Neuroanatomical-Based Machine Learning Prediction of Alzheimer's Disease Across Sex and Age

Bhaavin Kishore Jogeshwar

Advised by

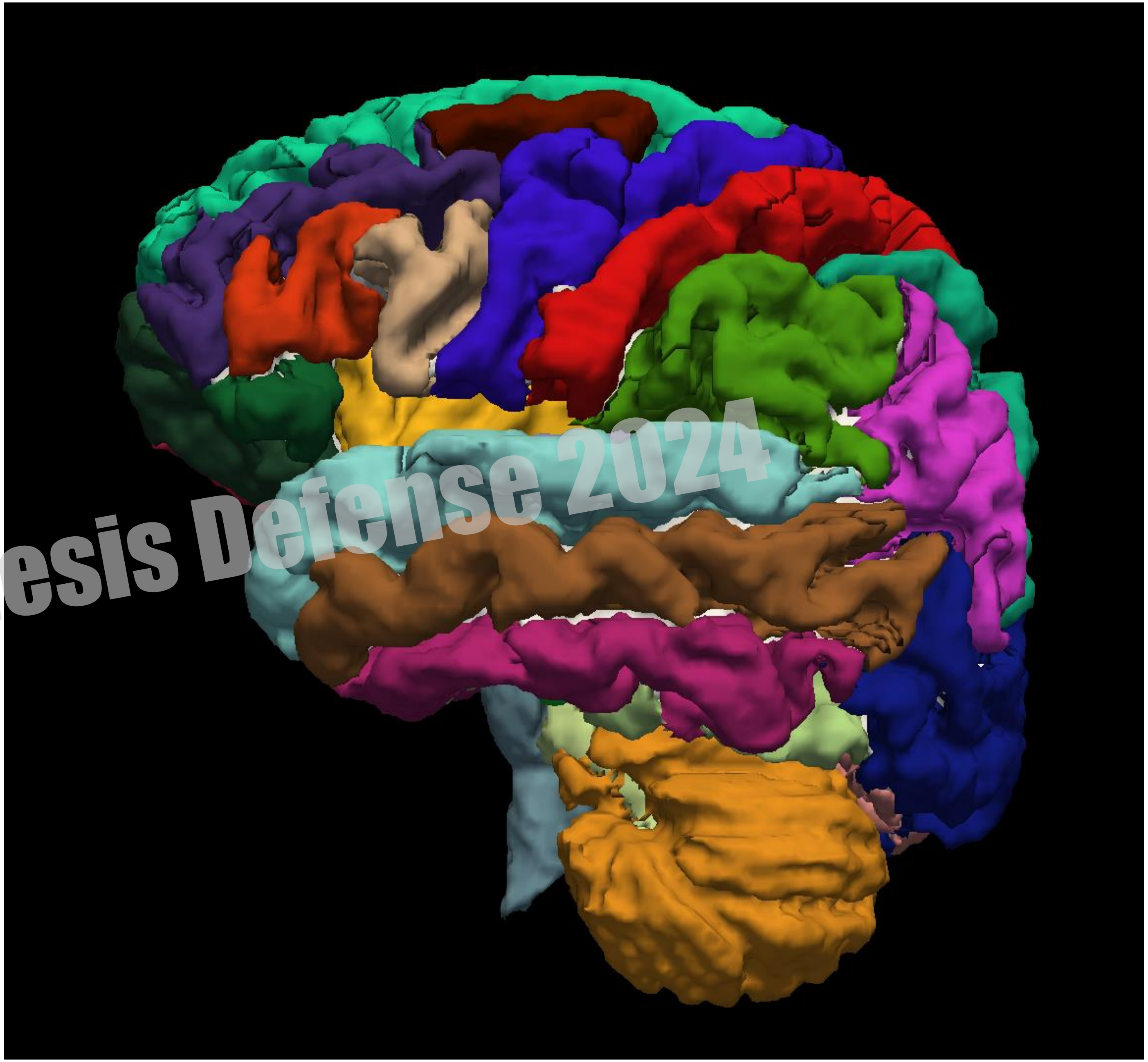
Prof. Benjamin Nephew[a]

Prof. Loris Fichera[b]

[a]Biology & Biotechnology Department

[b]Robotics Engineering Department

WPI



Lateral view of the brain

Introduction

Understanding concepts – Cognitive Normal (CN)

A chef cooking. Image source: Copilot

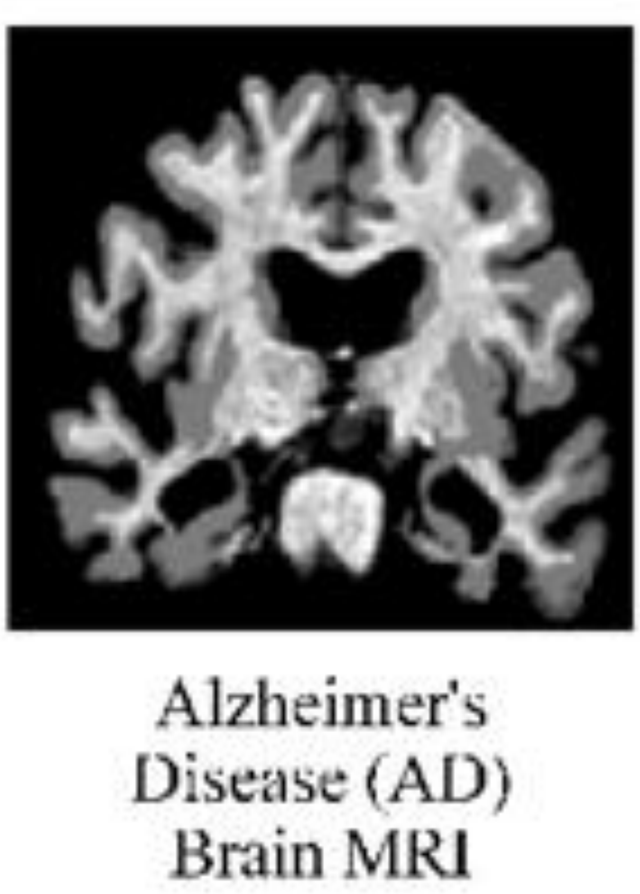
Cognitive Normal (CN) Brain MRI

Understanding concepts – Mild Cognitive Impairment (MCI)

Chef cooking with an upside-down spatula. Image source: Copilot

Understanding concepts – Alzheimer's Disease (AD)

A chef with memory loss. Image source: Copilot



Understanding Alzheimer's Disease

- Rationale:
  - In 2024, nearly two-thirds of Americans with Alzheimer's are women
  - The lifetime risk at age 45:
    - 1 in 5 for women
    - 1 in 10 for men (2024)
  - About 110 in 100,000 Americans aged 30-64 get Alzheimer's before 65

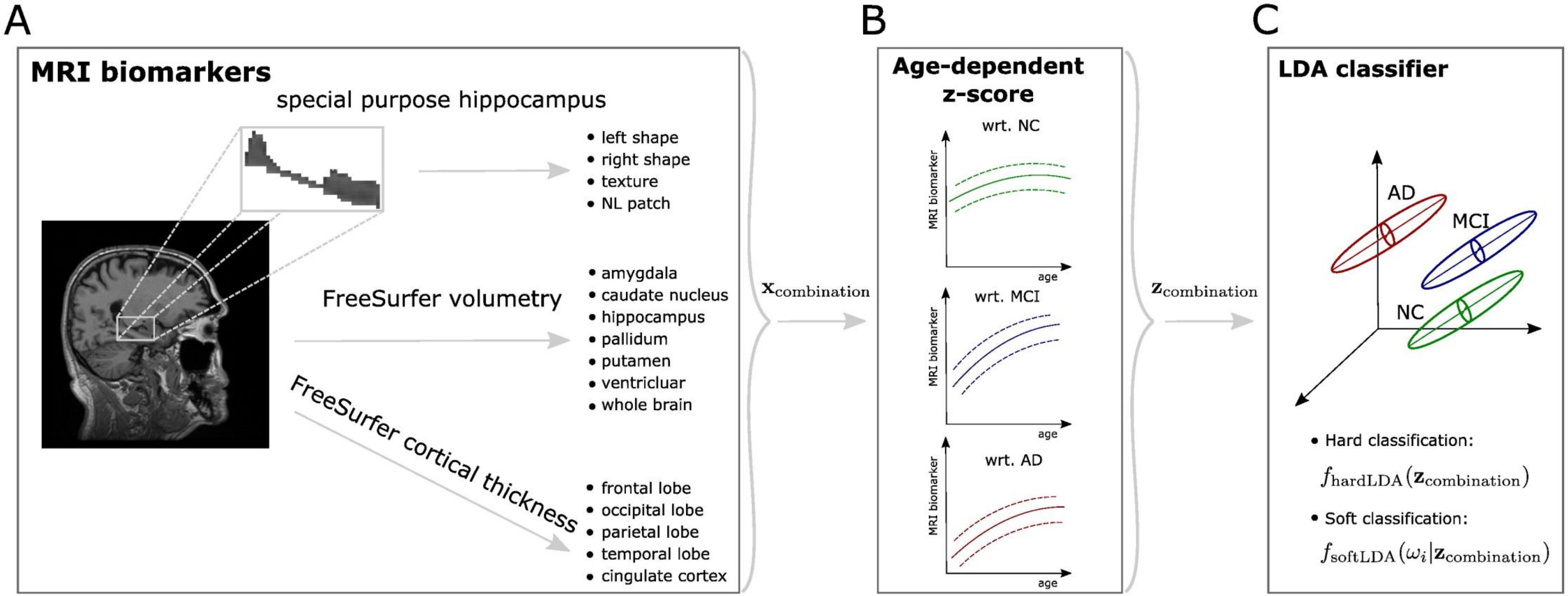
Image source: NIH National Institute on Aging

Understanding Alzheimer's Disease

- Neuroanatomical markers
  - Brain changes indicating Alzheimer's, like shrinking areas
  - Helps with early detection and treatment tracking

