Adaptive Shrinkage Estimation for Personalized Deep Kernel Regression in Modeling Brain Trajectories

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Problem Statement

Alzheimer's Disease and Brain Aging are **manifested** through progressive alternations in brain structure.

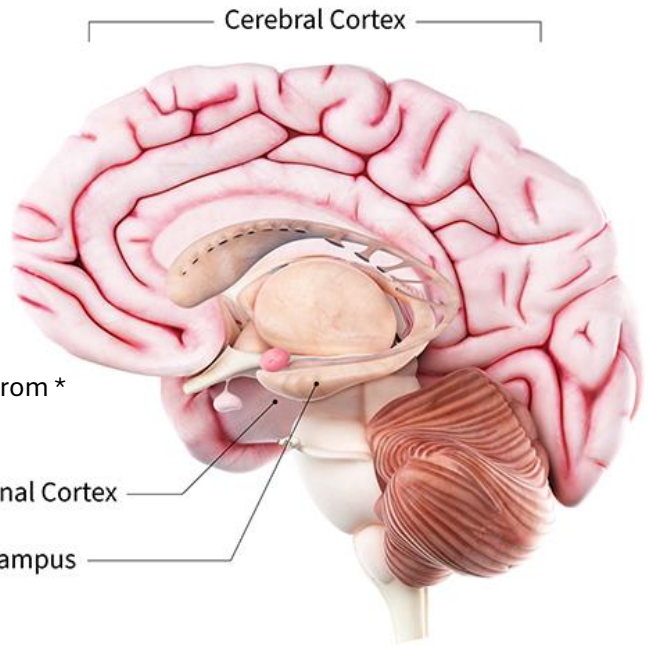
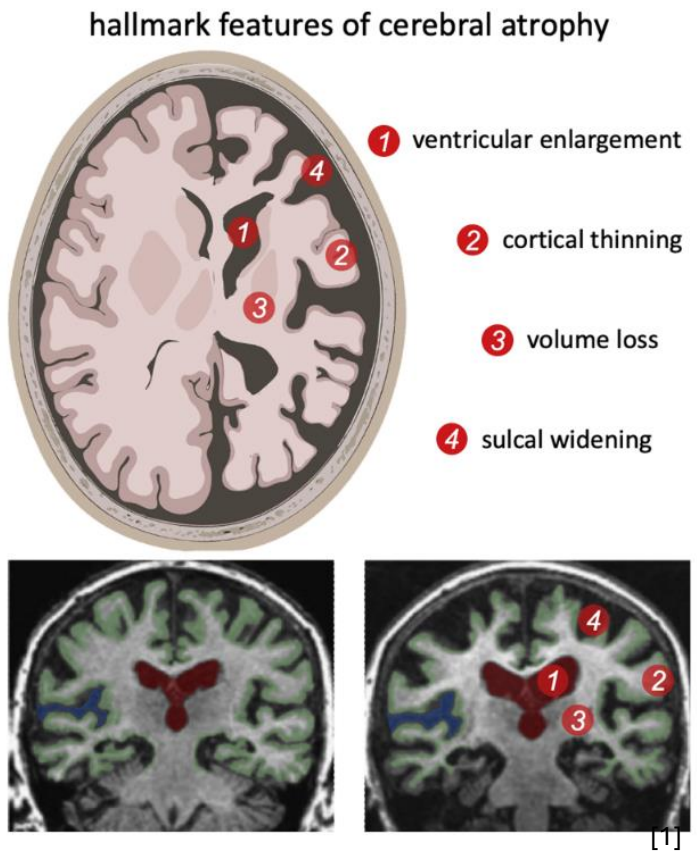


Figure from *



[1]

Brain Aging is a complex process that affects everything from the subcellular to the organ level.

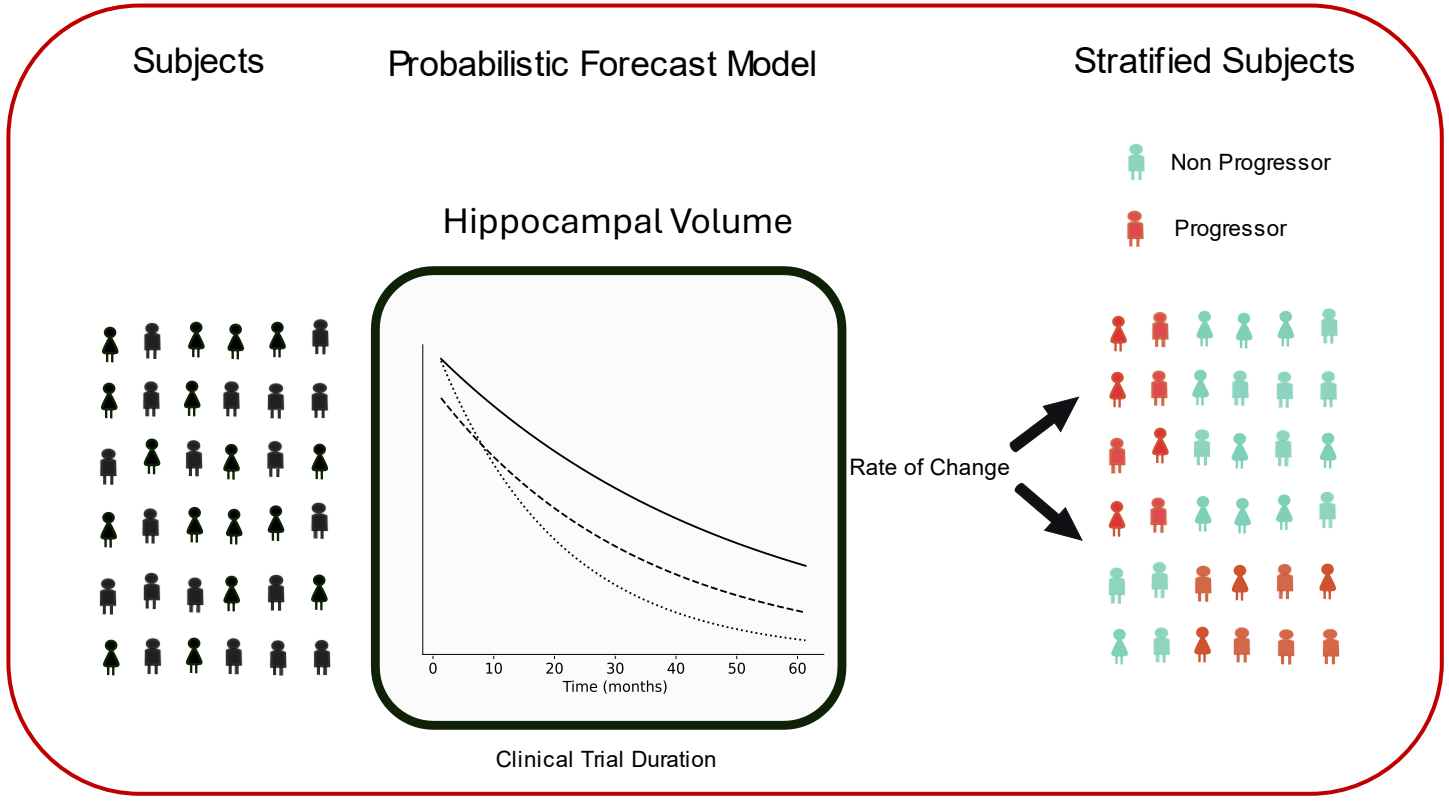
Morphologically, brain aging is primarily characterized by **brain volume loss**, cortical thinning, white matter degradation, loss of gyrification, and **ventricular enlargement**. [1]

