Hemispheric Functional Connectivity-Based Brain Age Prediction for Alzheimer's Disease using fMRIs

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Meet The Team - Team SARA

Sara

Ananya

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Alzheimer's Disease

*Alzheimer's Disease (AD) is a **progressive neurodegenerative disorder** in which abnormal protein deposits disrupt communication between brain regions, leading to irreversible cognitive decline and memory loss typically starts appearing in **population in the age bracket of mid-60s or later***

Alzheimer's Disease is characterised by:

- *Accumulation of amyloid-beta plaques and tau tangles*
- *Breakdown of functional connectivity between brain regions*
- *Disruption of inter-hemispheric communication via the corpus callosum*
- *Progressive decline in memory, language, and executive function*

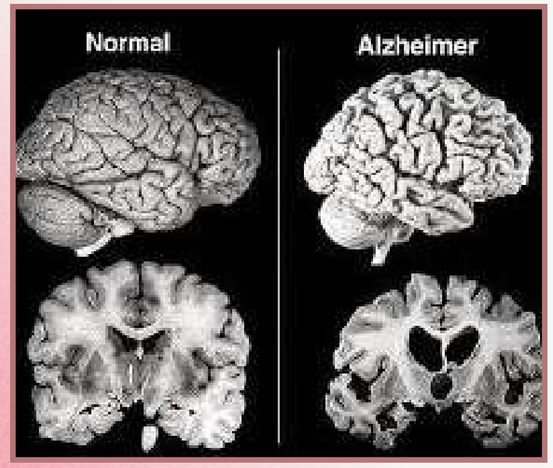


Figure. 1: Normal ex-vivo brain compared to a brain with Alzheimer's disease.

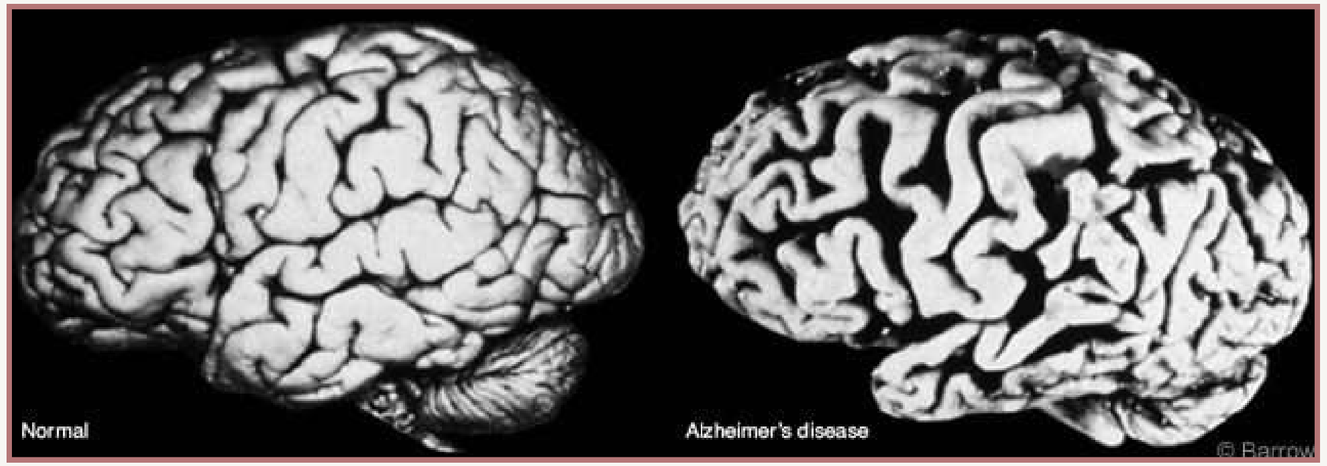


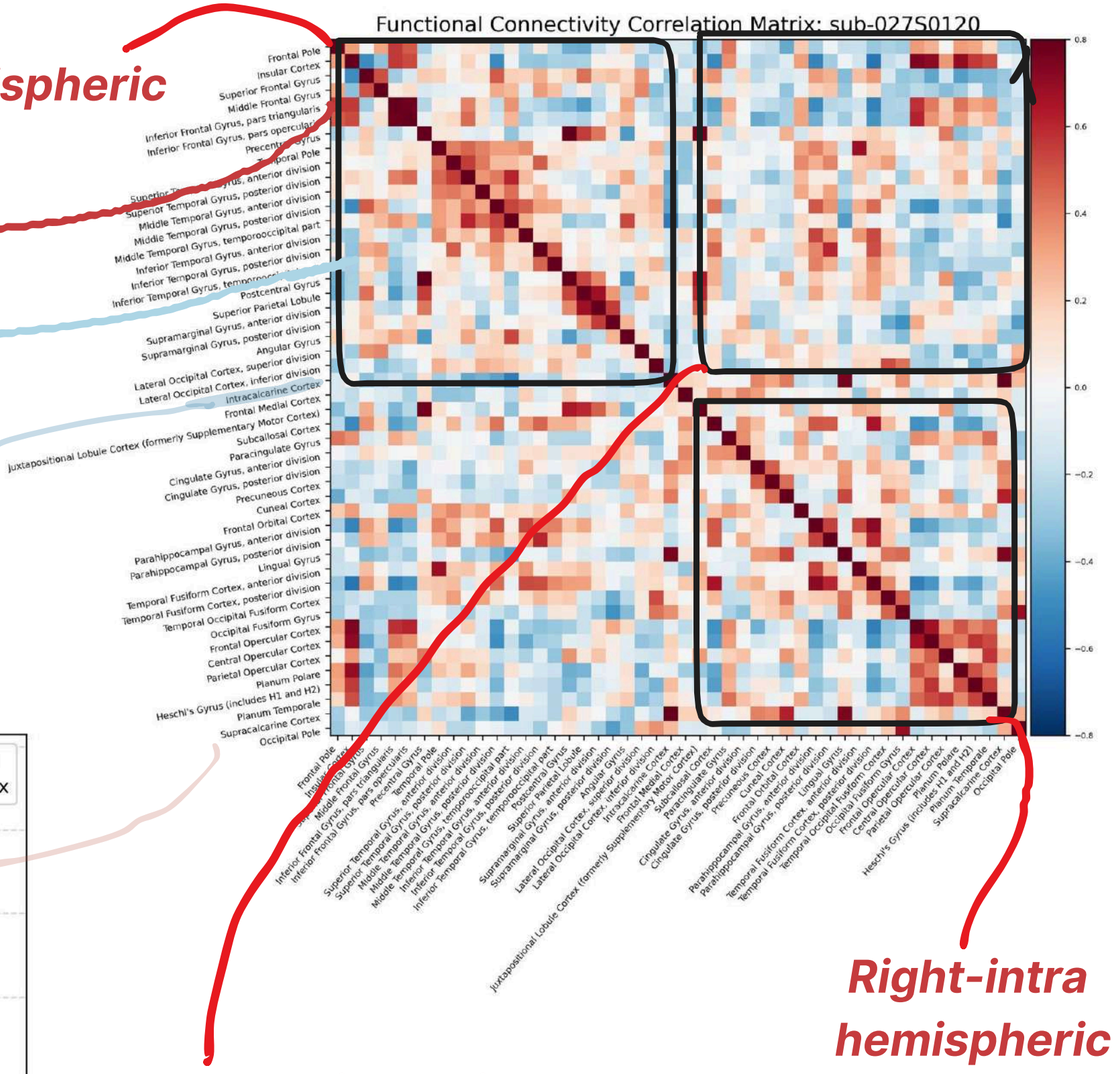
Figure. 2: Side-by-side comparison of a normal brain and an atrophied Alzheimer's brain