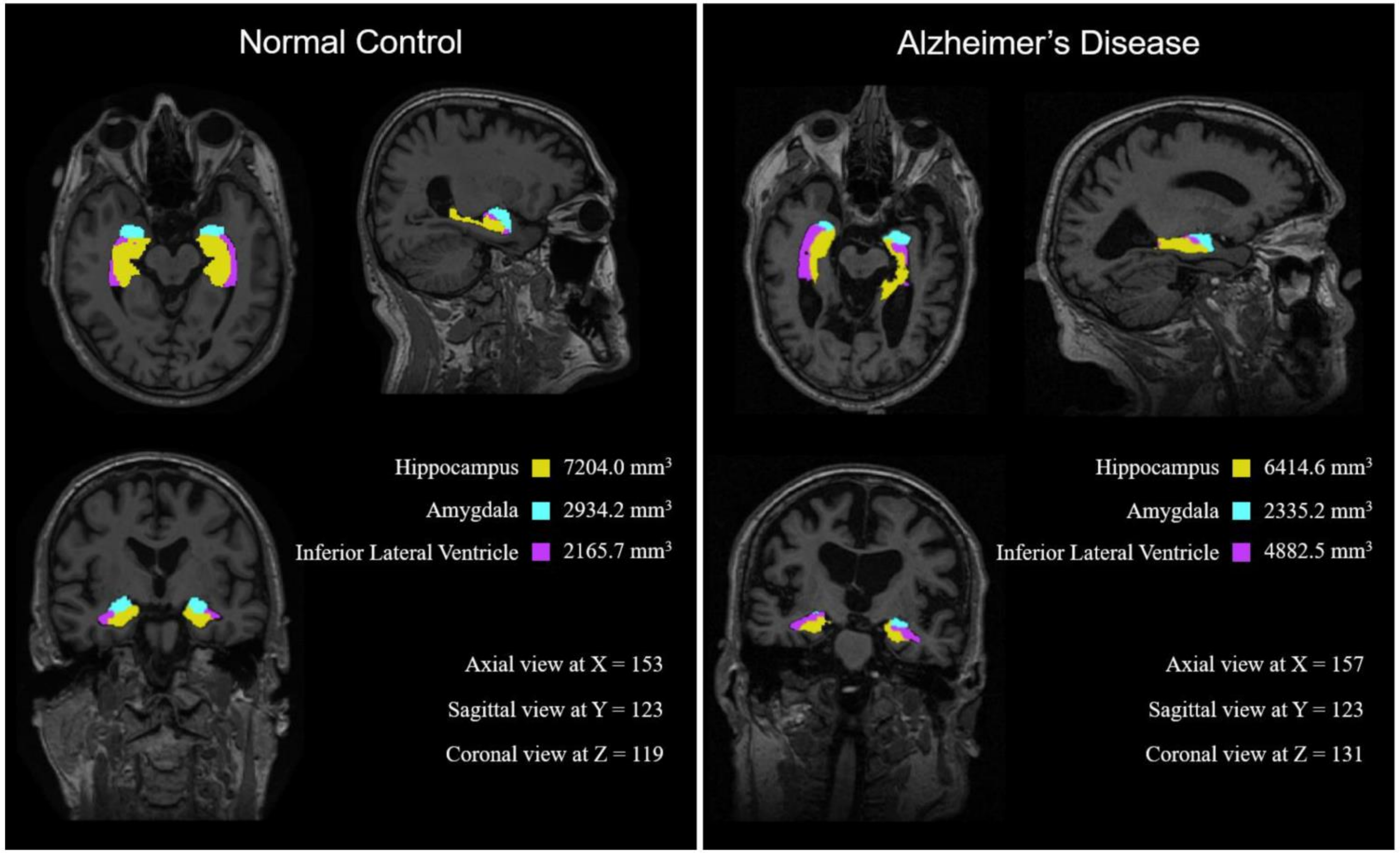
Image source: iStock

Literature review



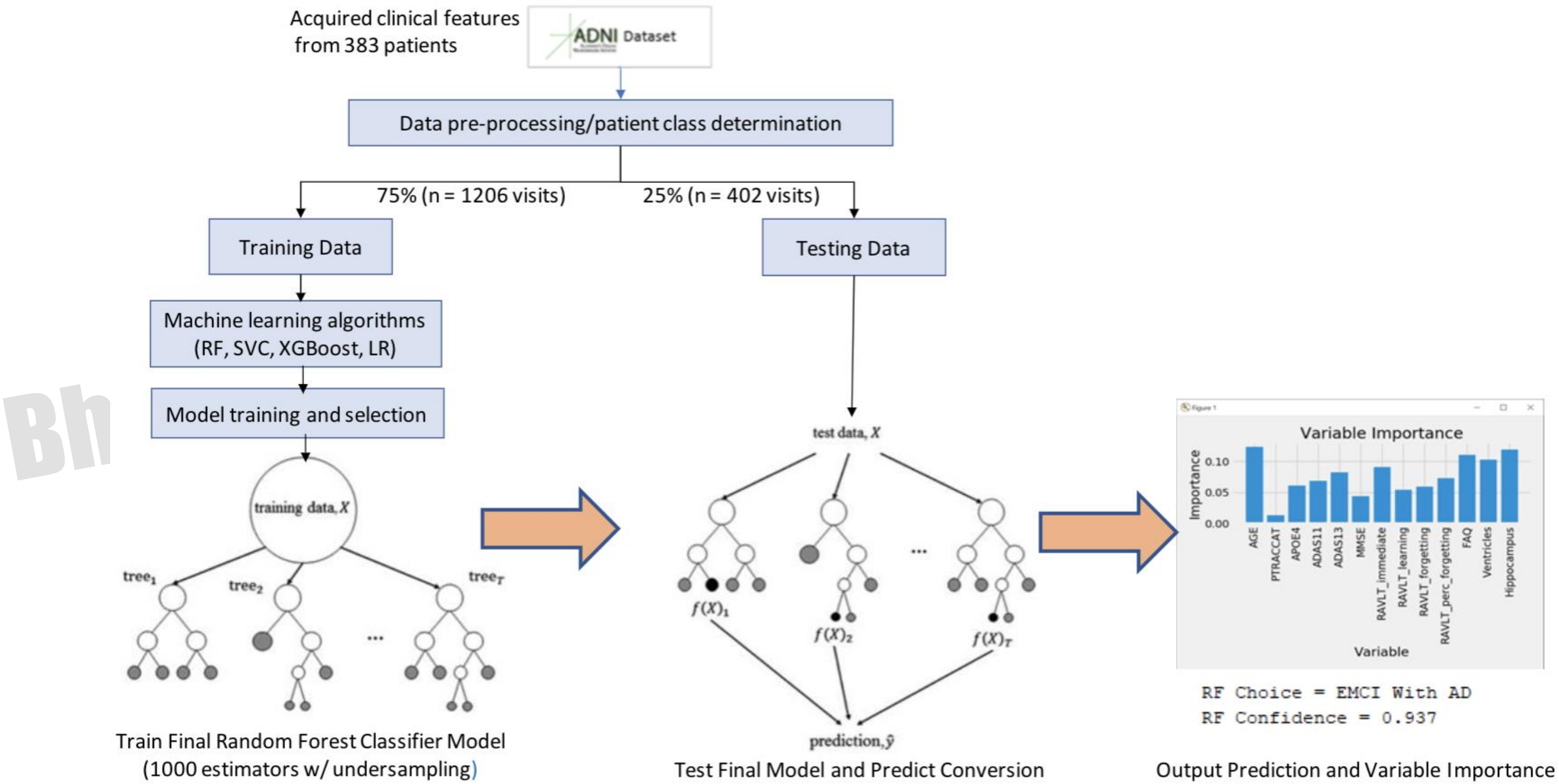
LDA Algorithm in [2]

Literature review



Two representative MRI images from the NC and AD groups indicating their top features. [3]

Literature review



Model workflow in [4]

ADNI (Alzheimer's Disease Neuroimaging Initiative) dataset

	N	Sex (F:M)	Age (years)
CN	281	171:110	73.7-81.0
MCI	332	104:228	71.6-83.0
AD	202	108:94	69.4-83.6
	815	**383:432**	**69.4-83.6**

ADNI demographic characteristics table

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	815	**383:432**	**69.4-83.6**

Dataset for subgroup analyses

Age Group (in years)	Group	N: Both sexes (M+F)	N: Males (M)	N: Females (F)
Ages 69-84	CN	281	110	171
	MCI	332	228	104
	AD	202	94	108
		815	**432**	**383**
Ages 69-76	CN	117	51	66
	MCI	151	112	39
	AD	106	39	67
		374	**202**	**172**
Ages 77-84	CN	164	59	105
	MCI	181	116	65
	AD	96	55	41
		441	**230**	**211**

The nine subgroups are:

1. Both sexes, 69-84
2. Males, 69-84
3. Females, 69-84

4. Both sexes, 69-76
5. Males, 69-76
6. Females, 69-76

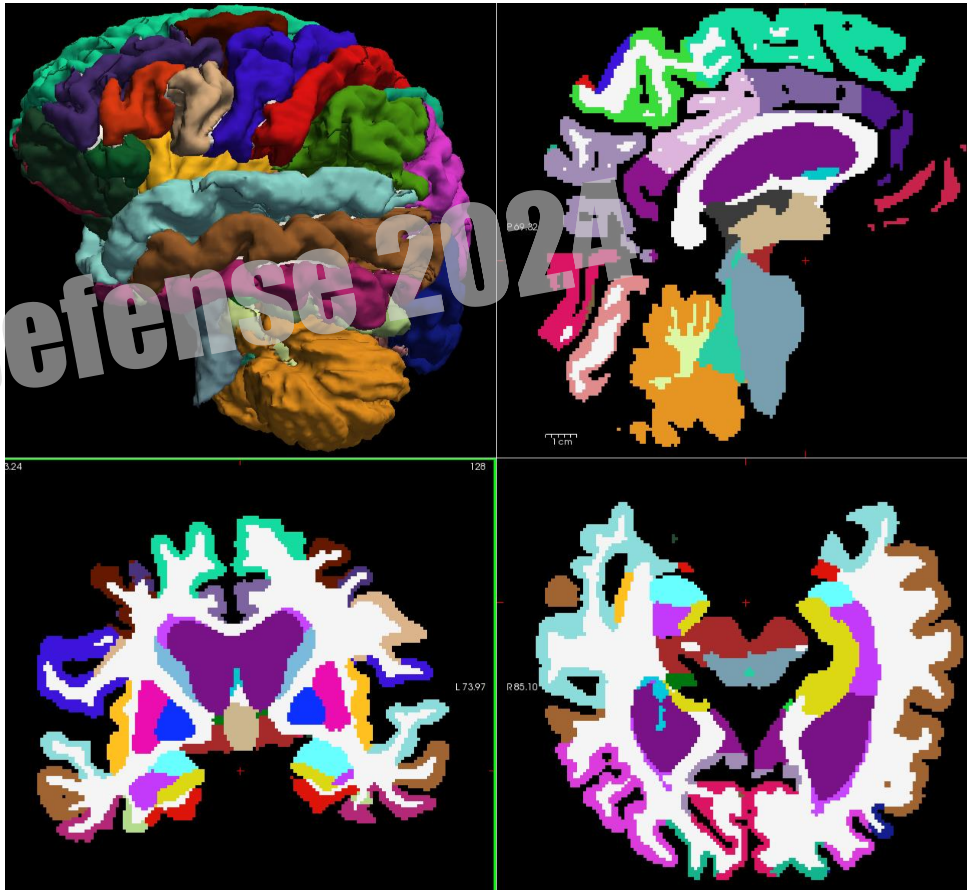
7. Both sexes, 77-84
8. Males, 77-84
9. Females, 77-84

Neuroimaging Pipeline – FastSurfer

- Performs segmentation
- Calculates brain region volumes

Measure: volume	Brain region #1	Brain region #2	Brain region #...	Brain region #95
subject_1	20442.213	3406.848	##	1471.716
subject_2	20664.388	3490.035	##	1426.638
subject_..	##	##	##	##
subject_815	19909.568	3246.525	##	1321.207