* https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease#:~:text=At%20first%2C%20Alzheimer%27s%20usually%20damages,Ultimately%2C%20the%20disease%20is%20fatal.

Clinical Relevance

Predicting longitudinal changes of neuroimaging biomarkers is a challenging task due to the **heterogeneity** of the neurodegenerative processes as well as the **data scarcity.**

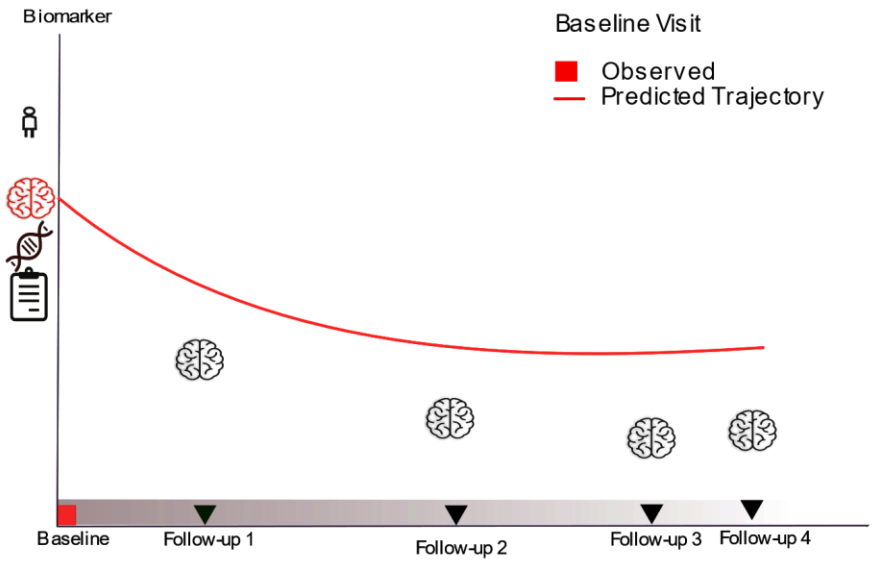
However, robust prediction of neurodegeneration is beneficial in **clinical practice**, **clinical trial design**, **prognosis and early intervention** and **treatment effect estimation**