Functional Connectivity

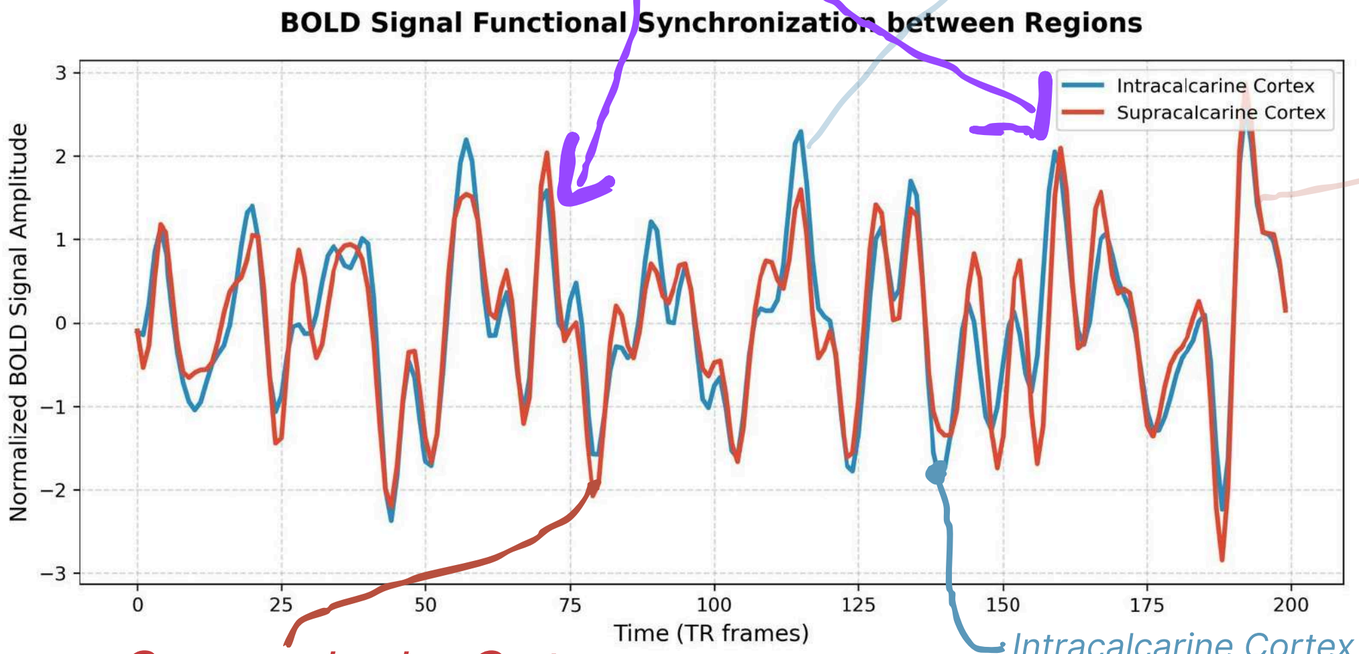
Left-intra hemispheric

Strong +ve correaltion

Weak -ve correaltion



Synchronised BOLD Activity



Superacalcarine Cortex

Intracalcarine Cortex

Right-intra hemispheric

Interhemispheric Corelation

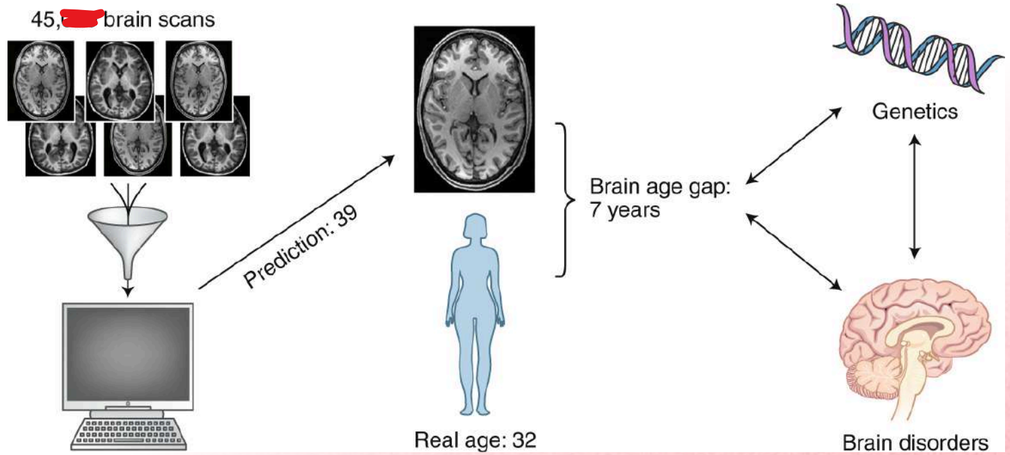
Correlated timeseries → High FC value → Red cell in matrix

WHY BRAIN AGE AS A BIOMARKER FOR ALZHEIMER'S DISEASE?

- *Alzheimer's diagnosis currently relies on invasive/expensive tests — amyloid PET scans, CSF lumbar punctures*
- *By the time symptoms appear, neurodegeneration is already advanced*
- *We need early, accessible, non-invasive indicators*

Why Brain Age Works:

Brain age is estimated purely from resting-state fMRI so, no invasive procedures.
Healthy brains age predictably therefore deviations from this trajectory signal pathology



Brain Age Gap (BAG) = Predicted Age – Chronological Age
Positive BAG → brain appears "older" than it should → neurodegeneration
Negative BAG → suppressed connectivity → preclinical AD

Problem Statement

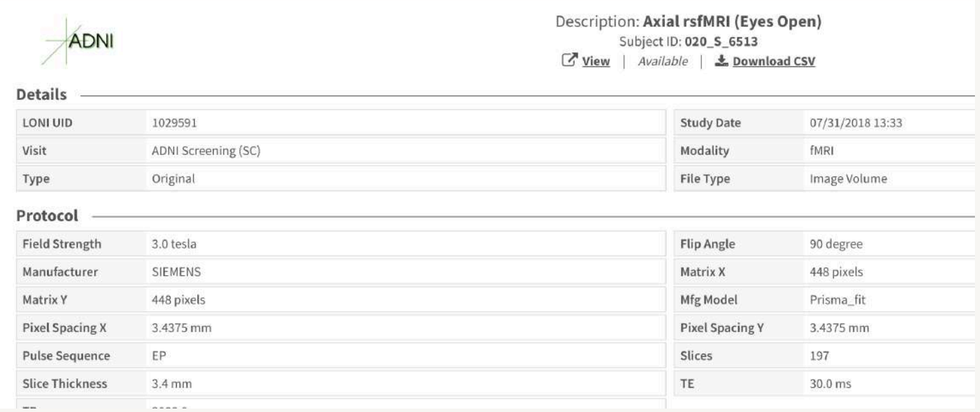
Develop a pipeline that predicts brain age from resting-state fMRI functional connectivity, computes hemispheric Brain Age Gap (BAG) scores, and classifies Alzheimer's Disease progression using ADNI neuroimaging data.

Input:

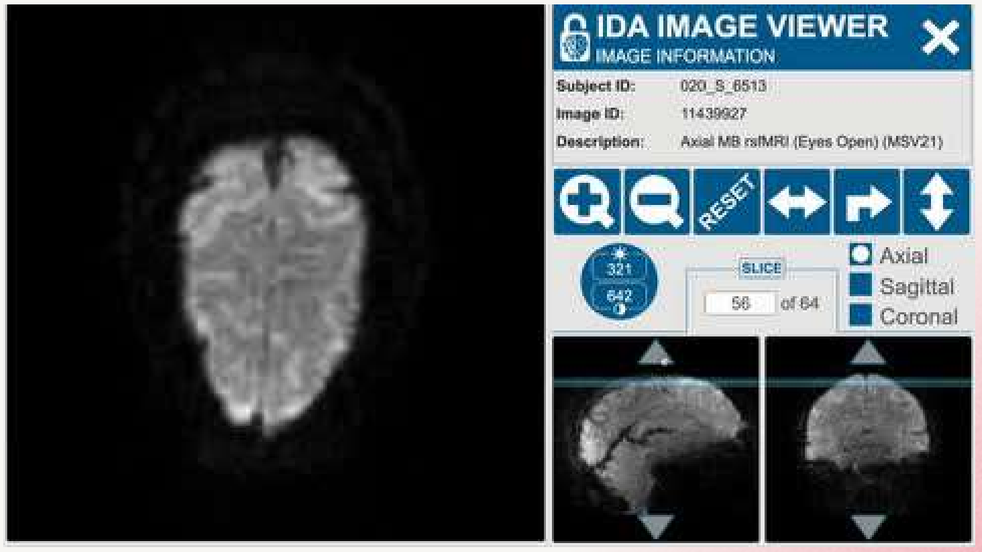
- *rs-fMRI scan (.nii)*
- *Chronological age*
- *Clinical diagnosis (CN / MCI / AD)*
- *MMSE score (Mini-Mental State Examination)*

Output:

- *BAG_full, BAG_left, BAG_right, BAG_inter*
- *CN / MCI / AD classification*
- *Per-subject brain health report card*



ADNI data portal showing our actual subject



a rs-fMRI scan of subject as visualised by image viewer

LITERATURE REVIEW

Paper 1: *Harmonization of multi-site functional connectivity measures in tangent space improves brain age prediction*

Dataset

- 4,259 rs-fMRI scans, 7 sites (iSTAGING: BLSA, OASIS-3, CARDIA, PENN-ABC, UK Biobank), ages 22–97

Methodology

- Multi-scale FC networks (17–150) extracted via NMF
- FC matrices → tangent space → ComBat-GAM harmonization to remove site effects
- Ridge Regression & SVR with 5-fold CV for brain age prediction

Results

- Best model: Ridge on multi-scale tangent-space harmonized features
- MAE: 5.57 years | Correlation: 0.78

Observations

- Multi-scale FC outperforms single-scale; tangent-space harmonization improves cross-site prediction
- Key networks: Default Mode, Frontoparietal, Somatomotor

Gaps

- Only healthy aging since there no neurodegenerative groups
- No inter-hemispheric decomposition; no early-stage AD biomarker analysis.