Overview of the volumetric dataset



Brain parcellation

Preparing Dataset for Machine Learning

Normalization (N)

- Context:
  - Ensures equal contribution of each volume to the analysis
  - Advised by Dr. Marcelo Febo to use entire brain volume as a covariate

$$N = \frac{Volume\ of\ a\ Brain\ Region}{Sum\ of\ Every\ Brain\ Region\ of\ That\ Subject}$$

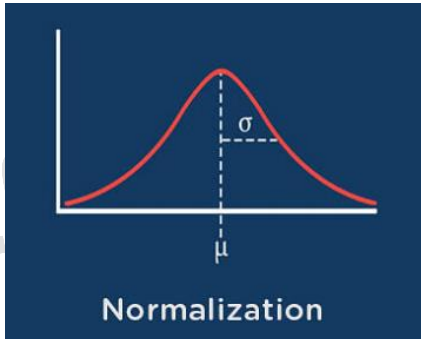


Image source: Simplilearn

Equal contribution. Image source: iStock

Preparing Dataset for Machine Learning

SMOTE

Synthetic Minority Over-sampling Technique

- Purpose:
  - Balance dataset with equal number of AD, MCI, and CN subjects
- Method:
  - Generates synthetic samples from the minority class using interpolation

Age Group (in years)	Group	N Both sexes (M+F)	Males (M)	Females (F)
Ages 69-84	CN	281	110	171
	MCI	332	228	104
	AD	202	94	108
		815	**432**	**383**
Ages 69-76	CN	117	51	66
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		441	**230**	**211**

Class imbalance in dataset

Preparing Dataset for Machine Learning

Statistical Testing

- Z-tests and Benjamini-Hochberg (BH) Correction
- Purpose:
  - Check if brain regions are statistically different
- Outcome:
  - Most brain regions were statistically different with p<0.01

- Dataset is now prepared for Machine Learning

Brain Region	CN vs MCI	CN vs AD	MCI vs AD	MCI vs CN	AD vs CN	AD vs MCI
Left-Hippocampus	8.89e-22	2.24e-91	8.89e-22	2.69e-30	2.24e-91	2.69e-30
Right-Hippocampus	8.77e-17	4.71e-68	8.77e-17	3.44e-23	4.71e-68	3.44e-23
Left-Amygdala	2.22e-13	6.27e-69	2.22e-13	1.89e-25	6.27e-69	1.89e-25
Right-Amygdala	6.16e-09	7.95e-47	6.16e-09	2.50e-19	7.95e-47	2.50e-19
ctx-lh-entorhinal	4.41e-12	1.36e-55	4.41e-12	1.95e-18	1.36e-55	1.95e-18
ctx-rh-entorhinal	3.64e-09	1.66e-68	3.64e-09	7.63e-29	1.66e-68	7.63e-29
Left-Inf-Lat-Vent	9.54e-20	5.72e-27	9.54e-20	7.60e-07	5.72e-27	7.60e-07
ctx-lh-inferiorparietal	0.136	2.60e-15	0.136	1.99e-09	2.60e-15	1.99e-09
ctx-lh-inferiortemporal	0.0821	2.75e-29	0.0821	3.48e-20	2.75e-29	3.48e-20
ctx-lh-middletemporal	3.17e-04	2.17e-23	3.17e-04	1.08e-11	2.17e-23	1.08e-11

P-values of a few brain regions after Benjamini-Hochberg correction

Random Forest - ML Algorithm

- Why Random Forest?
- “Group of experts” analogy
- Flowchart to classify AD, MCI, or CN

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An example flowchart of Random Forest classifier

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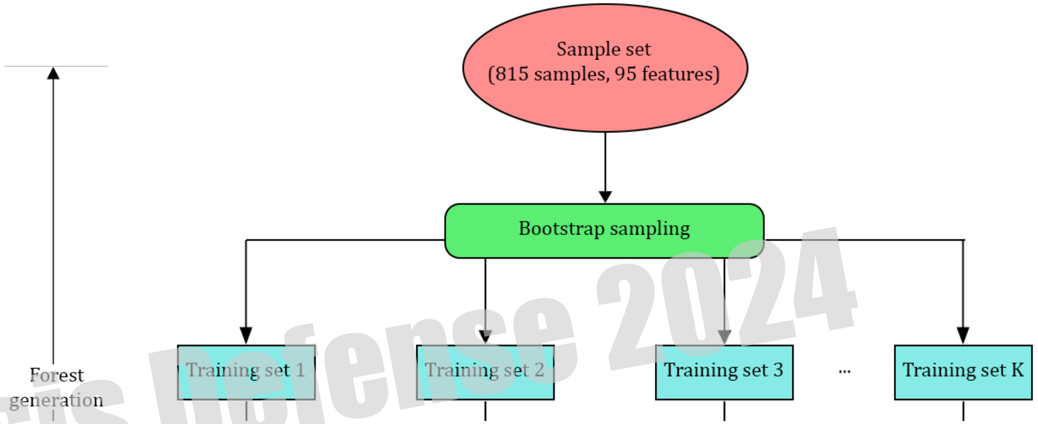

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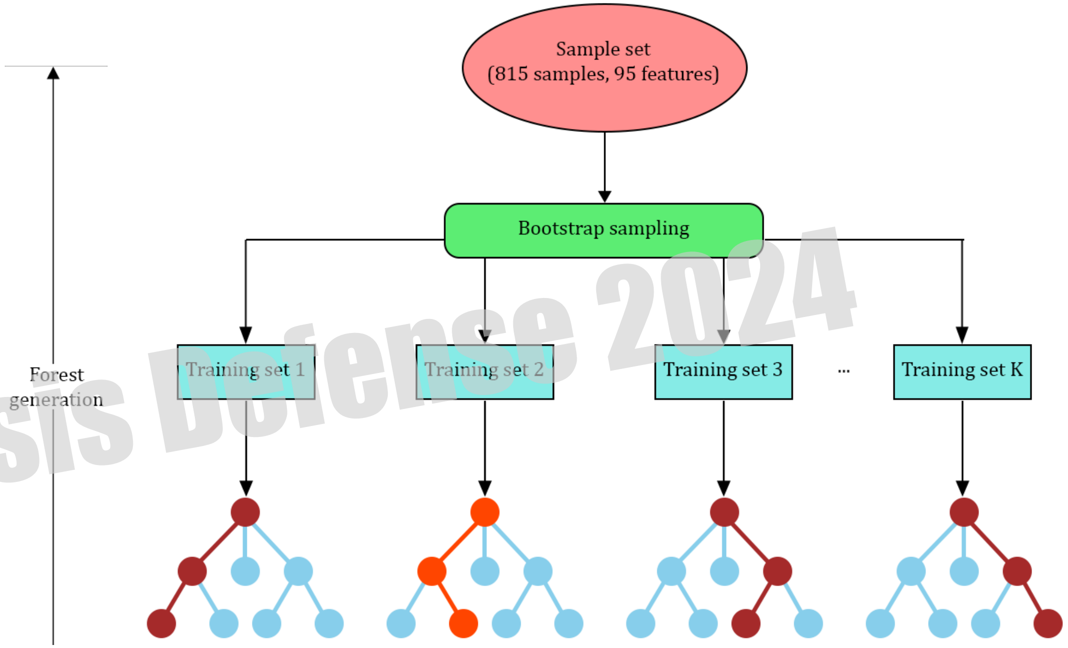

An example flowchart of Random Forest classifier

Random Forest - ML Algorithm

- Why Random Forest?
- "Group of experts" analogy
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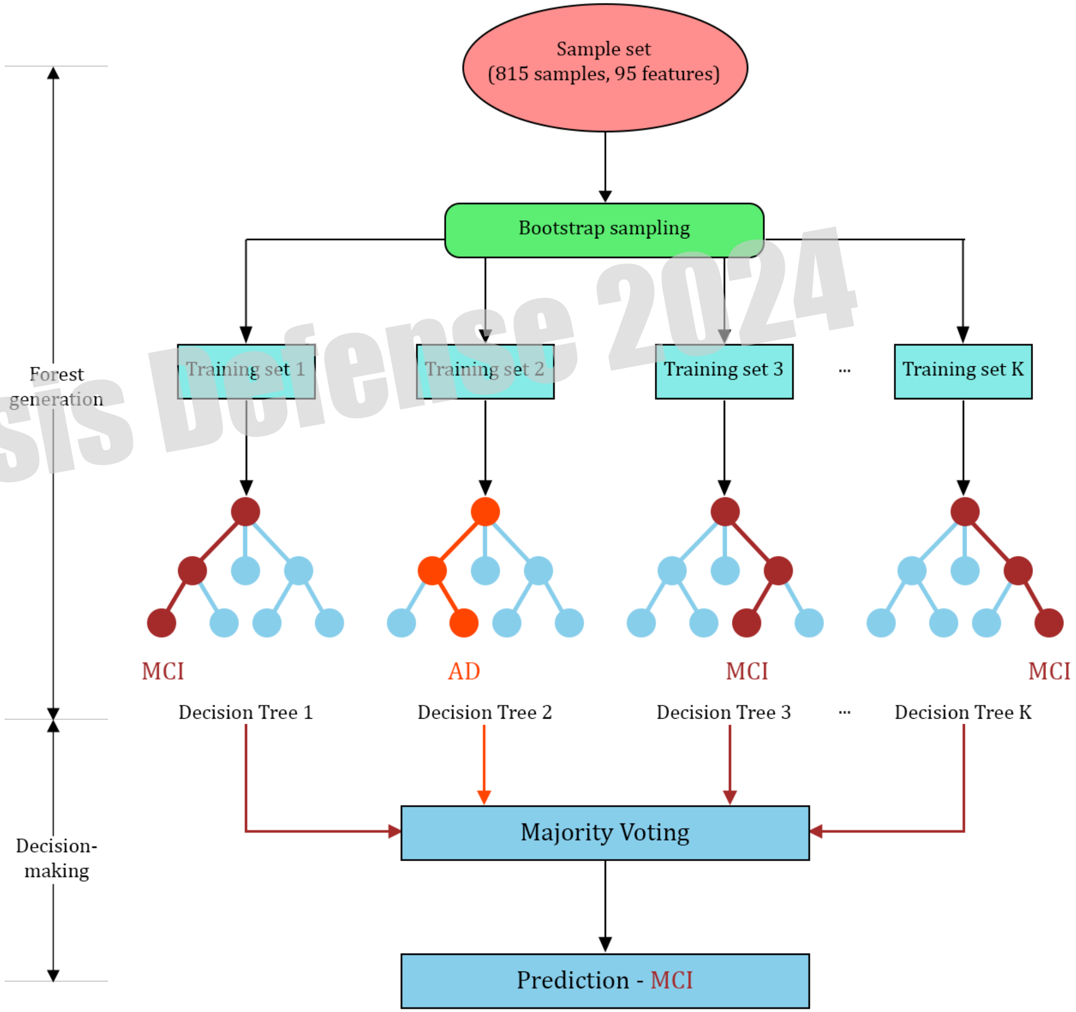