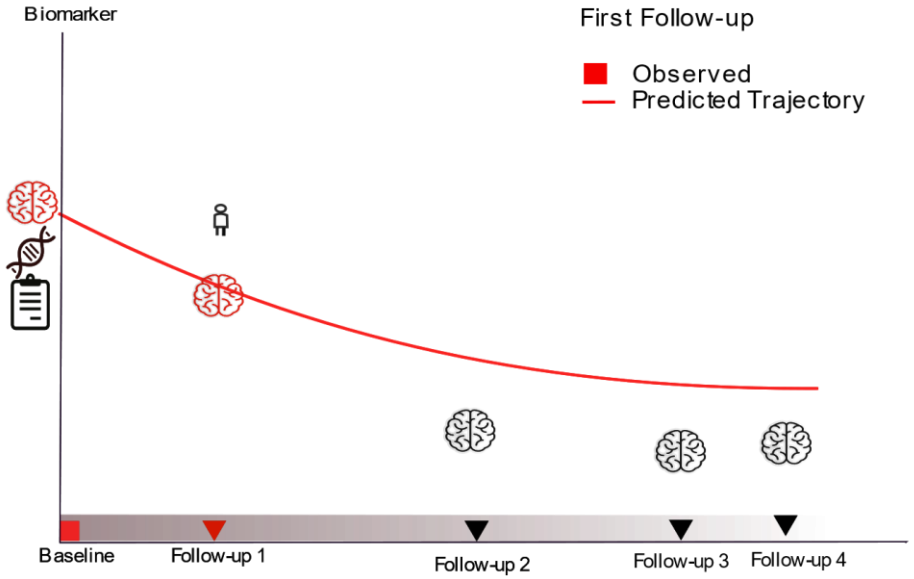


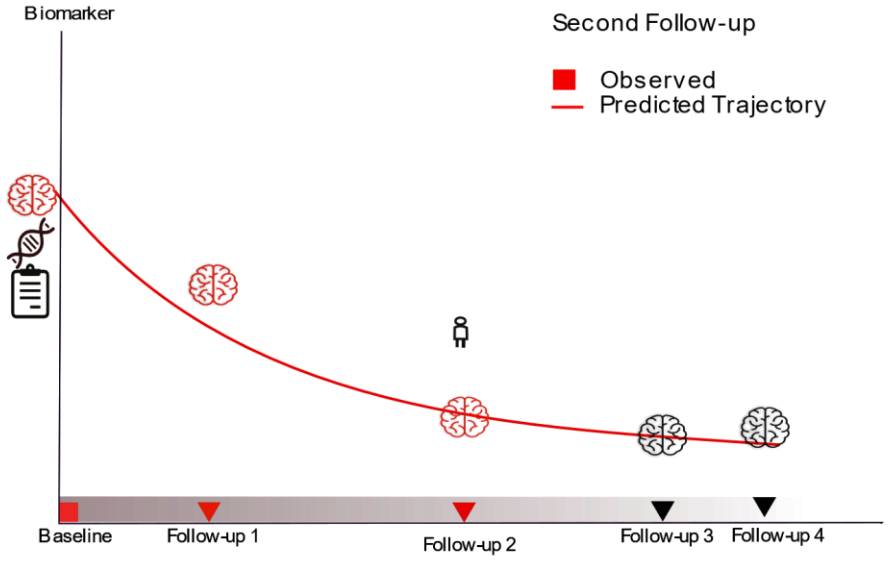
Use Case:

Subject selection for clinical trials. Predicted biomarker trajectories can guide the process of subject recruitment in clinical trials

Adaptive Trajectories



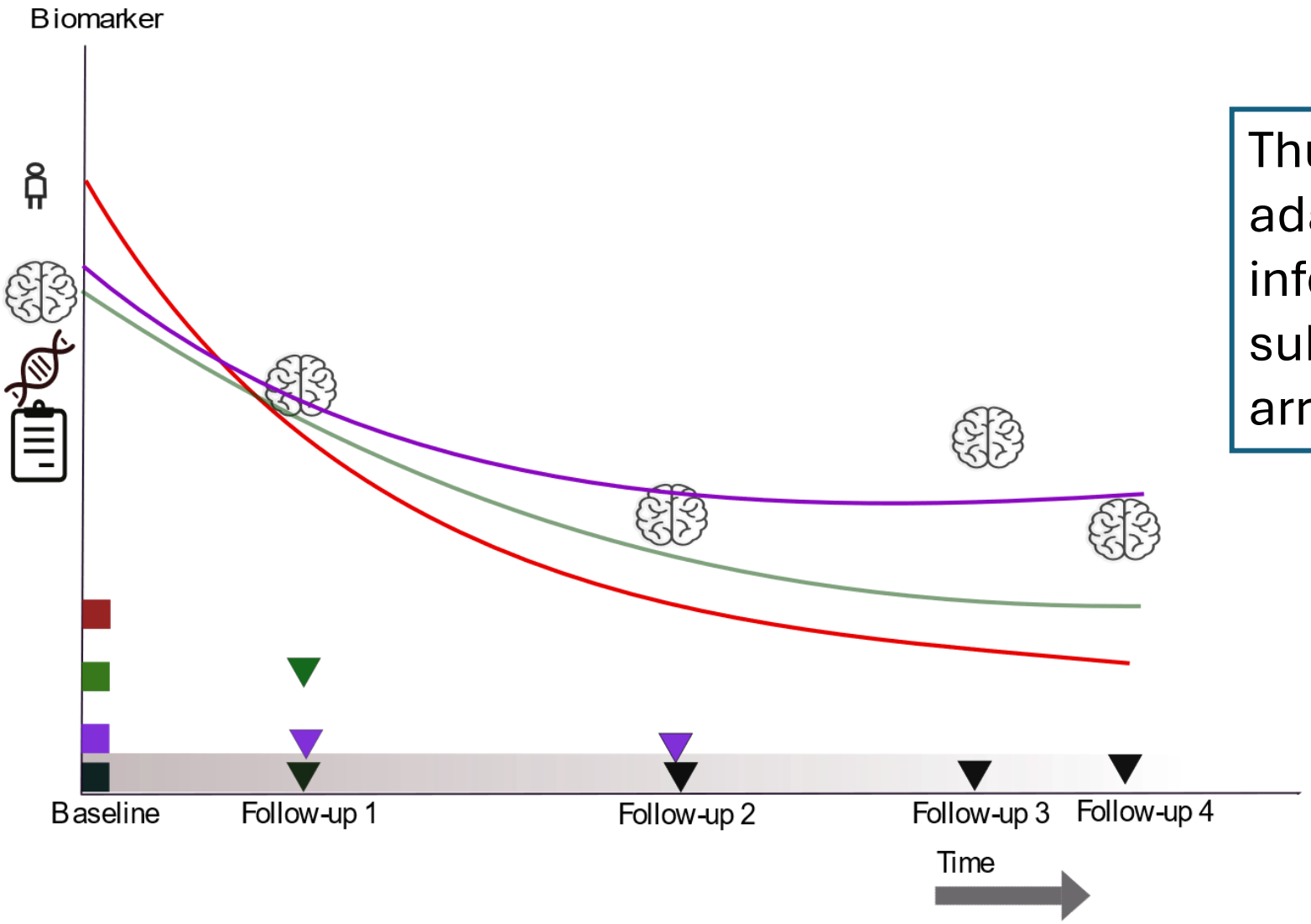




Biomarker trajectories should adapt as new subject-specific data arrive!

Adaptive Inference

Inference with increasing Follow-ups



Thus, we need to apply adaptive/personalized inference, as new subject-specific data arrive.