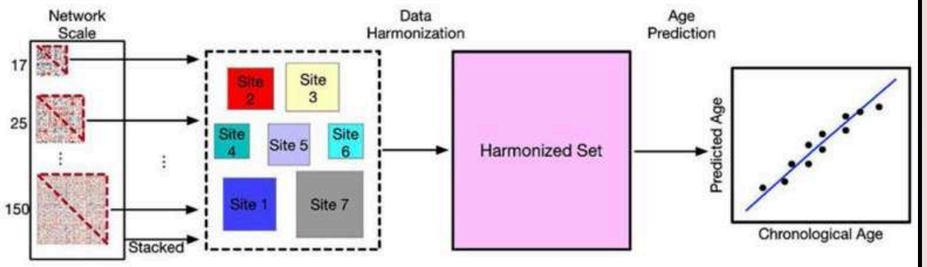


Figure 1.
Personalized functional networks were computed at multiple scales, each with 17, 25, 50, 75, 100, 125 or 150 networks, within each scale functional connectivity measures between functional networks were computed and harmonized in their tangent space across sites, and finally brain age prediction models were built on the harmonized functional connectivity measures.

Five-fold cross validation results (MAE) of the age prediction models built using different regression methods (SVR or Ridge regression), on functional connectivity features of individual scales and the multi-scale features in their original space or tangent space, with or without harmonization.

Feature space	Harmonization	Regression method	17	25	50	75	100	125	150	Multiscale
Original	No	SVR	8.26±0.13	7.67±0.15	7.46±0.14	7.45±0.24	7.32±0.19	7.17±0.20	7.21±0.09	6.86±0.14
		Ridge	8.45±0.12	7.88±0.16	7.67±0.14	7.92±0.18	8.28±0.13	8.26±0.24	8.56±0.19	7.65±0.17
	Yes	SVR	8.47±0.19	8.05±0.23	7.96±0.19	8.10±0.27	8.10±0.26	7.86±0.28	7.89±0.20	7.64±0.22
		Ridge	8.34±0.14	8.12±0.17	8.23±0.12	8.74±0.27	9.30±0.16	8.88±0.25	8.86±0.09	8.29±0.18
Tangent	No	SVR	7.31±0.18	6.88±0.13	6.49±0.16	6.46±0.23	6.41±0.23	6.48±0.24	6.56±0.20	6.22±0.21
		Ridge	8.00±0.11	7.38±0.15	7.21±0.16	7.91±0.11	8.01±0.08	7.19±0.12	6.70±0.09	5.92±0.11
	Yes	SVR	7.81±0.19	7.34±0.16	6.81±0.17	6.62±0.28	6.54±0.23	6.55±0.28	6.66±0.24	6.29±0.24
		Ridge	7.96±0.12	7.43±0.18	7.33±0.16	8.17±0.19	7.80±0.10	6.96±0.15	6.45±0.09	5.57±0.11

Five-fold cross validation results (correlation coefficient) of the age prediction models built using different regression methods (SVR or Ridge regression), on functional connectivity features of individual scales and the multi-scale features in their original space or tangent space, with or without harmonization.

Feature space	Harmonization	Regression method	17	25	50	75	100	125	150	Multiscale
Original	No	SVR	0.43	0.55	0.58	0.59	0.60	0.63	0.63	0.68
		Ridge	0.42	0.52	0.56	0.55	0.53	0.54	0.52	0.59
	Yes	SVR	0.40	0.48	0.50	0.46	0.46	0.50	0.51	0.54
		Ridge	0.42	0.47	0.46	0.41	0.36	0.42	0.42	0.46
Tangent	No	SVR	0.59	0.66	0.71	0.72	0.73	0.74	0.74	0.78
		Ridge	0.49	0.58	0.64	0.61	0.60	0.65	0.68	0.76
	Yes	SVR	0.53	0.59	0.67	0.70	0.72	0.73	0.74	0.77
		Ridge	0.51	0.58	0.62	0.59	0.61	0.67	0.71	0.78

Z. Zhou, D. Srinivasan, H. Li, A. Abdulkadir, H. Shou, C. Davatzikos, and Y. Fan, "Harmonization of multi-site functional connectivity measures in tangent space improves brain age prediction," Proc. SPIE, 2022.

Paper 2 : *Predicting Brain Age from Functional Connectivity in Symptomatic and Preclinical Alzheimer Disease*

Dataset

- rs-fMRI → FC matrices, 300 ROI Gordon parcellation
- Train: 391 CN amyloid-negative (ages 18–89) | Test: 151 preclinical AD, 156 symptomatic AD, 145 CN
- Source: WUSTL cohort + DIAN

Methodology

- Upper triangle FC → Ridge regression (trained on CN only)
- BAG = predicted – chronological age, residualized against age
- Stratified k-fold CV across CN, preclinical, symptomatic groups

Results

- FC-BAG significantly older in symptomatic AD, younger in preclinical AD vs controls
- FC-BAG correlated with amyloid and tau burden

Observations

- Biphasic response: FC-BAG reduced pre-symptomatically but elevated at symptomatic stage
- Networks driving age prediction differ from networks disrupted by AD

Gaps

- Single whole-brain FC i.e. no inter-hemispheric decomposition
- DIAN = genetic AD; our project uses sporadic AD (ADNI), more representative
- No PCA dimensionality reduction; no SVM classification stage

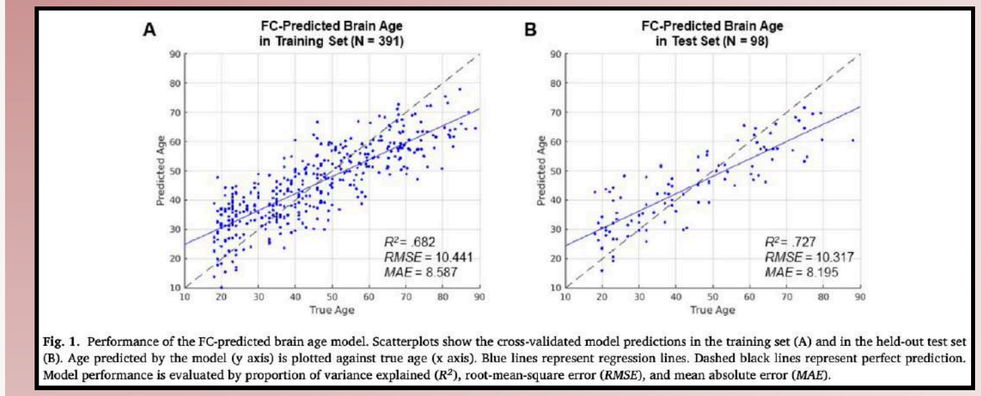


Fig. 1. Performance of the FC-predicted brain age model. Scatterplots show the cross-validated model predictions in the training set (A) and in the held-out test set (B). Age predicted by the model (y axis) is plotted against true age (x axis). Blue lines represent regression lines. Dashed black lines represent perfect prediction. Model performance is evaluated by proportion of variance explained (R^2), root-mean-square error (*RMSE*), and mean absolute error (*MAE*).

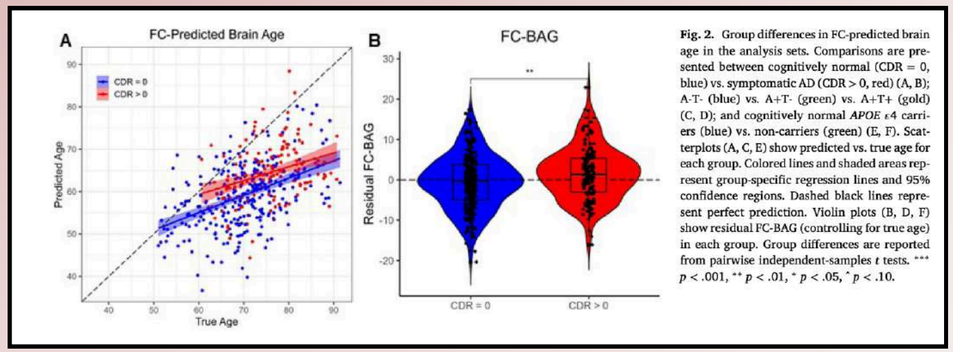


Fig. 2. Group differences in FC-predicted brain age in the analysis sets. Comparisons are presented between cognitively normal (CDR = 0, blue) vs. symptomatic AD (CDR > 0, red) (A, B); A-T- (blue) vs. A+T- (green) vs. A+T+ (gold) (C, D); and cognitively normal *APOE* ε4 carriers (blue) vs. non-carriers (green) (E, F). Scatterplots (A, C, E) show predicted vs. true age for each group. Colored lines and shaded areas represent group-specific regression lines and 95% confidence regions. Dashed black lines represent perfect prediction. Violin plots (B, D, F) show residual FC-BAG (controlling for true age) in each group. Group differences are reported from pairwise independent-samples *t* tests. *** $p < .001$, ** $p < .01$, * $p < .05$, ^ $p < .10$.

Table 2
Linear regression models predicting FC-BAG. Model estimates are presented as beta weight (standard error). CDR = Clinical Dementia Rating. *** $p < .001$, ** $p < .01$, * $p < .05$, ^ $p < .10$.

