinal pattern of amyloid accumulation** is crucial for the **early detection and intervention** in Alzheimer's disease (AD).
- The **PiB+ Age (PA)** when amyloid accumulation crosses a critical threshold is one of the earliest signs of AD progression of **risk-enriched cohort** *(Koscik et al., 2019, Bilgel et al., 2016).*
- Challenge: The **early amyloid accumulations** (i.e., PiB-PETs before PAs) of middle- to late-middle aged participants are often **not observed.**
- Solution: Estimate the longitudinal pattern of amyloid accumulation **retrospectively** (i.e., earlier than the observed ages) via **deep conditional recurrent neural networks** *(Hwang et al., 2019).*

OBJECTIVES

Develop and use a sequential neural network model to:

I. Extrapolate the PiB-PET amyloid trajectories **retrospectively**.

II. Estimate the **subject- and region-wise** PAs.

III. Investigate their **associations** with an AD-risk factor (APOE4) in a preclinical cohort.

METHODS

- **Dataset**: Cognitively asymptomatic participants from the Wisconsin Registry for Alzheimer's Prevention (N=234, mean=63.8/s.d.=6.7 age) with three longitudinal [C11] PiB-PET scans separated by mean=3.42 (std=1.57) years were included (**Table 1**). For each timepoint and subject, we measure the PiB distribution volume ratio (PiB-DVR) in 8 bilateral (combined) AAL regions and the age at scan (regions listed on **Table 2**).
- **Model**: A deep conditional recurrent neural network *(Hwang et al., 2019)* which maps PiB-DVR trajectories to corresponding ages and predicts PiB-DVR trajectories beyond observed ages (**Figure 1**). *This is essentially a function* $\mathbf{v}^t = [\mathbf{v}_1^t, \mathbf{v}_2^t] = f([\mathbf{u}_1^t, \mathbf{u}_2^t]) = f(\mathbf{u}^t)$ *of the following form*:

$$\mathbf{v}_1^t = \mathbf{u}_1^t \otimes \exp(q_{s_2}(\mathbf{u}_2^t, \mathbf{h}_2^{t-1})) + q_{r_2}(\mathbf{u}_2^t, \mathbf{h}_2^{t-1})$$
$$\mathbf{v}_2^t = \mathbf{u}_2^t \otimes \exp(q_{s_1}(\mathbf{v}_1^t, \mathbf{h}_1^{t-1})) + q_{r_1}(\mathbf{v}_1^t, \mathbf{h}_1^{t-1})$$

- **Prediction**: Use all 234 subjects to train the model and retrospectively predict their PiB+ Ages (PAs). Following prior studies, the age when PiB-DVR reaches 1.2 was considered as the PA (minimum at 45 / Wisconsin Life Expectancy Table for PiB- subjects) (**Figure 2**).

Time Points	T = 1	T = 2	T = 3	T = 4	T = All
Number of subjects	63	57	106	8	234
Sex (M/F)	16 / 47	19 / 38	37 / 69	1 / 7	73 / 161
Age (mean/s.d.)	63.0 / 7.0	63.5 / 7.2	63.5 / 6.4	69.4 / 5.3	63.8 / 6.7
Interval years (mean/s.d.)	- / -	3.87 / 2.20	3.42 / 1.37	2.33 / 0.58	3.42 / 1.57
APOE (+/-)	27 / 36	24 / 33	41 / 65	5 / 3	97 / 137

Table 1. Demographics of Wisconsin Registry for Alzheimer's Prevention dataset.

FIGURES & TABLES

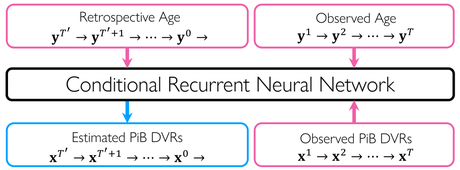

Figure 1. (1) Train the model (Hwang et al., 2019) using Observed Age and its corresponding Observed PiB DVRs. (2) Estimate the retrospective PiB DVRs given Retrospective Age.

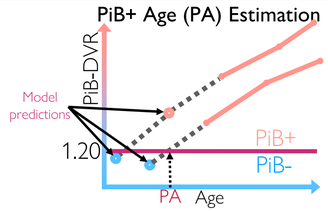

Figure 2. For each subject and ROI, we predict the PiB-DVRs in the past and estimate the PA.