Our Contributions

We achieve that with Deep Kernel Regression with Adaptive Shrinkage!

In detail:

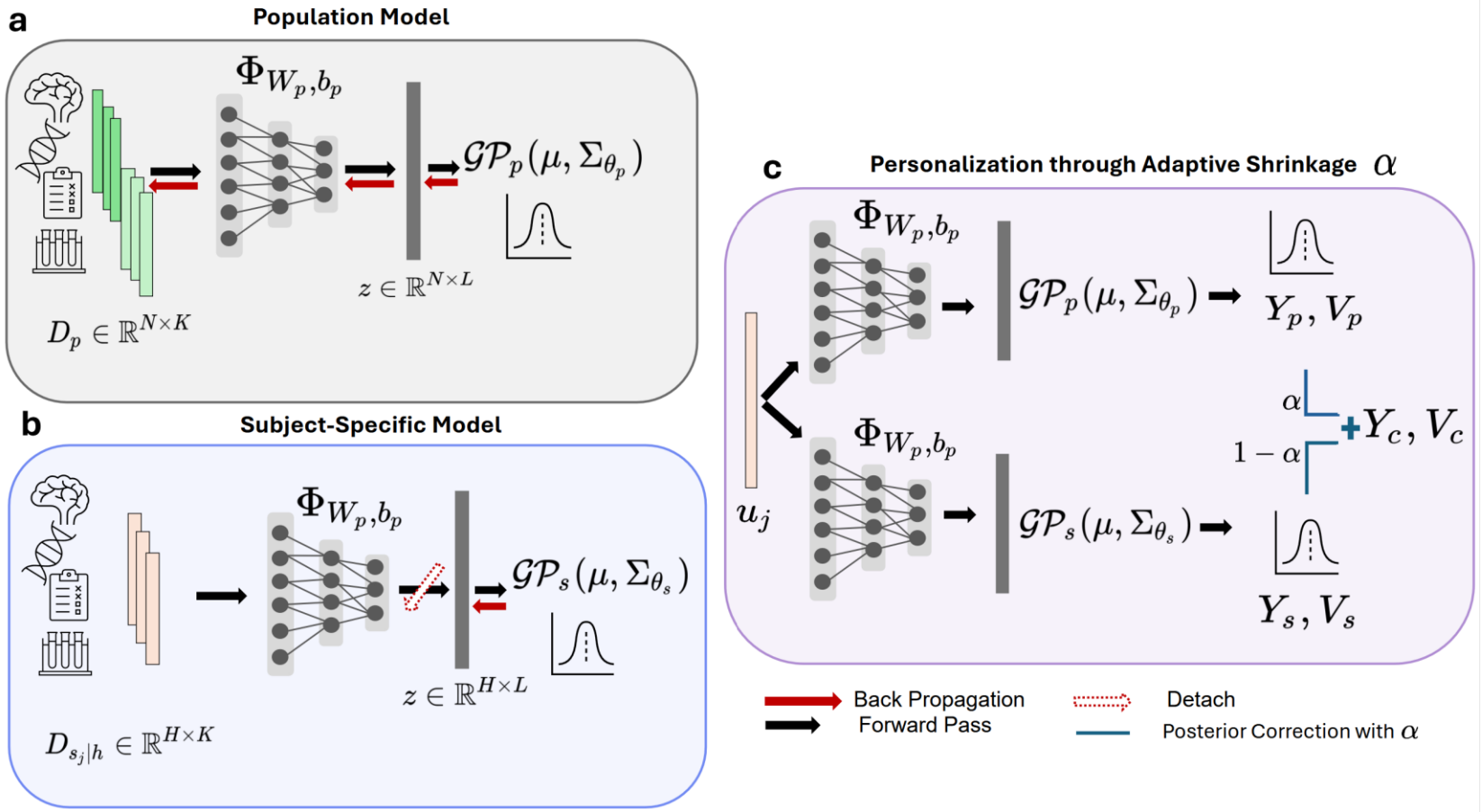
[1] We propose a novel **deep kernel regression framework** for predicting biomarker trajectories from sparse longitudinal observations. Our approach naturally accommodates randomly-timed and temporally unaligned observations without requiring imputation.

[2] We introduce Adaptive Shrinkage Estimation that fuses the population and subject-specific models. This framework enables incremental updates to personalized predictions as new data arrive and it also refines historical observations to reduce noise.

[3] We showcase the versatility of our method to be applied for the prediction of two additional composite neuroimaging biomarkers from high-dimensional multivariate imaging data and clinical covariates

[4] We demonstrate the generalizability of our method in different clinical contexts, showing its ability to generalize in three external clinical studies

Deep Kernel Regression with Adaptive Shrinkage



1. Oracle Estimation

$$J_{s|h}(\alpha) = \sum_{t=0}^{t_n} (y_t - (\alpha \cdot y_{p_t} + (1-\alpha) \cdot y_{s_t}))^2$$

2. Train the Adaptive Shrinkage Function $q = \{y_p, y_s, v_p, v_s, T_{\text{obs}}\}$

$$g_a(q;\theta)$$

3. Adaptive Shrinakge Inference

$$\hat{\alpha} = g_a(q;\theta)$$

4. Posterior Correction

- Posterior Correctected Predictive Mean:

$$y_c = \alpha y_p + (1-\alpha) y_s$$

- Posterior Correctected Predictive Variance:

$$v_c = \alpha^2 v_p + (1-\alpha)^2 v_s$$

- α: Shrinkage parameter reflecting confidence in each model.

Experiments

- We use T1-weighted (T1w) MR imaging and clinical data from the iSTAGING consortium.