	MODELS				
	A. Symptomatic AD	B. Preclinical Amyloid	C. Preclinical Amyloid & Tau	D. Preclinical APOE	E. Full Model
Test Sample	All analysis sets	Cognitively normal only	Cognitively normal only	Cognitively normal only	All analysis sets
Predictors					
Intercept	32.39 (3.53)***	27.81 (4.24)***	33.22 (4.59)***	30.91 (4.28)***	33.54 (4.28)***
CDR > 0	2.88 (0.69)***				3.71 (1.17)**
Amyloid +		-1.92 (0.81)*	0.03 (0.99)		0.15 (0.99)
Tau +			-2.15 (1.01)*		-1.39 (0.92)
APOE ε4 +				-1.88 (0.78)*	-1.44 (0.80)^
Age (y)	-0.62 (0.04)***	-0.56 (0.05)***	-0.65 (0.05)***	-0.59 (0.05)***	-0.65 (0.05)***
Sex = female	-1.58 (0.63)*	-1.10 (0.79)	-1.25 (0.83)	-1.15 (0.79)	-1.44 (0.76)^
Education (y)	-0.07 (0.11)	-0.01 (0.15)	-0.01 (0.15)	-0.04 (0.15)	-0.001 (0.14)
Race = white	2.51 (0.93)**	2.18 (1.17)^	2.92 (1.53)^	2.11 (1.17)^	2.74 (1.47)^

P. R. Millar, P. H. Luckett, B. A. Gordon, T. L. S. Benzinger, S. E. Schindler, A. M. Fagan, C. Cruchaga, R. J. Bateman, R. Allegri, M. Jucker, J.-H. Lee, H. Mori, S. P. Salloway, I. Yakushev, J. C. Morris, and B. M. Ances, "Predicting brain age from functional connectivity in symptomatic and preclinical Alzheimer disease," NeuroImage, vol. 256, p. 119228, 2022, doi: 10.1016/j.neuroimage.2022.119228

Paper 3 : *Interhemispheric Functional and Structural Disconnection in Alzheimer's Disease: A Combined Resting-State fMRI and DTI Study*

Dataset

- rs-fMRI + DTI; 16 AD, 16 MCI, 16 CN
- VMHC for interhemispheric FC; DTI FA in corpus callosum subregions

Methodology

- VMHC: synchrony between each voxel and its contralateral mirror voxel
- ANOVA + post-hoc t-tests; FA in genu, body, splenium of corpus callosum
- Partial correlations with MMSE

Results

- Anterior VMHC: AD < MCI < CN (prefrontal, subcortical)
- Posterior: hyperconnectivity in MCI sensorimotor; reduced in AD occipital
- VMHC and FA both significantly correlated with MMSE ($p < 0.05$)

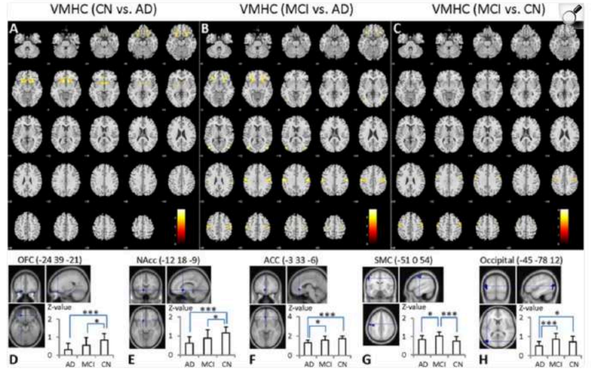
Observations

- VMHC is a valid biomarker for interhemispheric degeneration in AD
- Anterior-posterior dissociation: anterior degrades, posterior shows compensatory hyperconnectivity in MCI
- Corpus callosum integrity directly mediates interhemispheric breakdown

Gaps

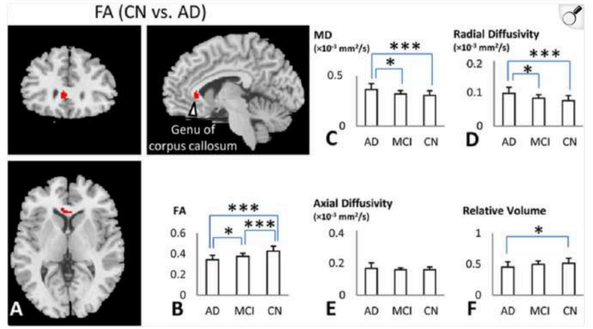
- Voxel-level VMHC requires structural alignment; n=48 only
- No brain age prediction; no ML classification

Fig 2. Cross-cohort comparisons of VMHC.



A: The AD subjects showed significantly decreased VMHC in the OFC, ACC, POC, NAcc, putamen, caudate and insula compared to CN. **B**: The AD subjects showed significantly decreased VMHC in the OFC, putamen, caudate, insula, SMC, and OcG compared to MCI. **C**: The MCI subjects showed significantly increased VMHC in the SMC compared to CN. **D-H** show the locations of the five anatomical structures where the VMHC was significantly different across the three cohorts. The values in the bar graphs are z-scores transformed from the VMHC values. * represents statistical differences between groups (*, $p \leq 0.05$; ***, $p \leq 0.001$).

Fig 3. DTI and volumetric differences among AD, MCI and CN.



A: Voxel-based analysis showed significant difference of FA between AD and CN in the genu of the corpus callosum (family-wise error corrected, $p < 0.05$, extent threshold = 10). **B-F**: Group comparisons revealed the patterns of diffusion parameters and volume changes in the genu of the corpus callosum (FA: AD < MCI < CN; MD: AD > CN / MCI; $\lambda_\perp$: AD > CN / MCI; $\lambda_\parallel$: no difference; Volume: AD < CN/MCI). * represents statistical difference between groups (*, $p \leq 0.05$; ***, $p \leq 0.001$)

Table 2. VMHC differences between AD, MCI and CN.

	Brain Regions	Cluster- size	Coordinates (MNI)			*t*-score	*p*-value corrected/ uncorrected
			x	y	z		
CN>AD	OFC/ ACC/ POC/ NAcc putamen/ caudate/ insula	591	-24	39	-21	4	0.000/0.000
MCI>CN	SMC (postcentral/ precentral gyrus)	116	-48	3	54	3.54	0.069/0.001
MCI>AD	OFC/ putamen/ caudate/ insula	109	-33	39	-9	3.75	0.091/0.001
	OcG (middle/ inferior occipital gyrus)	99	-45	-78	12	3.90	0.137/0.002
	SMC (postcentral/ precentral gyrus)	218	-60	-18	39	3.58	0.002/0.000

Z. Wang, J. Wang, H. Zhang, R. Mchugh, X. Sun, K. Li, and Q. X. Yang, "Interhemispheric functional and structural disconnection in Alzheimer's disease: a combined resting-state fMRI and DTI study," PLOS ONE, vol. 10, no. 5, p. e0126310, 2015, doi: 10.1371/journal.pone.0126310.

OVERVIEW

Paper	*What the Paper Studied*	*Main Idea from the Model*	*What They Found*	*Key Takeaway*
Zhou et al., 2022	Brain age from multi-site fMRI (n=4,259)	Multi-scale FC + tangent-space harmonization improves prediction	Default Mode, Frontoparietal, Somatomotor networks key	Site harmonization is critical for robust brain age models
Millar et al., 2022	FC-BAG in symptomatic and preclinical AD	Ridge regression on FC detects abnormal aging in AD	FC-BAG older in symptomatic AD, younger in preclinical AD	FC alone is a sensitive non-invasive AD biomarker
Wang et al., 2015	Interhemispheric disconnection in AD via fMRI + DTI	VMHC captures mirror-region synchrony across hemispheres	Anterior interhemispheric connectivity: AD < MCI < CN	Interhemispheric asymmetry is a measurable AD biomarker

What Existing Approaches Miss and Our Novelties:

1

The Miss: *Most brain age studies rely on structural MRI which mainly deals with detecting damage only after neurons are already lost.*

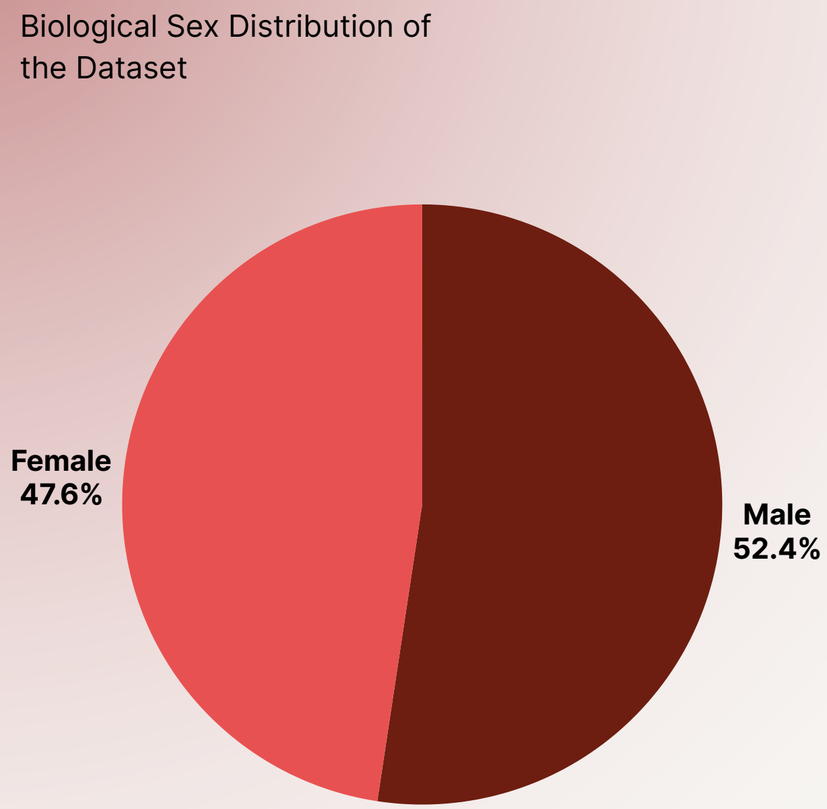
The Novelty: *Functional MRI captures connectivity breakdown years earlier, yet it remains underexplored in the brain age framework, we wanted to explore the nuances involved with using this datatype instead of the standard sMRIs.*