An example flowchart of Random Forest classifier

Performance Metrics

- Accuracy: The ratio of correct predictions out of the total predictions made

Groups	Unified Sex (M+F)	
	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9086
	Precision	0.9084
	Recall	0.9086
	F1-score	0.9080
	Training accuracy	1.0

Performance using K-fold Cross-Validation

Groups	Unified Sex (M+F)	
	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9187
	Precision	0.9190
	Recall	0.9187
	F1-score	0.9178
	Training accuracy	1.0

Performance using Stratified K-fold Cross-Validation

Groups	Unified Sex (M+F)	
	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9287
	Precision	0.9284
	Recall	0.9287
	F1-score	0.9284
	Training accuracy	1.0

Performance using Leave-One-Out Cross-Validation

Performance Metrics

Groups	Unified Sex (M+F)		Males (M)		Females (F)	
	Metric	Value	Metric	Value	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9086	Accuracy	0.9415	Accuracy	0.9357
	Precision	0.9084	Precision	0.9414	Precision	0.9358
	Recall	0.9086	Recall	0.9415	Recall	0.9357
	F1-score	0.9080	F1-score	0.9413	F1-score	0.9355
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Younger age group Ages 69-76	Accuracy	0.9051	Accuracy	0.9315	Accuracy	0.9403
	Precision	0.9052	Precision	0.9313	Precision	0.9403
	Recall	0.9051	Recall	0.9315	Recall	0.9403
	F1-score	0.9041	F1-score	0.9312	F1-score	0.9403
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Older age group Ages 77-84	Accuracy	0.9098	Accuracy	0.9282	Accuracy	0.9365
	Precision	0.9095	Precision	0.9284	Precision	0.9366
	Recall	0.9098	Recall	0.9282	Recall	0.9365
	F1-score	0.9095	F1-score	0.9281	F1-score	0.9360
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
Total execution time for K-fold: **1.31 minutes** (78.76 seconds)						

Performance using K-fold Cross-Validation

Groups	Unified Sex (M+F)		Males (M)		Females (F)	
	Metric	Value	Metric	Value	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9287	Accuracy	0.9547	Accuracy	0.9435
	Precision	0.9284	Precision	0.9547	Precision	0.9435
	Recall	0.9287	Recall	0.9547	Recall	0.9435
	F1-score	0.9284	F1-score	0.9546	F1-score	0.9434
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Younger age group Ages 69-76	Accuracy	0.9205	Accuracy	0.9435	Accuracy	0.9303
	Precision	0.9212	Precision	0.9435	Precision	0.9307
	Recall	0.9205	Recall	0.9435	Recall	0.9303
	F1-score	0.9200	F1-score	0.9430	F1-score	0.9304
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Older age group Ages 77-84	Accuracy	0.9263	Accuracy	0.9397	Accuracy	0.9460
	Precision	0.9272	Precision	0.9396	Precision	0.9477
	Recall	0.9263	Recall	0.9397	Recall	0.9460
	F1-score	0.9257	F1-score	0.9396	F1-score	0.9455
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
Total execution time for Leave-One-Out: **23.73 minutes**						

Performance using Leave-One-Out Cross-Validation

Groups	Unified Sex (M+F)		Males (M)		Females (F)	
	Metric	Value	Metric	Value	Metric	Value
Unified age group Ages 69-84	Accuracy	0.9187	Accuracy	0.9503	Accuracy	0.9357
	Precision	0.9190	Precision	0.9502	Precision	0.9359
	Recall	0.9187	Recall	0.9503	Recall	0.9357
	F1-score	0.9178	F1-score	0.9502	F1-score	0.9355
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Younger age group Ages 69-76	Accuracy	0.8962	Accuracy	0.9583	Accuracy	0.9353
	Precision	0.8962	Precision	0.9583	Precision	0.9355
	Recall	0.8962	Recall	0.9583	Recall	0.9353
	F1-score	0.8957	F1-score	0.9582	F1-score	0.9351
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
	Metric	Value	Metric	Value	Metric	Value
Older age group Ages 77-84	Accuracy	0.9116	Accuracy	0.9224	Accuracy	0.9365
	Precision	0.9123	Precision	0.9222	Precision	0.9363
	Recall	0.9116	Recall	0.9224	Recall	0.9365
	F1-score	0.9107	F1-score	0.9222	F1-score	0.9363
	Training accuracy	1.0	Training accuracy	1.0	Training accuracy	1.0
Total execution time for Stratified K-fold: **1.34 minutes** (80.67 seconds)						

Performance using Stratified K-fold Cross-Validation

Random Forest – Feature Importance

- Achieved 92.87% accuracy in predicting AD, MCI, and CN
- Next step: Use Feature Importance to find key brain regions
- **Feature Importance**: Measures how each brain region affects prediction accuracy
- Focused on the top six ranked brain regions in subgroup analyses

Comparison of Top Contributing Features

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus ctx-lh-inferiortemporal	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal Right-Hippocampus ctx-lh-middletemporal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal ctx-lh-inferiortemporal ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-lh-entorhinal ctx-rh-entorhinal ctx-rh-middletemporal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala ctx-lh-parahippocampal ctx-lh-middletemporal ctx-lh-entorhinal ctx-lh-inferiortemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal Right-Hippocampus	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala ctx-lh-entorhinal Right-Hippocampus

Using K-fold Cross-Validation

Comparison of Top Contributing Features

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus ctx-lh-inferiortemporal	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal Right-Hippocampus ctx-lh-middletemporal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal ctx-lh-inferiortemporal ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-lh-entorhinal ctx-rh-entorhinal ctx-rh-middletemporal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala ctx-lh-parahippocampal ctx-lh-middletemporal ctx-lh-entorhinal ctx-lh-inferiortemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal Right-Hippocampus	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala ctx-lh-entorhinal Right-Hippocampus

Using K-fold Cross-Validation

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal Right-Hippocampus Right-Amygdala ctx-lh-inferiortemporal	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala Right-Amygdala ctx-lh-inferiorparietal Right-Hippocampus	Left-Hippocampus ctx-lh-entorhinal Left-Amygdala Right-Hippocampus ctx-lh-inferiortemporal Right-Amygdala
Younger age group Ages 69-76	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-rh-entorhinal Right-Amygdala ctx-rh-middletemporal	Right-Hippocampus Left-Hippocampus ctx-rh-entorhinal Right-Amygdala ctx-rh-supramarginal Left-Amygdala	Left-Hippocampus ctx-lh-middletemporal Left-Amygdala Right-Hippocampus ctx-lh-inferiortemporal ctx-rh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal ctx-lh-middletemporal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-rh-entorhinal ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-lh-supramarginal	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal ctx-lh-middletemporal Right-Hippocampus
Total execution time for Stratified K-fold: **1.34 minutes** (80.67 seconds)			

Using Stratified K-fold Cross-Validation

Comparison of Top Contributing Features

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus ctx-lh-inferiortemporal	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal Right-Hippocampus ctx-lh-middletemporal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal ctx-lh-inferiortemporal ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-lh-entorhinal ctx-rh-entorhinal ctx-rh-middletemporal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala ctx-lh-parahippocampal ctx-lh-middletemporal ctx-lh-entorhinal ctx-lh-inferiortemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal Right-Hippocampus	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala ctx-lh-entorhinal Right-Hippocampus

Using K-fold Cross-Validation

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-rh-entorhinal Right-Amygdala ctx-lh-entorhinal	Left-Hippocampus ctx-rh-entorhinal Right-Amygdala Left-Amygdala ctx-lh-inferiorparietal ctx-lh-middletemporal	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-lh-entorhinal ctx-rh-entorhinal ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-rh-entorhinal ctx-lh-entorhinal Right-Amygdala	Right-Hippocampus Left-Hippocampus ctx-rh-entorhinal Right-Amygdala Left-Amygdala ctx-lh-middletemporal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal ctx-lh-entorhinal Right-Hippocampus ctx-rh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal ctx-lh-entorhinal ctx-lh-inferiortemporal Left-Amygdala ctx-lh-middletemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal	Left-Hippocampus Right-Amygdala Left-Amygdala ctx-rh-entorhinal ctx-lh-middletemporal ctx-lh-entorhinal
Total execution time for Leave-One-Out: **23.73 minutes**			

Using Leave-One-Out Cross-Validation

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal Right-Hippocampus Right-Amygdala ctx-lh-inferiortemporal	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala Right-Amygdala ctx-lh-inferiorparietal Right-Hippocampus	Left-Hippocampus ctx-lh-entorhinal Left-Amygdala Right-Hippocampus ctx-lh-inferiortemporal Right-Amygdala
Younger age group Ages 69-76	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-rh-entorhinal Right-Amygdala ctx-rh-middletemporal	Right-Hippocampus Left-Hippocampus ctx-rh-entorhinal Right-Amygdala ctx-rh-supramarginal Left-Amygdala	Left-Hippocampus ctx-lh-middletemporal Left-Amygdala Right-Hippocampus ctx-lh-inferiortemporal ctx-rh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal ctx-lh-middletemporal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-rh-entorhinal ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-lh-supramarginal	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal ctx-lh-middletemporal Right-Hippocampus
Total execution time for Stratified K-fold: **1.34 minutes** (80.67 seconds)			

Using Stratified K-fold Cross-Validation

- Next step: Evaluate consistency of top features by checking overlap across three tables (54 features each)

Consistent Top Contributing Features

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

Consistent Top Contributing Features using K-fold, Stratified K-fold, and Leave-One-Out Cross-Validation

- 39 overlapping features
- Consistency score = 39/55 =72.22%

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

Consistent Top Contributing Features using K-fold, Stratified K-fold, and Leave-One-Out Cross-Validation

- Both sex- and age-specific predictors:

- Sex-specific predictors:

- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

Consistent Top Contributing Features using K-fold, Stratified K-fold, and Leave-One-Out Cross-Validation

- Both sex- and age-specific predictors:
  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
- Sex-specific predictors:
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

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  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
  - Right Amygdala – across younger males and older females
- Sex-specific predictors:
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

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  - Right Amygdala – across younger males and older females
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

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  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
  - Right Amygdala – across younger males and older females
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
  - ctx-lh-middletemporal is female-specific
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

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  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
  - Right Amygdala – across younger males and older females
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
  - ctx-lh-middletemporal is female-specific
  - ctx-rh-entorhinal is male-specific
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

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- Both sex- and age-specific predictors:
  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
  - Right Amygdala – across younger males and older females
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
  - ctx-lh-middletemporal is female-specific
  - ctx-rh-entorhinal is male-specific
  - ctx-lh-inferiorparietal is male-specific
- Age-specific predictors:

Neuroanatomical trends observed in AD

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus Left-Amygdala Right-Amygdala ctx-rh-entorhinal Right-Hippocampus	Left-Hippocampus Left-Amygdala ctx-rh-entorhinal ctx-lh-inferiorparietal	Left-Hippocampus Left-Amygdala Right-Hippocampus ctx-lh-entorhinal
Younger age group Ages 69-76	Left-Hippocampus Right-Hippocampus Left-Amygdala ctx-rh-entorhinal	Right-Hippocampus Left-Hippocampus Right-Amygdala ctx-rh-entorhinal Left-Amygdala	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal
Older age group Ages 77-84	Left-Hippocampus ctx-rh-entorhinal Left-Amygdala ctx-lh-entorhinal ctx-lh-inferiortemporal	Left-Hippocampus Left-Inf-Lat-Vent ctx-lh-inferiortemporal ctx-lh-entorhinal ctx-rh-entorhinal	Left-Hippocampus Left-Amygdala ctx-lh-middletemporal Right-Amygdala

Consistent Top Contributing Features using K-fold, Stratified K-fold, and Leave-One-Out Cross-Validation

- Both sex- and age-specific predictors:
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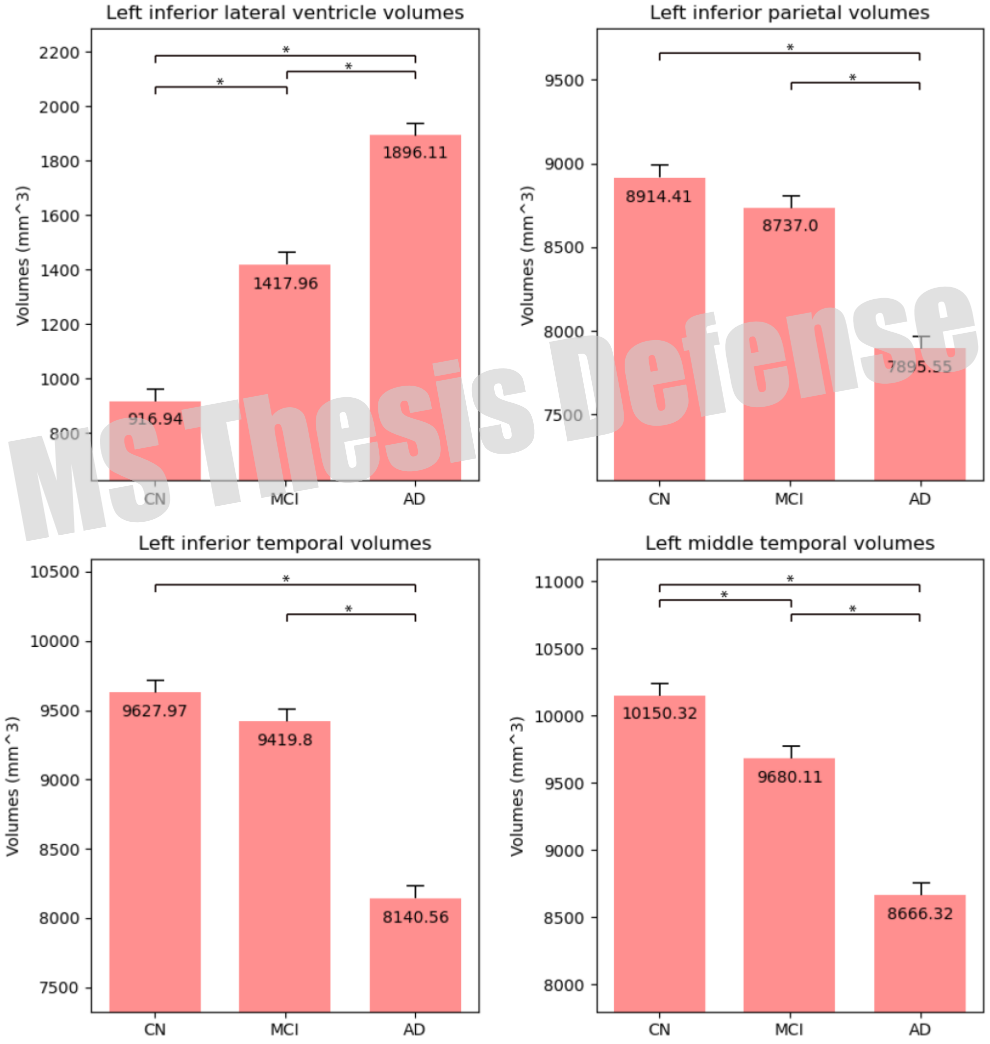
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
  - ctx-lh-middletemporal is female-specific
  - ctx-rh-entorhinal is male-specific
  - ctx-lh-inferiorparietal is male-specific
- Age-specific predictors:
  - ctx-lh-entorhinal – across older males

Ventricular Enlargement and Cortical Atrophy

Average volumes of Left Inferior Lateral Ventricle, left inferior parietal cortex, left inferior temporal cortex, and left middle temporal cortex in CN, MCI, and AD subjects. Statistical significance is marked with * ($p < 0.01$).



- Both sex- and age-specific predictors:
  - ctx-lh-inferiortemporal and Left-Inf-Lat-Vent is male-specific in the older age group
- Sex-specific predictors:
  - ctx-lh-middletemporal is female-specific
  - ctx-lh-inferiorparietal is male-specific

Identifying AD's Highest-Ranking Brain Regions

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	Left-Amygdala	Left-Amygdala	Left-Amygdala
	Right-Amygdala	ctx-rh-entorhinal	Right-Hippocampus
	ctx-rh-entorhinal	ctx-lh-inferiorparietal	ctx-lh-entorhinal
	Right-Hippocampus	Right-Hippocampus	ctx-lh-inferiortemporal
	ctx-lh-inferiortemporal	ctx-lh-middletemporal	ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus	Right-Hippocampus	Left-Hippocampus
	Right-Hippocampus	Left-Hippocampus	Left-Amygdala
	Left-Amygdala	Right-Amygdala	ctx-lh-parahippocampal
	ctx-lh-entorhinal	ctx-rh-entorhinal	ctx-lh-middletemporal
	ctx-rh-entorhinal	Left-Amygdala	ctx-lh-entorhinal
	ctx-rh-middletemporal	ctx-lh-inferiorparietal	ctx-lh-inferiortemporal
Older age group Ages 77-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	ctx-rh-entorhinal	Left-Inf-Lat-Vent	Left-Amygdala
	Left-Amygdala	ctx-lh-inferiortemporal	ctx-lh-middletemporal
	ctx-lh-entorhinal	ctx-lh-entorhinal	Right-Amygdala
	ctx-lh-inferiortemporal	ctx-rh-entorhinal	ctx-lh-entorhinal
	Right-Hippocampus	Left-Amygdala	Right-Hippocampus

Using K-fold Cross-Validation

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	Left-Amygdala	ctx-rh-entorhinal	Right-Hippocampus
	Right-Hippocampus	Right-Amygdala	Left-Amygdala
	ctx-rh-entorhinal	Left-Amygdala	ctx-lh-entorhinal
	Right-Amygdala	ctx-lh-inferiorparietal	ctx-rh-entorhinal
	ctx-lh-entorhinal	ctx-lh-middletemporal	ctx-lh-middletemporal
Younger age group Ages 69-76	Left-Hippocampus	Right-Hippocampus	Left-Hippocampus
	Left-Amygdala	Left-Hippocampus	Left-Amygdala
	Right-Hippocampus	ctx-rh-entorhinal	ctx-lh-middletemporal
	ctx-rh-entorhinal	Right-Amygdala	ctx-lh-entorhinal
	ctx-lh-entorhinal	Left-Amygdala	Right-Hippocampus
	Right-Amygdala	ctx-lh-middletemporal	ctx-rh-middletemporal
Older age group Ages 77-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	ctx-rh-entorhinal	Left-Inf-Lat-Vent	Right-Amygdala
	ctx-lh-entorhinal	ctx-lh-inferiortemporal	Left-Amygdala
	ctx-lh-inferiortemporal	ctx-rh-entorhinal	ctx-rh-entorhinal
	Left-Amygdala	Left-Amygdala	ctx-lh-middletemporal
	ctx-lh-middletemporal	ctx-lh-entorhinal	ctx-lh-entorhinal
Total execution time for Leave-One-Out: **23.73 minutes**			

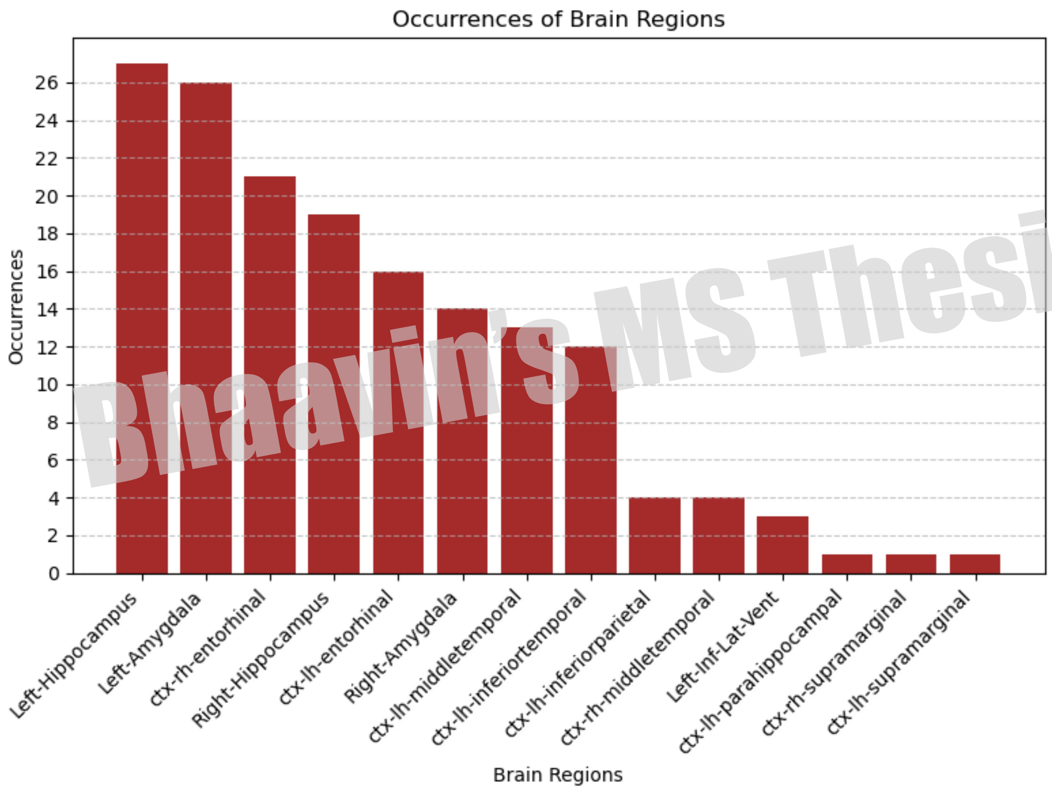
Using Leave-One-Out Cross-Validation

Groups	Unified Sex (M+F)	Males (M)	Females (F)
Unified age group Ages 69-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	Left-Amygdala	ctx-rh-entorhinal	ctx-lh-entorhinal
	ctx-rh-entorhinal	Left-Amygdala	Left-Amygdala
	Right-Hippocampus	Right-Amygdala	Right-Hippocampus
	Right-Amygdala	ctx-lh-inferiorparietal	ctx-lh-inferiortemporal
	ctx-lh-inferiortemporal	Right-Hippocampus	Right-Amygdala
Younger age group Ages 69-76	Left-Hippocampus	Right-Hippocampus	Left-Hippocampus
	Left-Amygdala	Left-Hippocampus	ctx-lh-middletemporal
	Right-Hippocampus	ctx-rh-entorhinal	Left-Amygdala
	ctx-rh-entorhinal	Right-Amygdala	Right-Hippocampus
	Right-Amygdala	ctx-rh-supramarginal	ctx-lh-inferiortemporal
	ctx-rh-middletemporal	Left-Amygdala	ctx-rh-middletemporal
Older age group Ages 77-84	Left-Hippocampus	Left-Hippocampus	Left-Hippocampus
	ctx-rh-entorhinal	Left-Inf-Lat-Vent	Left-Amygdala
	ctx-lh-middletemporal	ctx-rh-entorhinal	Right-Amygdala
	Left-Amygdala	ctx-lh-inferiortemporal	ctx-rh-entorhinal
	ctx-lh-entorhinal	ctx-lh-entorhinal	ctx-lh-middletemporal
	ctx-lh-inferiortemporal	ctx-lh-supramarginal	Right-Hippocampus
Total execution time for Stratified K-fold: **1.34 minutes** (80.67 seconds)			