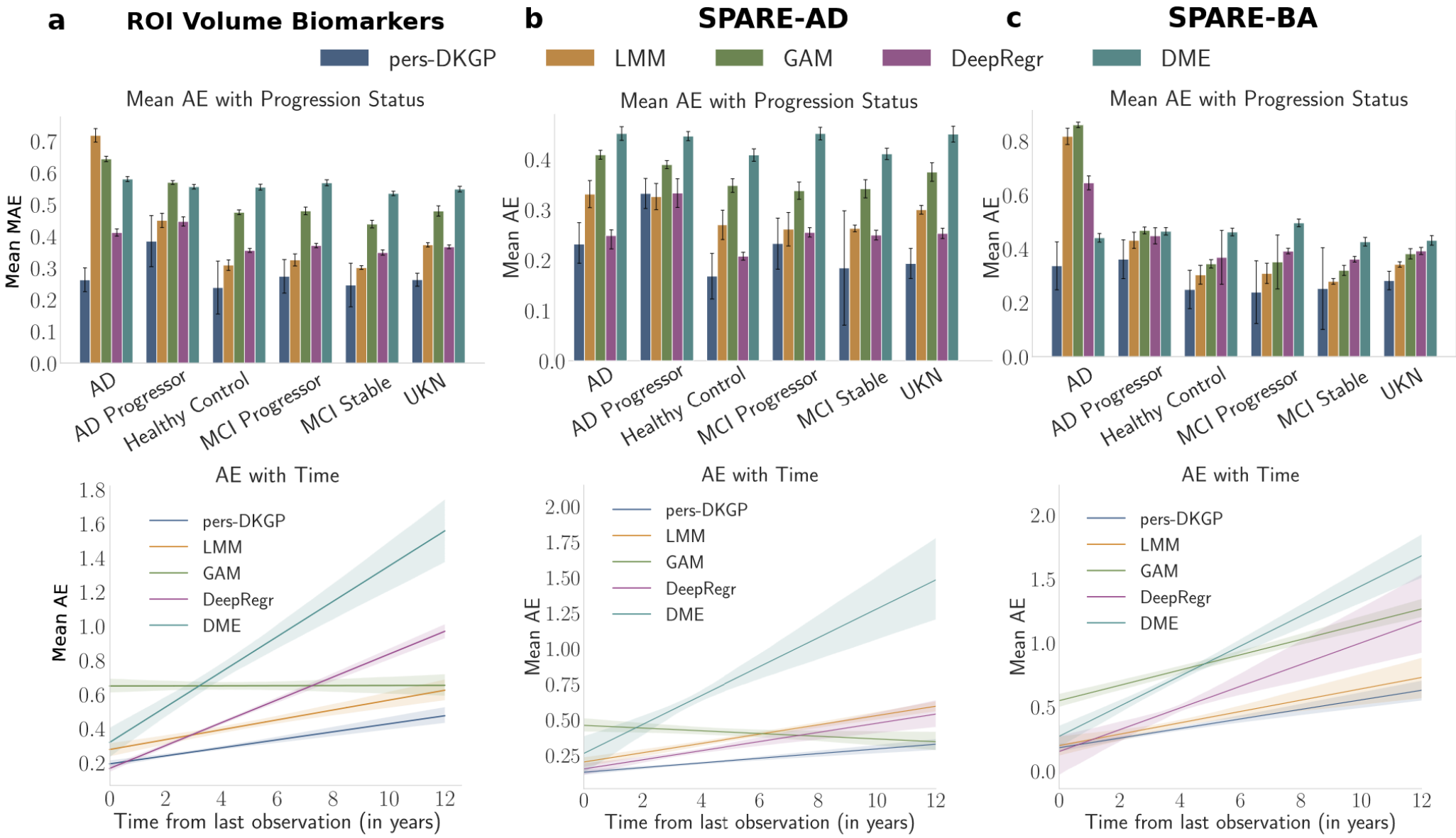
- Extract 145 Regions of Interest from brain volumes.

- Clinical covariates include Age, Diagnosis, Sex, Education, and APOE4 Alleles status

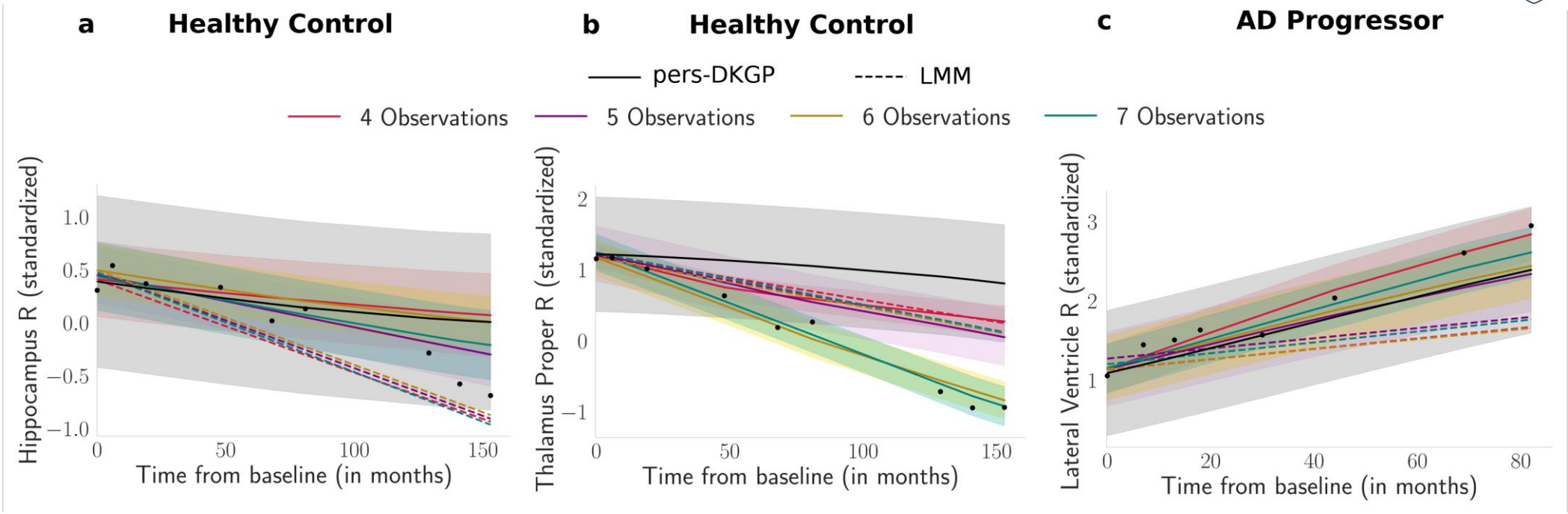
- Combined cohort: 3,100 subjects from five longitudinal studies—ADNI, BLSA, OASIS, AIBL and PreventAD