2

The Miss: *The Existing fMRI brain age models use whole-brain connectivity matrices which does make it close to impossible to identify which specific connections in the brain drive accelerated aging particularly.*

The Novelty: *We decompose by the brain by it's hemispheres to isolate the signal that may be missed when taking the brain as one component.*

DATASETS USED



https://adni.loni.usc.edu/data-samples/adni-data/

Alzheimer's Dataset

https://adni.loni.usc.edu/data-samples/adni-data/

Nature of the Dataset

- Type of data: fMRI brain scan images
- Classification Labels: Mild Dementia, Moderate Dementia, Non Demented, Cognitively Normal
- Format: dicom
- Dimension: 4 Dimension
- Scanner: 3 Tesla

Metadata

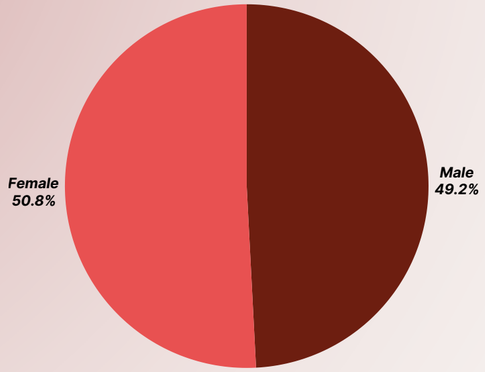
- Collection Methodology: **Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset**, available at adni.loni.usc.edu/data-samples/adni-data/study-cohort-information/.
- Extracted from ADNIMERGE.csv

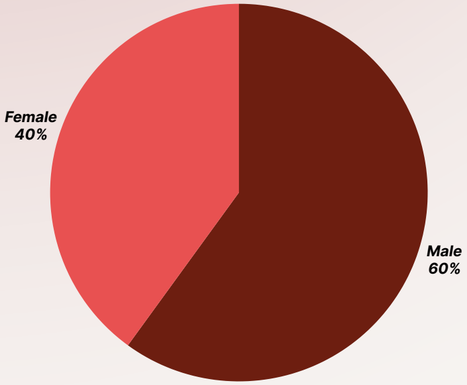
Why this dataset

- Contains fMRI scans across multiple stages of Alzheimer’s disease

Biological Sex Distribution of the Dataset

Control Subjects





Dementia Subjects

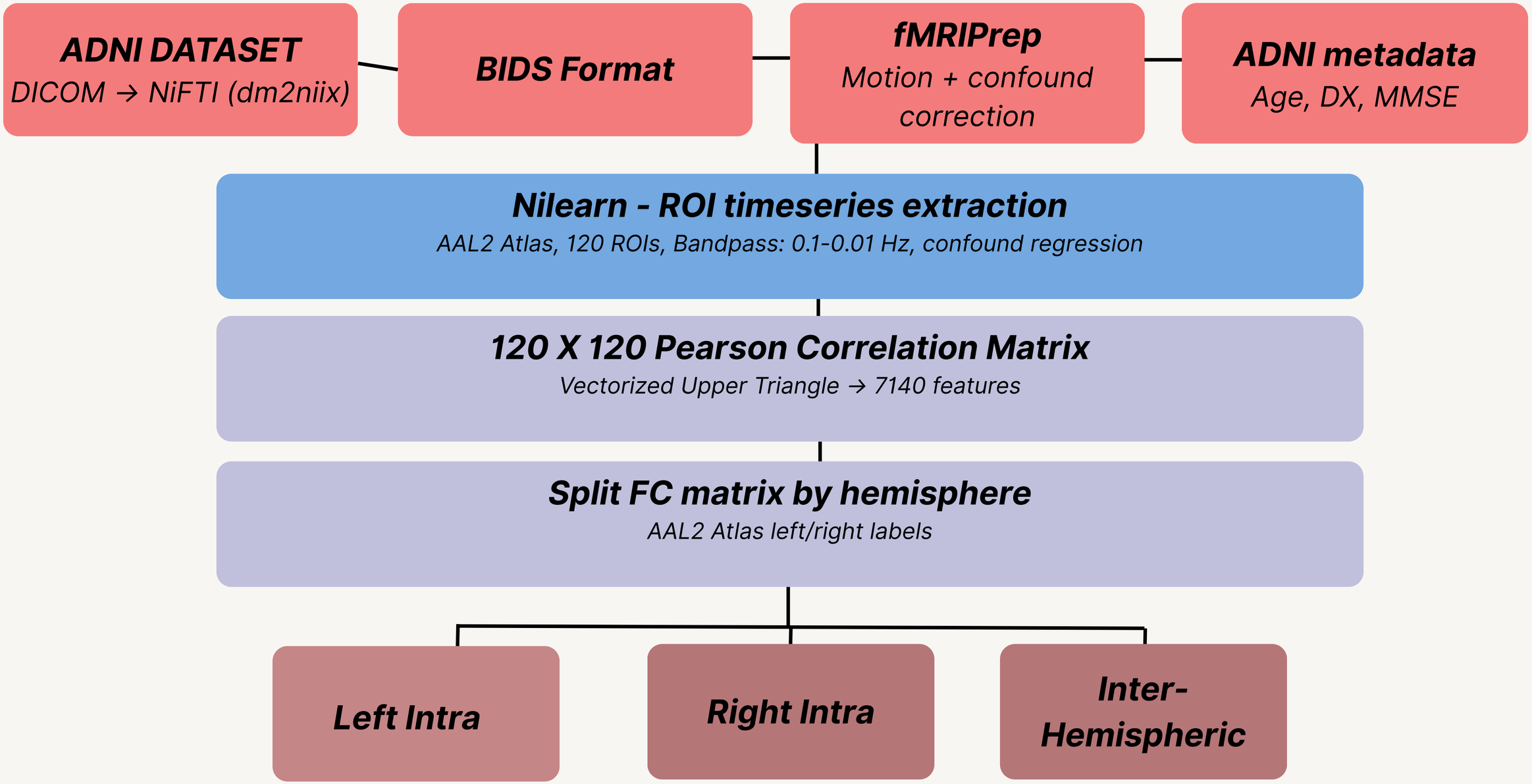
Data Selection

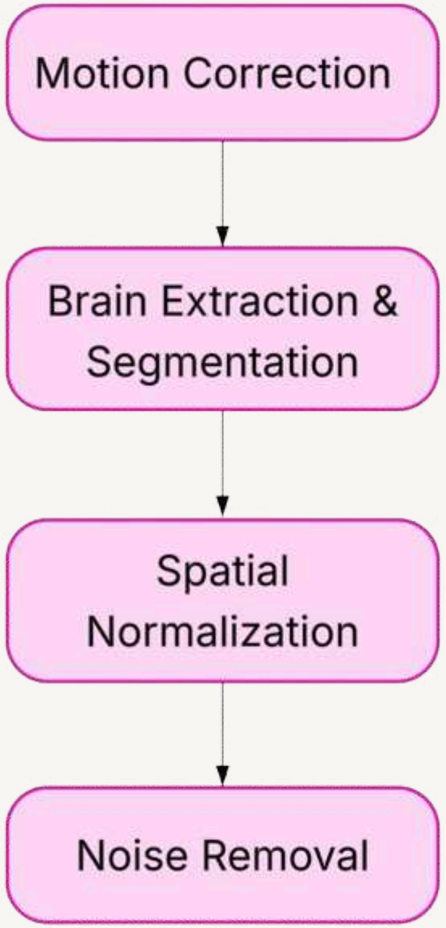
https://adni.loni.usc.edu/data-samples/adni-data/

Metric	Cognitively Normal (CN)	Alzheimer's Disease (AD)
Number of Subjects	**61**	**20**
Males, n (%)	30 (49.18%)	8 (38.10%)
Females, n (%)	31 (50.82%)	12 (61.90%)
Age (Mean ± SD)	71.69 ± 6.14 years	74.88 ± 5.50 years
Age Range	**60–86 years**	**60–84 years**
Age Median	72 years	76 years
MMSE (Mean ± SD)	**29.26 ± 1.09**	**24.86 ± 3.92**
MMSE Range	26–30	18–30
MMSE Median	30	25