ROI	Mean PA (APOE+ / APOE-)	*p*-value
angular	76.5 / 81.7	*0.0001
cingulum_ant	76.4 / 82.2	*0.0001
cingulum_post	77.4 / 82.0	*0.0004
frontal_med_orb	76.1 / 81.6	*0.0001
precuneus	76.9 / 81.6	*0.0003
supramarginal	77.4 / 82.0	*0.0004
temporal_mid	77.4 / 81.1	*0.0061
temporal_sup	77.6 / 81.8	*0.0012

Table 2. Mean PiB+ Age and the group difference results in each ROI. * indicates statistical significance after the Bonferroni correction.

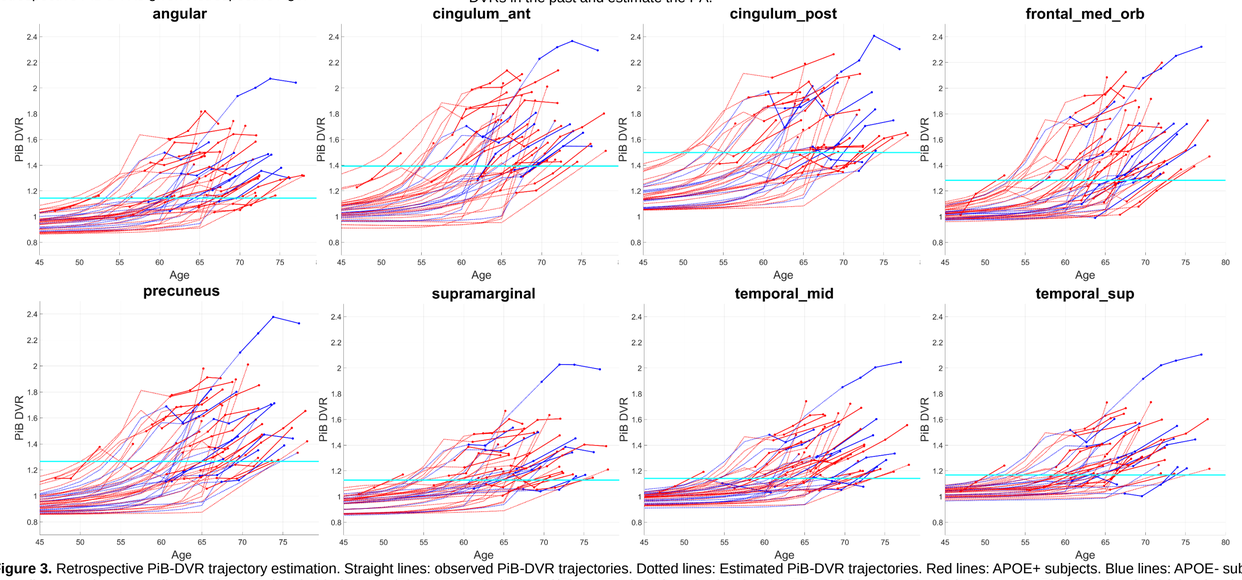

Figure 3. Retrospective PiB-DVR trajectory estimation. Straight lines: observed PiB-DVR trajectories. Dotted lines: Estimated PiB-DVR trajectories. Red lines: APOE+ subjects. Blue lines: APOE- subjects. Cyan lines: Region-wise adjusted PiB-DVR thresholds (≈ mean(PiB-DVR of PiB-) + 3*std(PiB-DVR of PiB-). Only showing the PiB+ subjects (i.e., those that cross the PiB-DVR thresholds) for visual clarity.

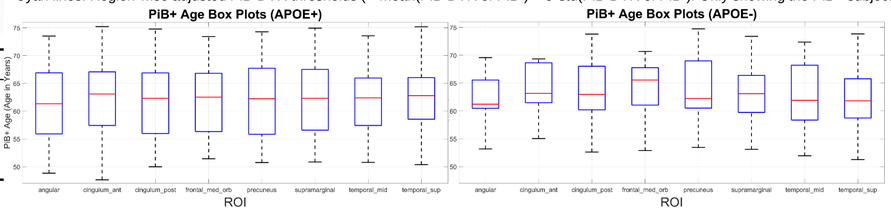

Figure 4. Box plot of PAs of APOE+ and APOE- for PiB+ subjects only (i.e., those with observed or estimated PAs). For each ROI, the top and bottom whiskers are the max and min PAs of that ROI respectively. The box indicates the 25th and 75th percentiles and the red line is the median. While the median PAs of the ROIs of APOE- (right) have noticeably different patterns (i.e., distinct median PAs with relatively small interquartile range), the median PAs of the ROIs of APOE+ (left) have less distinct patterns (i.e., median PAs are similar with large interquartile range).