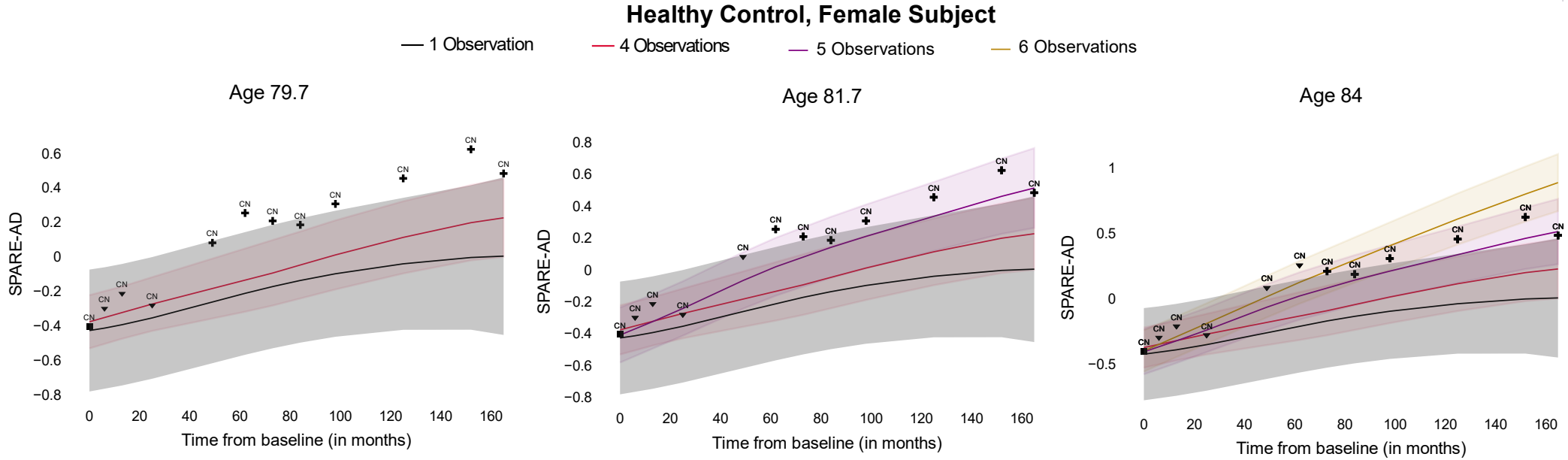
- Training set from ADNI+BLSA: 1,760 subjects; Testing set: 440 subjects.
- Population model (p-DKGP) trained on 1,560 subjects from ADNI+BLSA;
- Validation set of 200 subjects for estimating the oracle α.
- **OASIS**, **AIBL** and **PreventAD** were used as held-out clinical studies for external validation

Predictive Performance



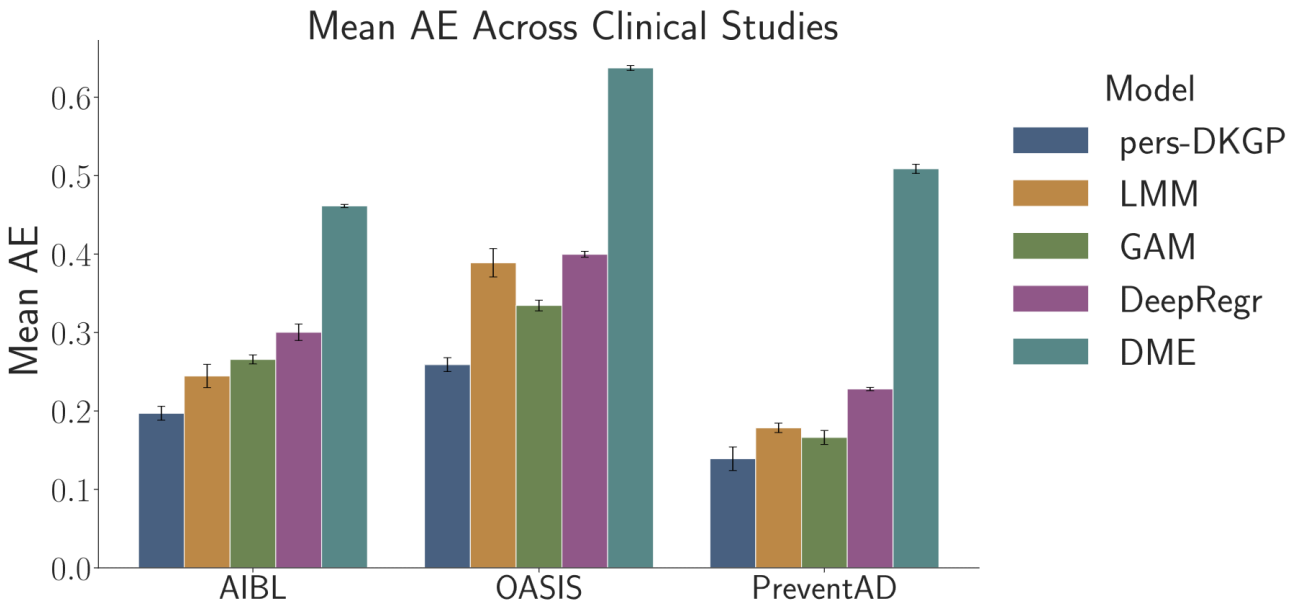
Qualitative Examples – ROI Volume Trajectories