DATA PRE-PROCESSING

PRE-PROCESSING PIPELINE

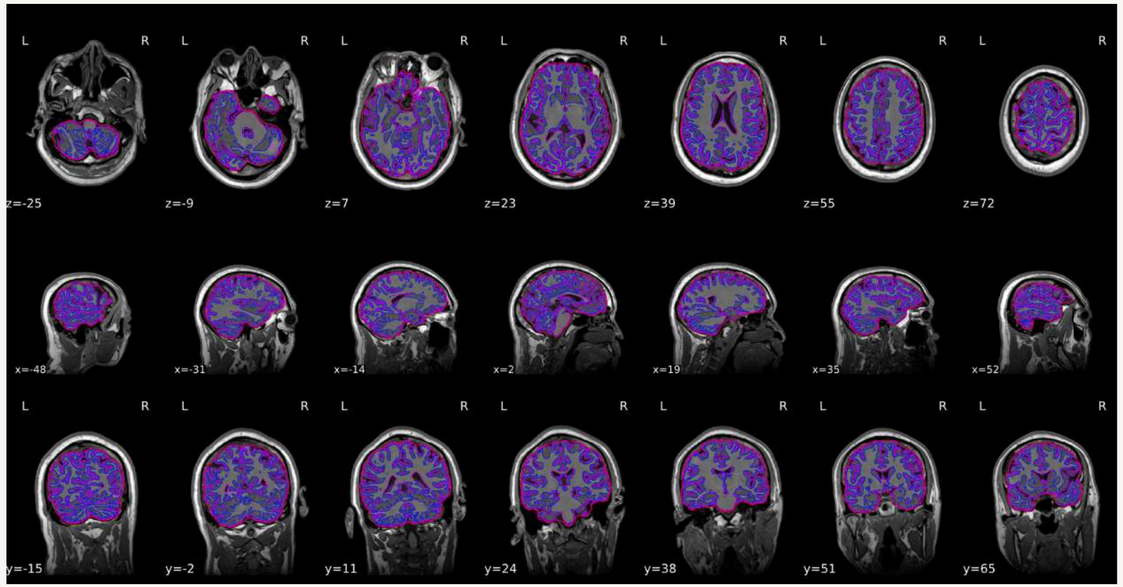




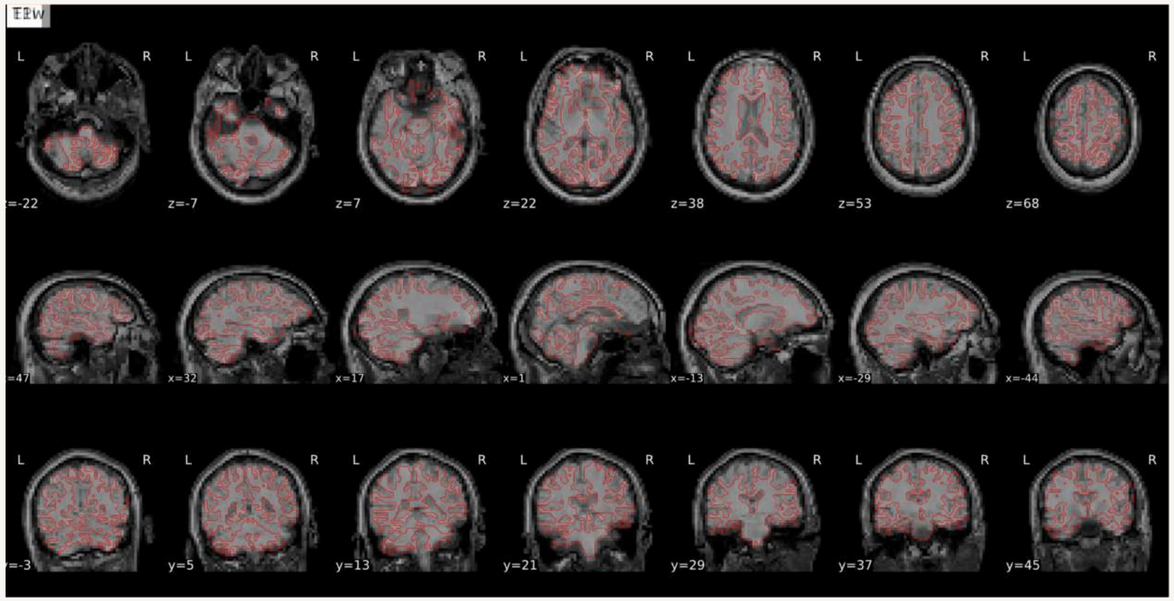
Pre-processing Tools

We have used the following specialised tools for data pre-processing:-

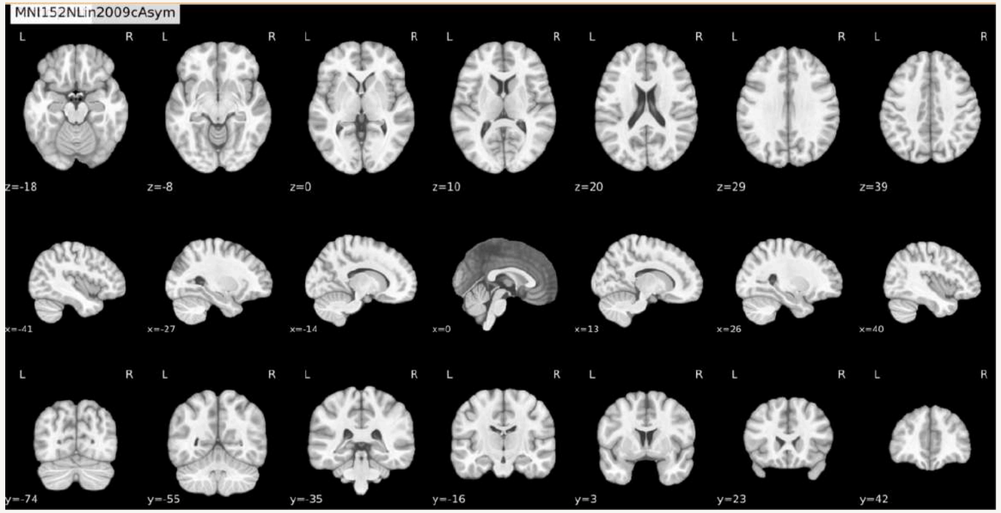
- ***DCM2niix***
  - *Raw MRI and fMRI scans from **ADNI** were converted into NiFTI files and also structured in a standardized format (BIDS format).*
- ***fMRIPrep***
  - *Performs automated preprocessing steps such as motion correction, normalisation, brain extraction, and noise removal. Computationally heavy*
- ***Nilearn (Python library) –***
  - *used for statistical analysis, connectivity identification, feature extraction, and machine learning on neuroimaging data.*



This panel shows the final, preprocessed T1-weighted image, with contours delineating the detected brain mask and brain tissue segmentations.

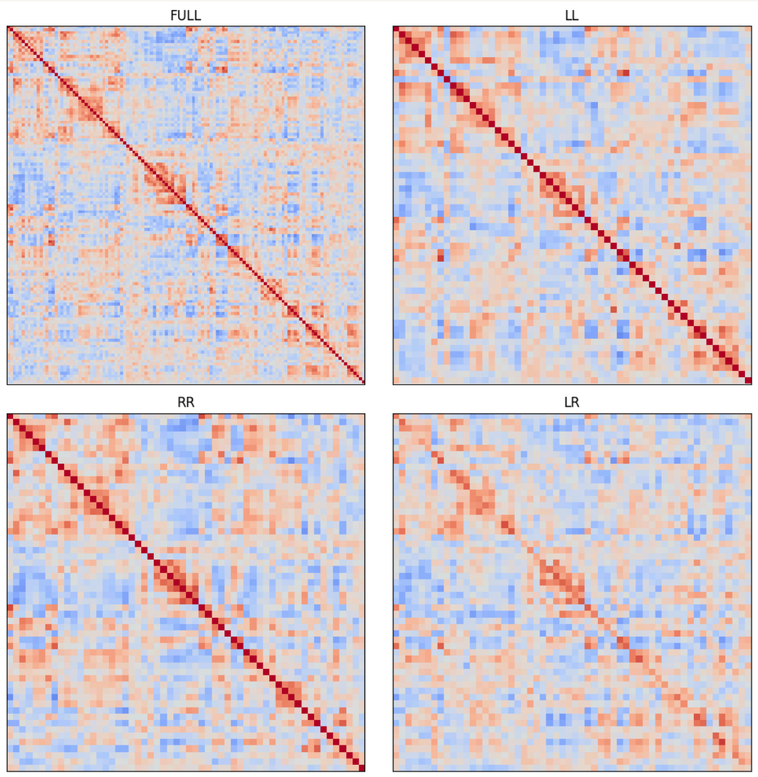


This panel shows the alignment of the BOLD reference image to the anatomical (T1-weighted) image.



Spatial normalization of the T1w image to the MNI152NLin2009cAsym template.