Using Stratified K-fold Cross-Validation

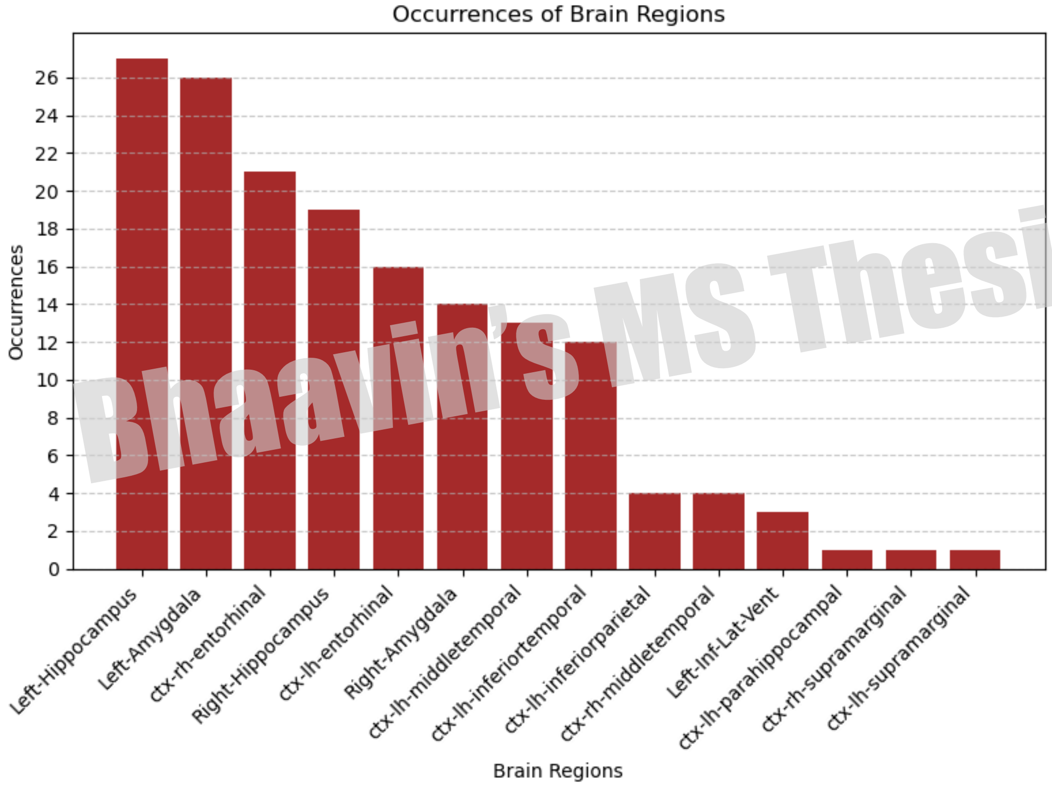
- Left Amygdala occurs 26 times across the three validation techniques

Identifying AD's Highest-Ranking Brain Regions

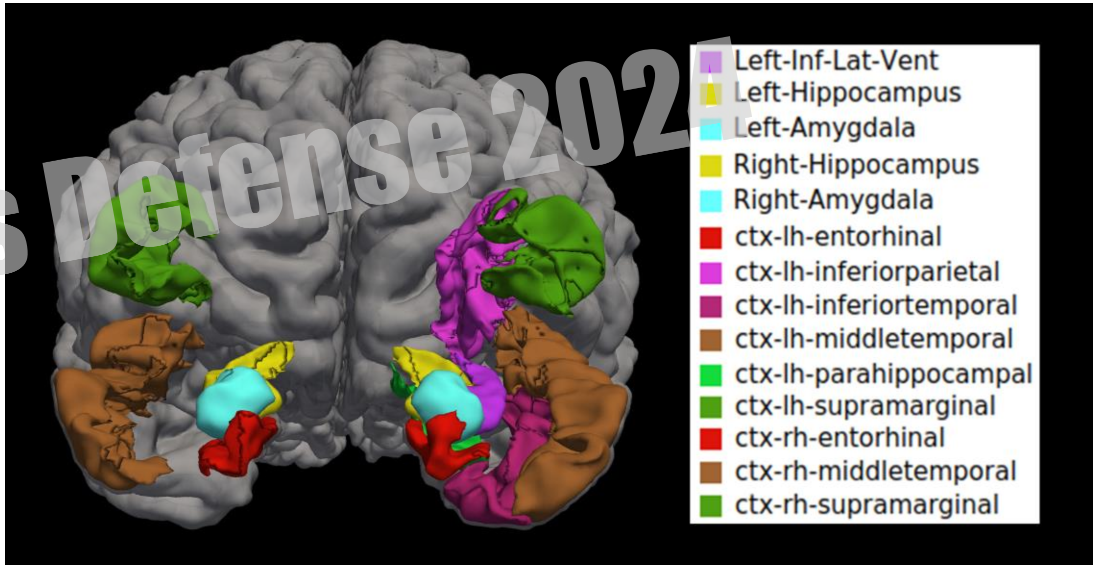


All occurrences of brain regions that drive AD across nine subgroups using a combination of three validation techniques

Identifying AD's Highest-Ranking Brain Regions

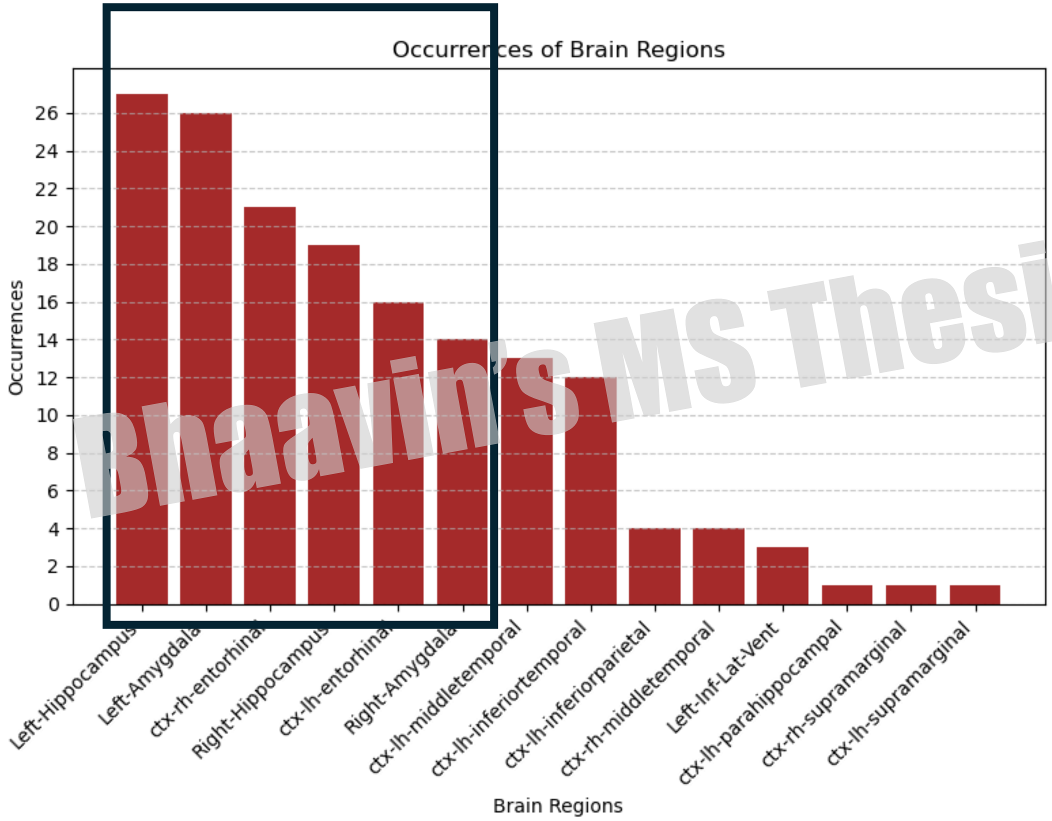


All occurrences of brain regions that drive AD across nine subgroups using a combination of three validation techniques

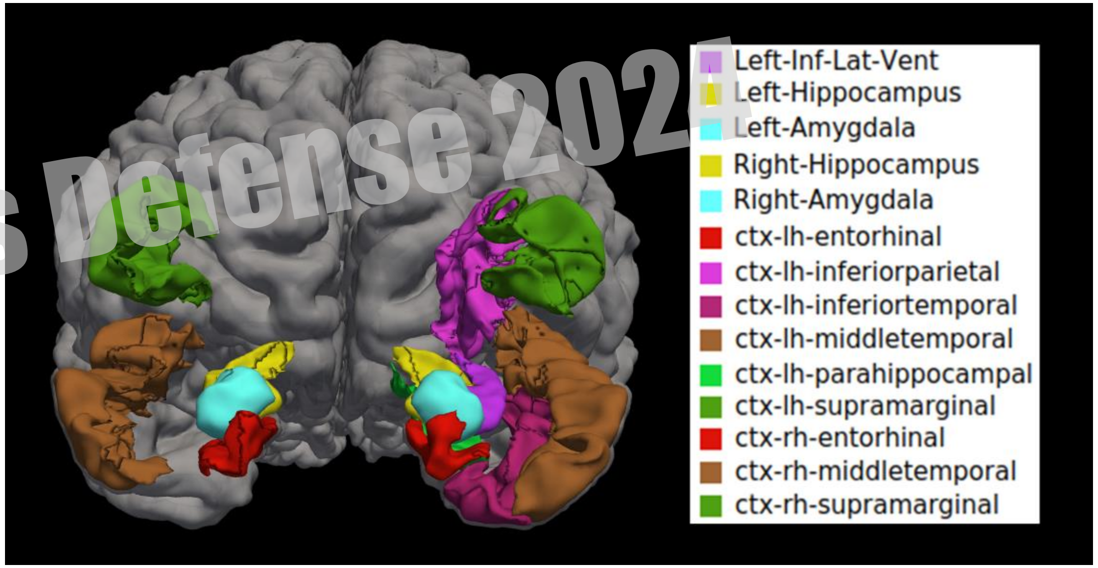


Visualization of unique brain regions that undergo substantial structural changes in Alzheimer's Disease across subgroups and validation techniques using FreeSurfer's Freeview