Generalization to External Studies

- **AIBL**: Includes individuals with a mean age of 75 years, which is slightly older than the ADNI cohort and comparable to BLSA. It is predominantly composed of Alzheimer's disease (AD) patients (91 subjects), followed by MCI and controls. On average, each subject has approximately 3 follow-up visits, with a mean interval of 24 months between visits.
- **OASIS**: Includes individuals younger on average (67.8 years) compared to both ADNI and BLSA. It is primarily composed of healthy controls, with smaller representations of MCI and AD cases. The average number of follow-ups is ~ 3 per subject, with a mean interval of 32 months.
- **PreventAD**: PreventAD focuses on pre-symptomatic early detection of AD in a healthier and younger population (mean age 65.3 years) with an average of 4 follow-up visits per subject and a shorter mean interval of 10 months.



Interpretation of Adaptive Shrinkage Function

-What influences most the decision making of Adaptive Shrinkage ?
-How the interaction between the y_ss, y_pp and Tobs affects the shrinkage estimation ?
-What's the role of the predictive variances in the Adaptive Shrinkage function?

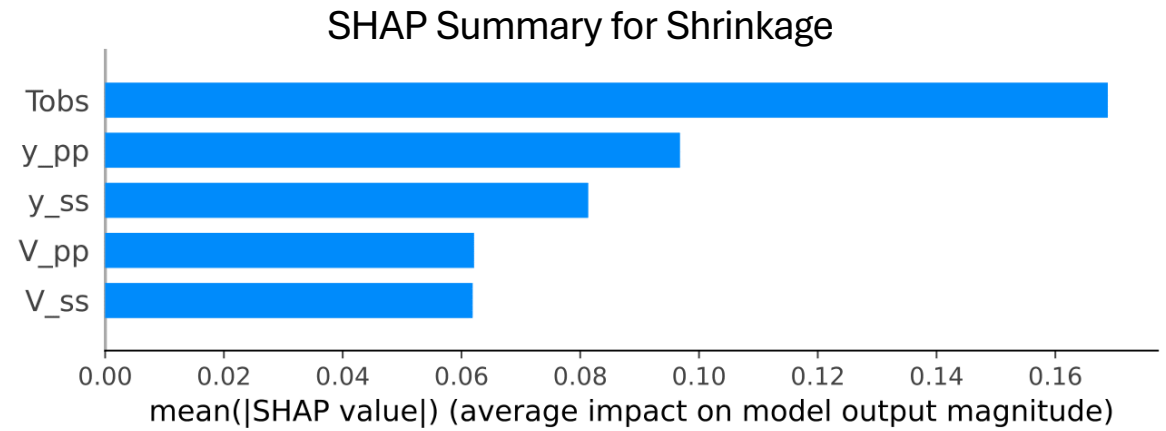
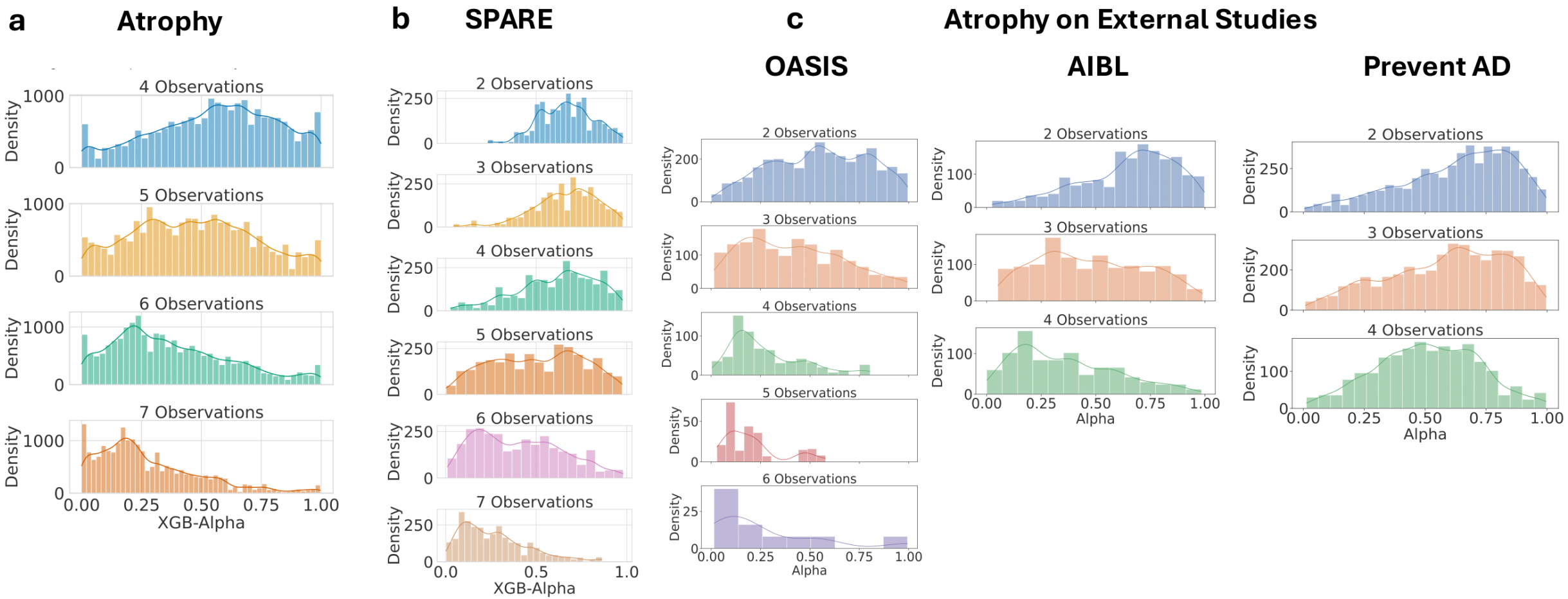