Functional Connectivity

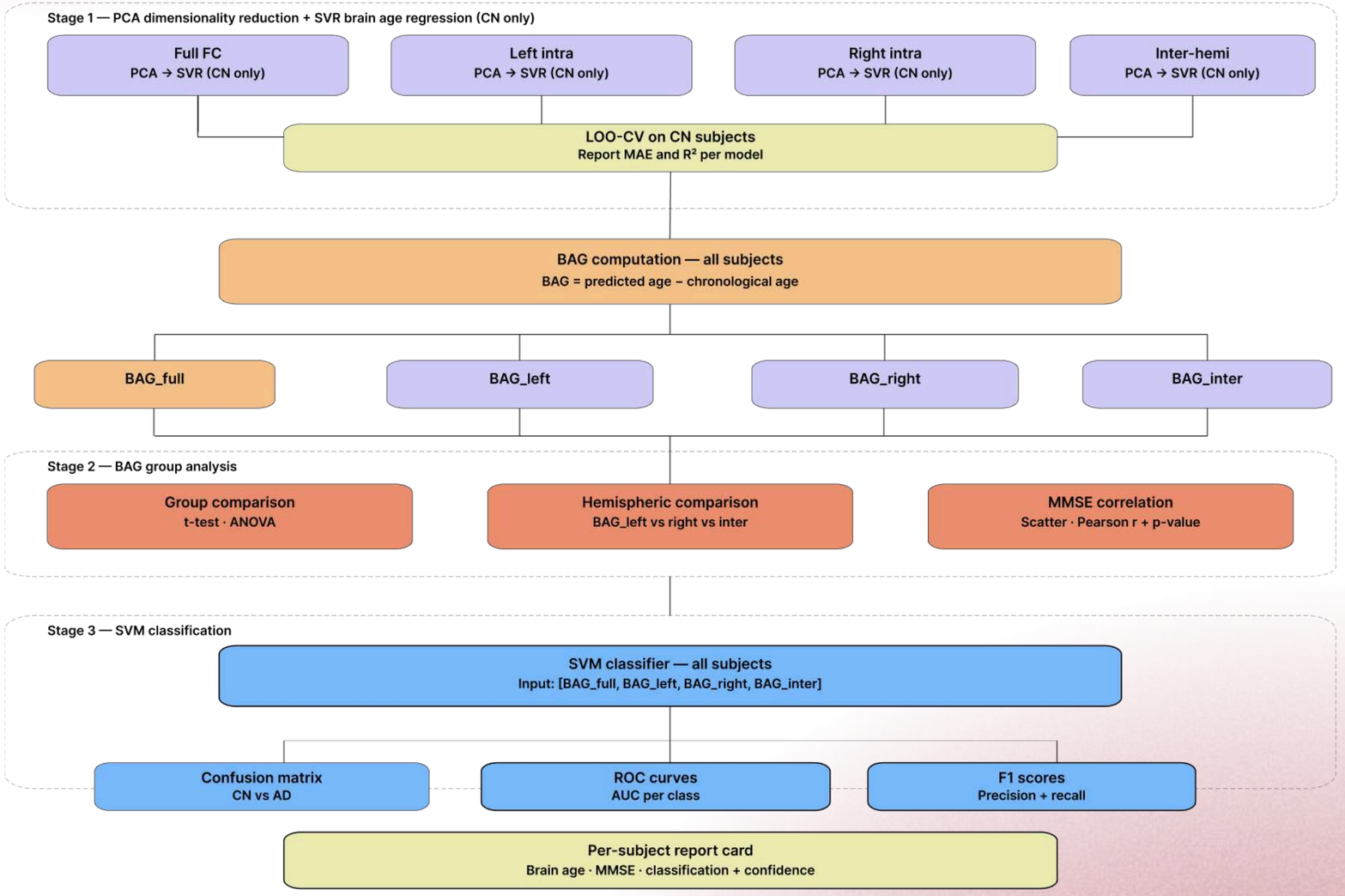


Functional Connectivity Matrices when split by hemisphere

- ***AAL2 Atlas (NOTE: Different from planned Harvard-Oxford Atlas)***
  - *Divided the brain into 120 regions*
  - *average fMRI activity signal from each region over time.*
  - *Used Pearson correlation to produce 120 × 120 functional connectivity matrices for every subject.*
- ***Hemispheric Connectivity Separation***
  - *Full whole-brain connectivity - 7140 features*
  - Left hemisphere connections (LL)-1540 features
  - Right hemisphere connections (RR)- 1540 features
  - Interhemispheric left-right connections (LR) - 3136 features
- **PCA**
  - We used a value of 5 as we had few data points and large number of features.

ML METHODOLOGY

Post Pre-Processing



Machine Learning Methodology

FINDINGS AND RESULTS

STAGE 1: PCA Dimensionality Reduction and SVR Brain Age Regression

FEATURES DIMENSIONALITY: BEFORE V/S AFTER

FULL: 7140 -> 5
LEFT: 1540 -> 15
RIGHT: 1540 -> 15
INTER: 3136 -> 5

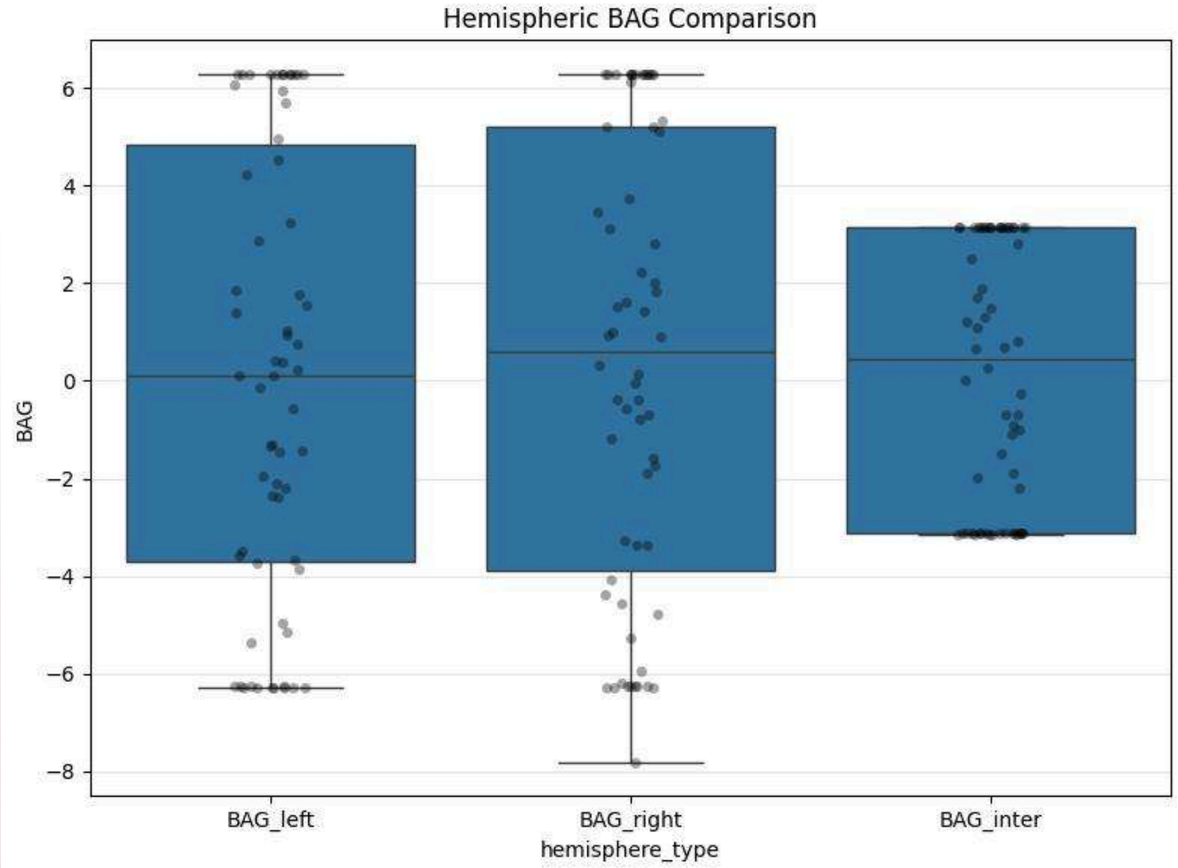
SVR REGRESSION

Model	MAE	RMSE	R^2	r
full	5.053884	6.288262	-0.005546	0.009777
left	5.23145	6.440074	-0.054684	-0.082433
right	5.255153	6.456026	-0.059915	-0.349607
inter	5.253443	6.515113	-0.079405	-0.227037

Models we tested for Brain-Age Prediction

Model	**Mean MAE (Years)**	**Mean R2**
SVR	5.05±0.924	-0.005
GNN	5.39±1.17	-0.059
CNN	5.43±1.35	-0.101
Ridge Regression	5.64±1.19	-0.104

STAGE 2: BAG Group Analysis



Our BAG Analysis demonstrates that The Left Hemispheric BAG shows a clearer aging pattern which indicates that the left hemisphere is more affected in Alzheimer's Disease than theright hemisphere.

Meanwhile, the variance of inter hemispheric BAG remains low showing that with normal healthy brain aging, the cross hemispheric connections are more stable.

Comparison between left, right and inter-hemispheric BAG Distributions.