Identifying AD's Highest-Ranking Brain Regions

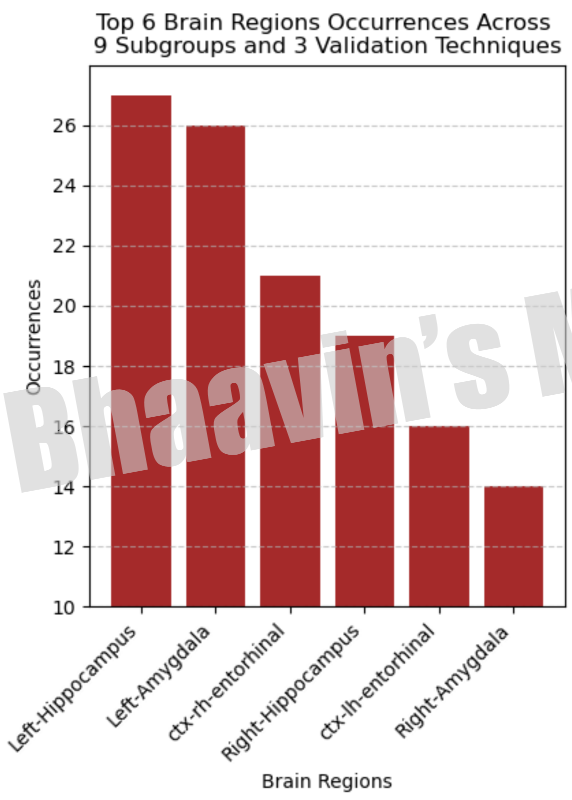


All occurrences of brain regions that drive AD across nine subgroups using a combination of three validation techniques

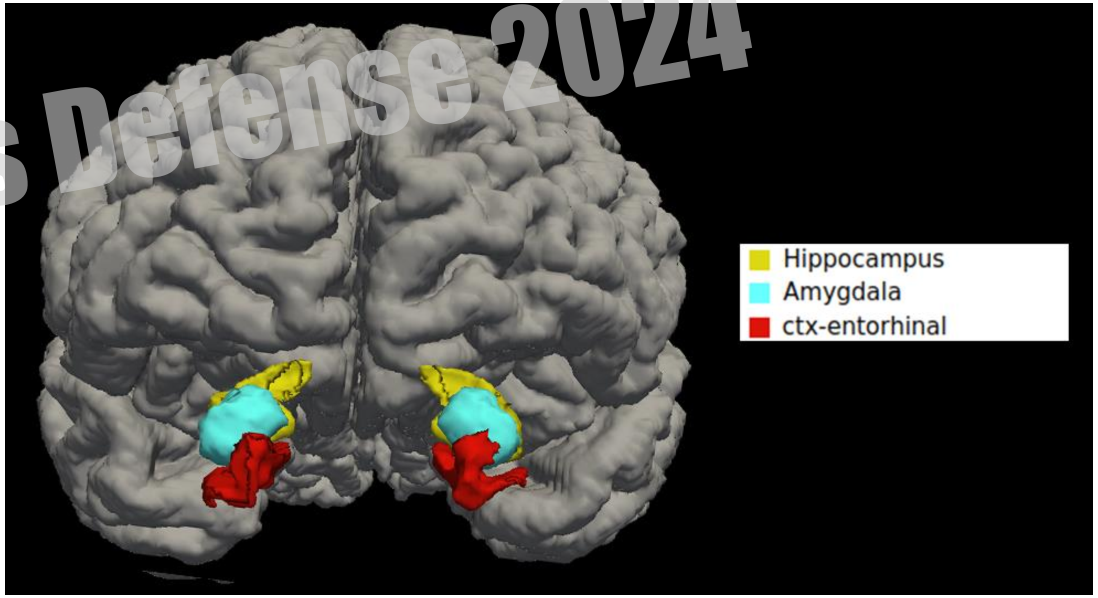


Visualization of unique brain regions that undergo substantial structural changes in Alzheimer's Disease across subgroups and validation techniques using FreeSurfer's Freeview

Identifying AD's Highest-Ranking Brain Regions

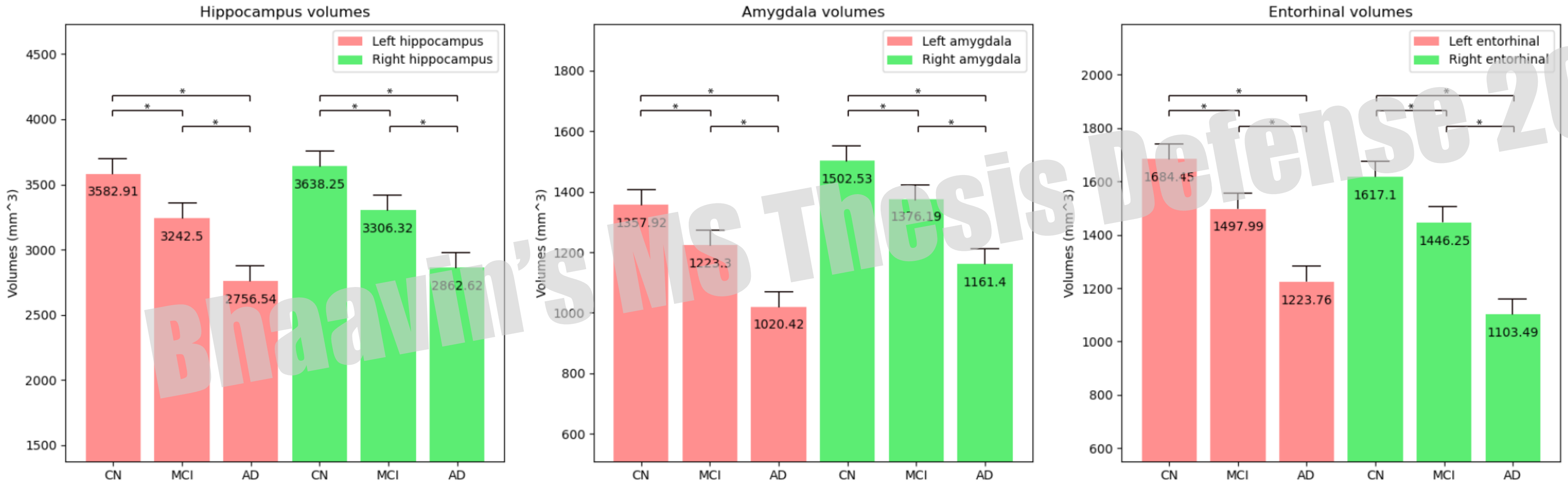


Top 6 occurrences of brain regions



Visualization of top 6 brain regions - the hippocampus, amygdala, and entorhinal cortex on Freeview

Identifying AD’s Highest-Ranking Brain Regions



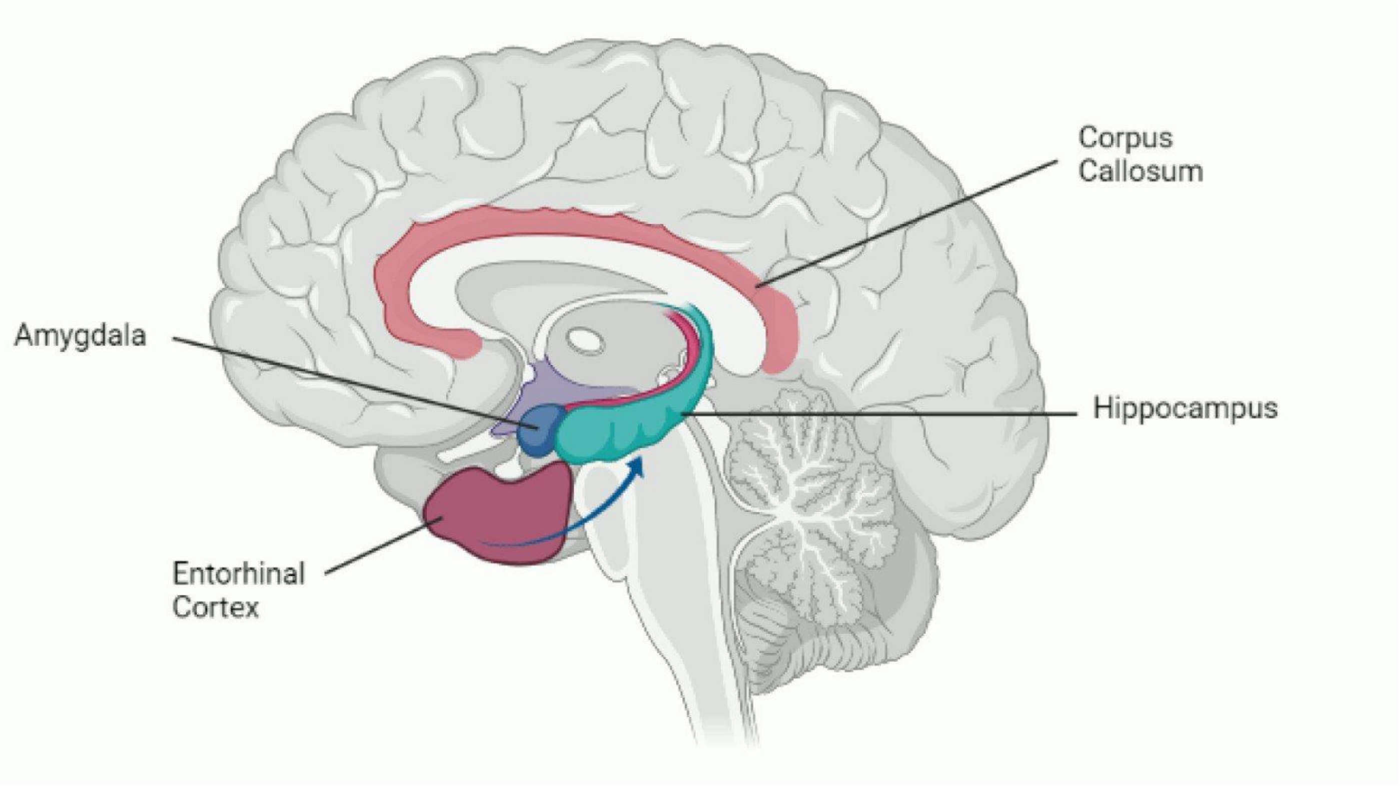
Average volumes of left and right hippocampus, amygdala, and entorhinal cortex in CN, MCI, and AD subjects. Statistical significance is marked with * ($p < 0.01$)