RESULTS 1: PA vs. APOE4

- **Analysis**: For each ROI, test the difference of the PAs between APOE+ (ε4-allele) and APOE- (no ε4-allele) groups using the two-sample t-test (**Table 2**).
- **Experiment**: **Figure 3** shows the predicted trajectories (dotted) given the original trajectories (solid) of the subjects with PAs in all 8 combined AAL ROIs. **Table 2** shows that all ROIs show significance differences in PAs between the APOE groups (α=0.05 with the Bonferroni correction).

RESULTS 2: PA vs. APOE4 for PiB+ Only

- **Analysis**: Look at the PAs of the PiB+ subjects only (i.e., those with observed or estimated PAs).
- **Experiment 1**: There were no statistical significances in the PAs of the PiB+ subjects between APOE+ and APOE- groups (**Table 3**).
- **Experiment 2**: **ROI analysis.** The PAs of the PiB+ subjects in APOE+ group (left of **Figure 4**) showed less distinct patterns (i.e., similar mean PAs, with high variation among ROIs) compared to those in APOE- group (right of **Figure 4**) with distinct mean PAs with smaller variations among ROIs.

ROI	Mean PA (APOE+ / APOE-)
angular	61.6 / 62.2
cingulum_ant	62.2 / 63.7
cingulum_post	62.3 / 63.3
frontal_med_orb	62.2 / 64.1
precuneus	62.2 / 64.2
supramarginal	62.4 / 63.2
temporal_mid	62.2 / 62.6
temporal_sup	62.0 / 62.5

Table 3. Mean PiB+ Age and the group difference results in each ROI of **PiB+ subjects only**. Although the PAs of APOE- subjects were higher, there were no statistically significant differences.

ROI	% of ROIs becoming PiB+ at i'th order (APOE+)							
	i=1	2	3	4	5	6	7	8
angular	0.16	0.13	0.09	**0.19**	0.16	0.13	0.13	0.03
cingulum_ant	0.14	0.14	0.11	0.14	**0.20**	0.11	0.00	0.14
cingulum_post	0.11	0.09	0.09	0.14	0.06	0.17	0.14	**0.20**
frontal_med_orb	0.13	**0.19**	0.06	0.10	0.13	**0.19**	0.13	0.06
precuneus	0.04	0.12	**0.23**	0.15	0.12	0.12	0.19	0.04
supramarginal	0.04	0.07	0.18	**0.25**	0.18	0.04	0.18	0.07
temporal_mid	**0.22**	**0.22**	0.11	0.04	0.04	0.11	0.11	0.15
temporal_sup	**0.23**	0.14	0.05	0.09	0.14	0.05	0.09	**0.23**

ROI	% of ROIs becoming PiB+ at i'th order (APOE-)							
	i=1	2	3	4	5	6	7	8
angular	0.09	0.09	**0.36**	0.09	0.18	0.18	0.00	0.00
cingulum_ant	0.00	0.08	0.00	0.00	0.08	0.17	**0.42**	0.25
cingulum_post	0.07	0.00	0.07	0.27	0.07	**0.33**	0.00	0.20
frontal_med_orb	0.13	0.13	0.00	0.06	**0.25**	0.00	**0.25**	0.19
precuneus	0.00	0.08	0.00	0.25	**0.42**	0.08	0.08	0.08
supramarginal	0.13	0.00	**0.31**	0.00	0.06	0.13	**0.31**	0.06
temporal_mid	**0.31**	0.23	0.08	0.23	0.00	0.00	0.08	0.08
temporal_sup	**0.27**	**0.27**	0.09	0.09	0.09	0.00	0.09	0.09

Table 4. Distribution of ROIs becoming PiB+ at i'th order for APOE+ (top) and APOE- (bottom). Each row shows the probability that the ROI is the i'th ROI to become PiB+. i.e., angular became PiB+ in 36% of the cases for APOE- group.

CONCLUSIONS

- Early amyloid accumulation is one of the promising avenues for preclinical AD detection, and our results support this by demonstrating **its association with APOE ε4-allele**, a high risk factor of developing late-onset AD.
- Our model **accurately extrapolates the PiB-DVR trajectories and estimates the PA** of critical amyloid accumulation of each subject in AD-related regions.
- The **order at which the ROIs become PiB+ is less consistent in the APOE+/PiB+ subjects** compared APOE-/PiB+ subjects.
- **Future work:** Investigate the relationship between PAs and other AD-related biomarkers and covariates such as cognition and neurofibrillary tangle.

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