Challenges Faced

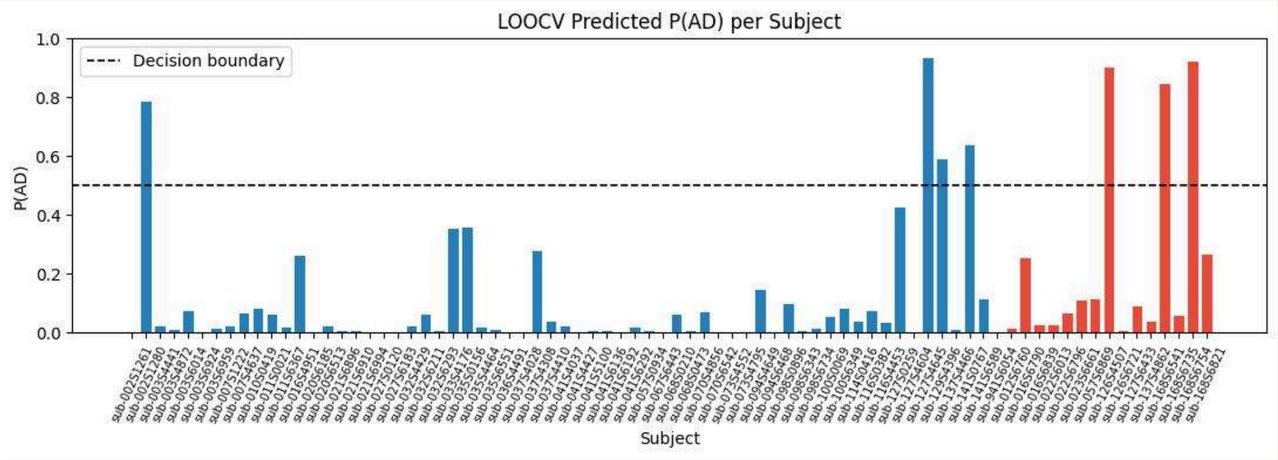
- *Pre-processing took wayyy too long... ~4 hours for fMRIPrep/scan*
- *Hardware constraints and time crunch*
- *ADNI Website didn't have many scans to fit our criterion.*
- *While downloading scans from ADNI Website, IP Address shifts caused loss of dowloads leading to long times required for loading data*
- *Very small dataset procured so far which we do plan to fix over the summer as we aim to submit our work in AI Challenge for Healthy Brain Aging*

FUTURE WORK

SVM Classifier

Currently, due to the lack of AD patients in our dataset our model is working on skewed data which is leading to it predicting the class as Cognitively Normal for most cases which has lead us to have very high **Recall** values.

We are actively working everyday to extract as much data as possible and preprocess it from the ADNI website using fMRIPrep but due to the previously mentioned constraints, we are lacking infrastructure for efficient processing.



Graph showing SVM's predictions of patients with threshold > 0.5

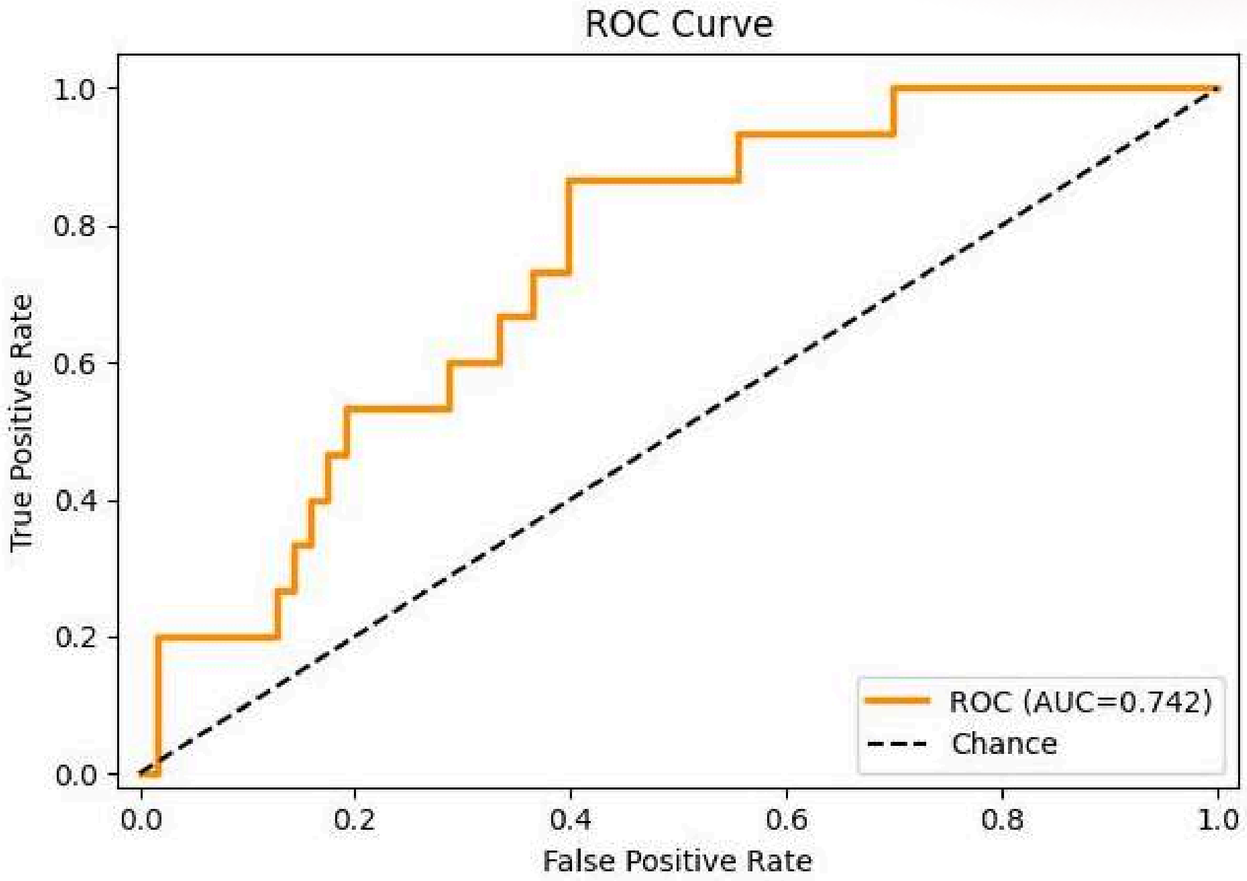
Results

```
============================================================
LOOCV Classification Report
============================================================
              precision    recall  f1-score   support

          CN     0.8286    0.9206    0.8722        63
          AD     0.3750    0.2000    0.2609        15

    accuracy                         0.7821        78
   macro avg     0.6018    0.5603    0.5665        78
weighted avg     0.7413    0.7821    0.7546        78

Confusion Matrix:
[[58  5]
 [12  3]]

Balanced Accuracy : 0.5603
ROC-AUC           : 0.7418
Avg features/fold : 610.0
```

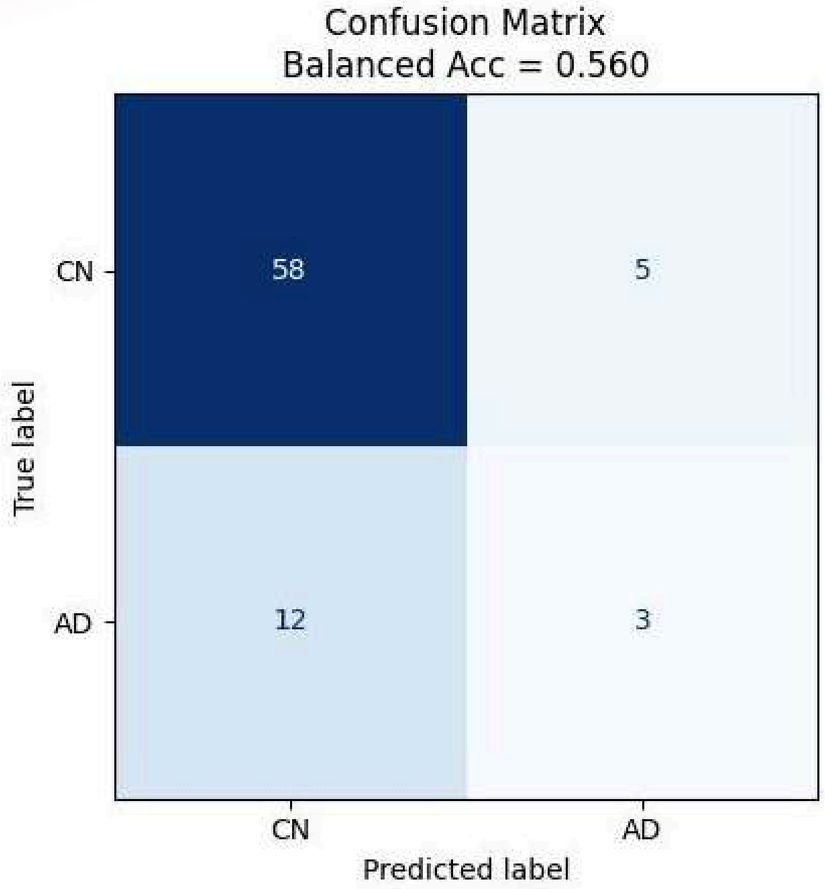
SVM Classification Report

The model achieved moderate overall accuracy but showed weak Alzheimer's detection performance, likely due to class imbalance and the limited number of AD subjects.

Results



ROC Curve of the SVM Classifier



Confusion Matrix of SVM Classifier

Thank You.