Table 5: Correlation Analysis between Deviation (δ_y) and Predicted α, and between T_{obs} and Predicted α for Large Deviation

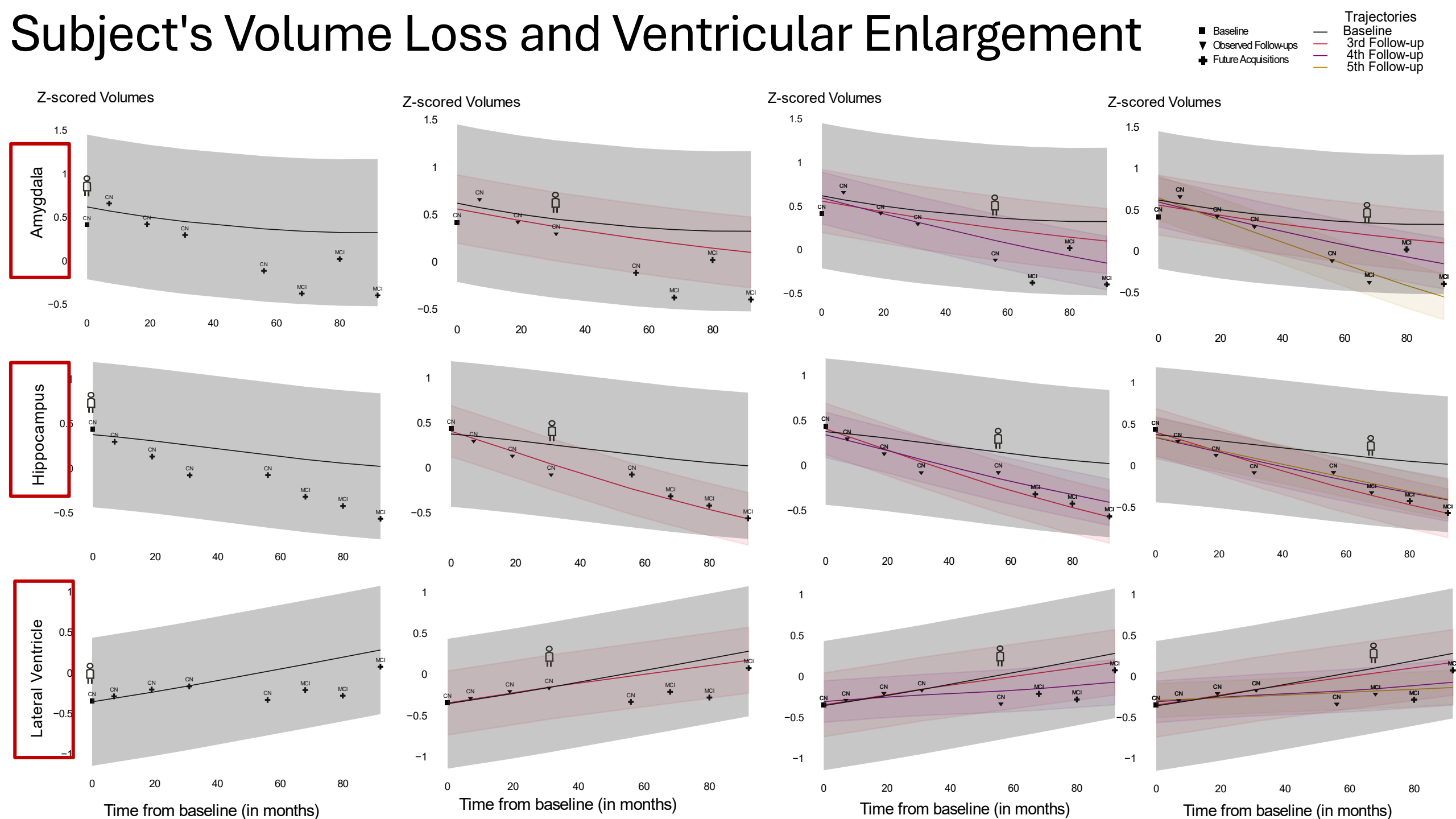
Biomarker	Correlation between T_{obs} and Predicted α for Large δ_y
SPARE_BA	-0.6402
SPARE_AD	-0.5292
Lateral Ventricle	-0.4843
Hippocampus L	-0.4014
Hippocampus R	-0.3805
Thalamus Proper R	-0.5551
PHG R	-0.4792
Amygdala R	-0.4385

- **Correlation Analysis:**
  - Reveals a consistent negative relationship between the observation time T_{obs} and the predicted α when the deviation δ_y is large
  - Indicates that when significant deviations exist between the predictors, Adaptive Shrinkage decreases the weight on the population-level model (p-DKGP) as T_{obs} increases.
  - This aligns with the intuition that more follow-up data increases trust in the subject-specific predictive distribution.

Interpretation of Adaptive Shrinkage



Subject's Volume Loss and Ventricular Enlargement



Summary

- We introduce **Deep Kernel Regression with Adaptive Shrinkage Estimation**: A method for forecasting and adapting biomarker trajectories with increasing follow-up subject data.

- We empirically show:
  - Its versatility for longitudinal prediction of progressive biomarkers ✓
  - Its generalizability to external clinical studies ✓

Our **Paper** and **Code** is available at:

https://vatass.github.io/projects/adaptive-shrinkage/