- Both sex- and age-specific predictors:
  - The Left Hippocampus and Left Amygdala - across both sexes and both age groups
  - Right Amygdala – across younger males and older females
- Sex-specific predictors:
  - ctx-rh-entorhinal is male-specific
- Age-specific predictors:
  - ctx-lh-entorhinal – across older males

Roles of AD’s Highest-Ranking Brain Regions

Hippocampus

- Key for learning & memory [5, 6]
- In AD:
  - Early tissue loss, disconnection from other brain regions [7]
  - Leads to memory loss, cognitive decline

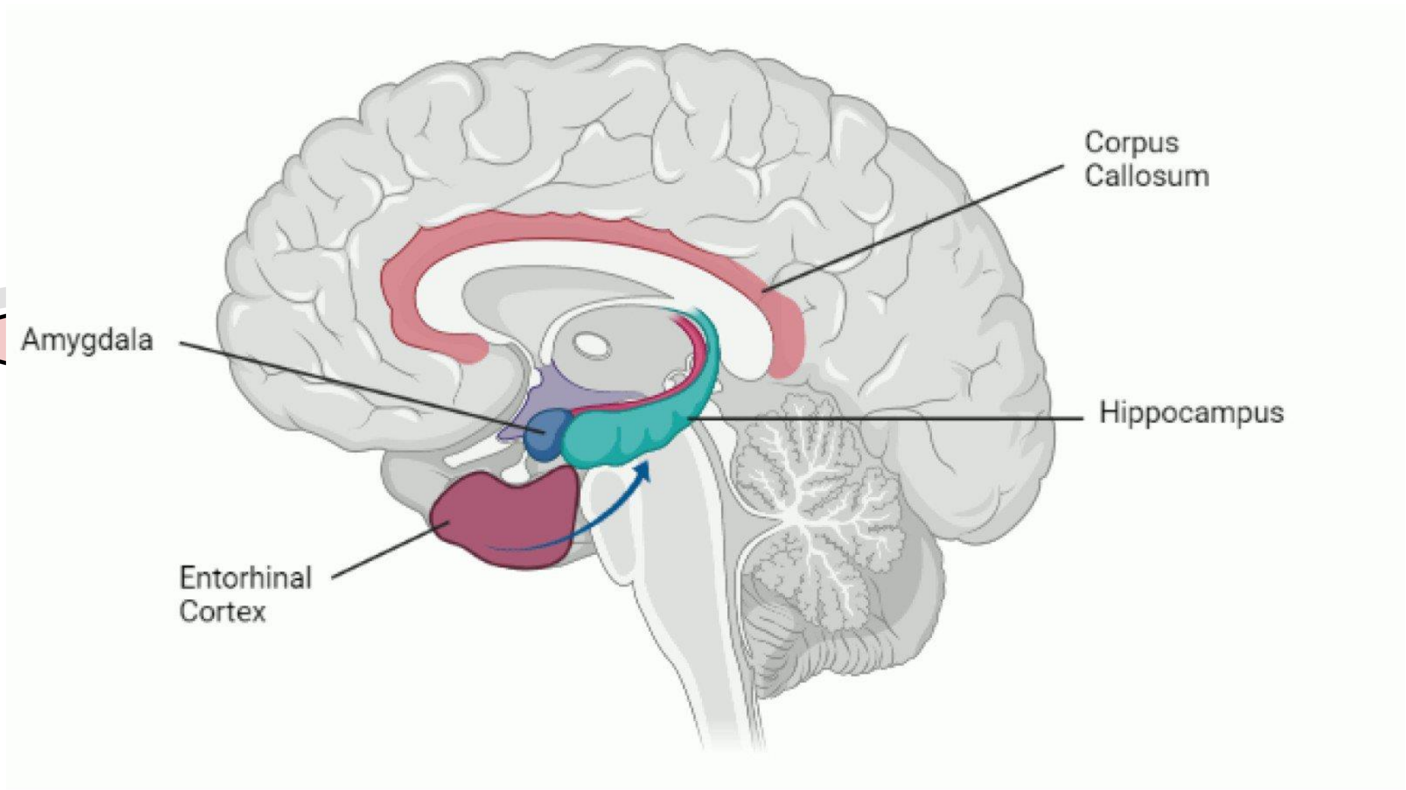


Hippocampus, Amygdala, and Entorhinal Cortex [8]

Roles of AD’s Highest-Ranking Brain Regions

Amygdala

- Processes emotions
- In AD:
  - Early changes cause personality changes, anxiety, irritability [9]
  - 80% experience hallucinations, delusions [10,11]

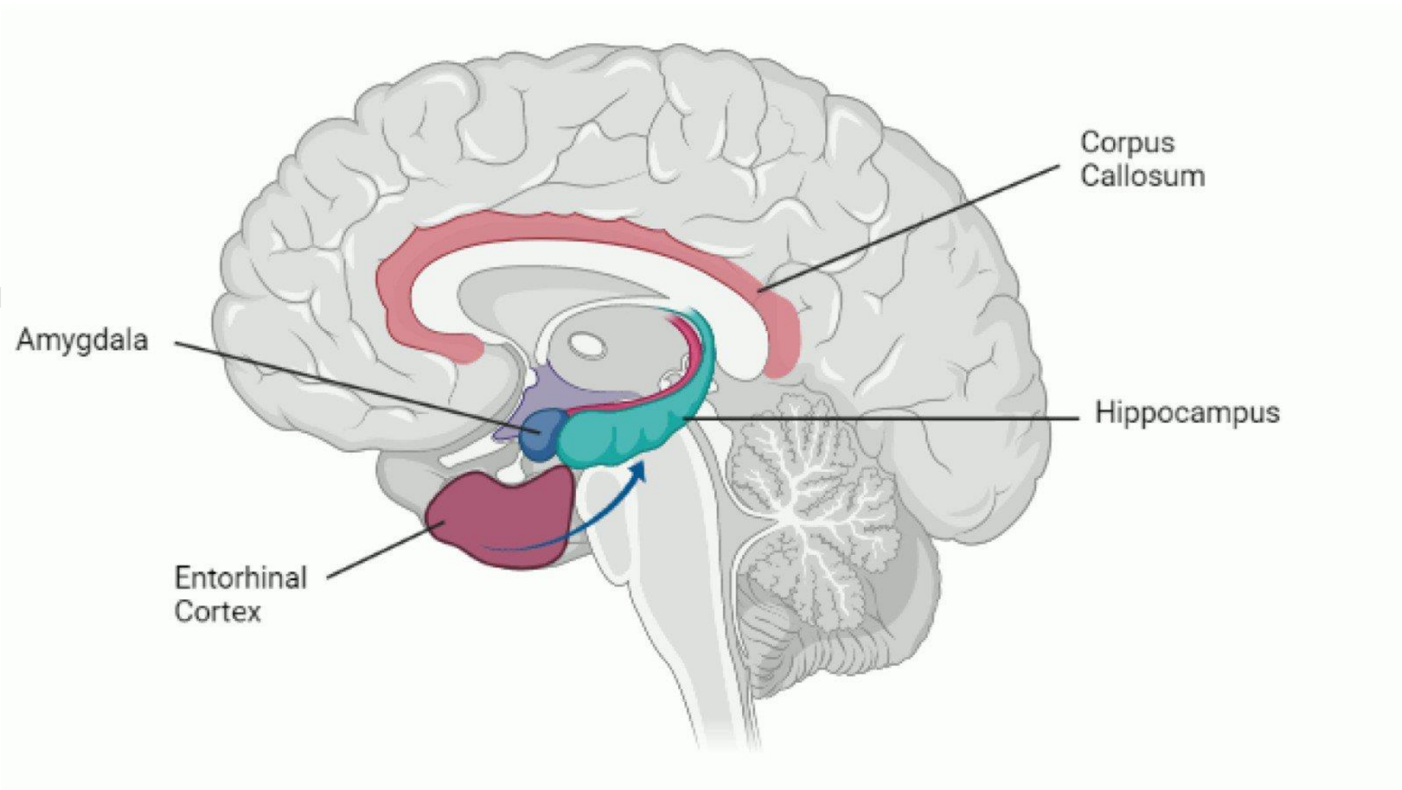


Hippocampus, Amygdala, and Entorhinal Cortex [8]

Roles of AD's Highest-Ranking Brain Regions

Entorhinal Cortex

- Hub for sensory info, memory consolidation [12]
- In AD:
  - Initial point for abnormal protein deposits [13]
  - Leads to memory decline, spatial navigation issues



Hippocampus, Amygdala, and Entorhinal Cortex [8]

Medications for AD

- Two categories of drugs:
  - Disease-modifying drugs
    - Lecanemab
    - Kisunla
    - Side effects: Brain swelling, nausea, difficulty walking

- Symptomatic Medications
  - Cholinesterase inhibitors
    - Donepzil
    - Galantamine
    - Side effects: nausea, diarrhea, muscle cramps, weight loss
  - Glutamate regulator: Memantine, protects nerve cells from excessive activity
    - Side effects: dizziness, agitation

How do our results align with these medications?

Treatments for AD

- Robots in Neuroscience
  - Transcranial Magnetic Stimulation (TMS),
  - Transcranial Direct Current Stimulation (tDCS)
  - Both stimulate neural activity to improve brain function in AD patients
  - Still in research phase

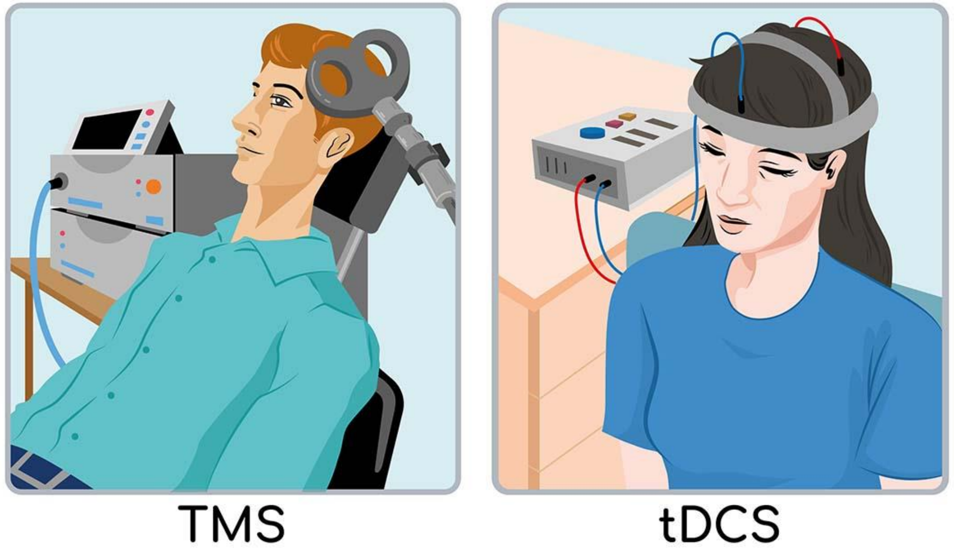


Image source: https://caputron.com/pages/tms-vs-tdcs

Risks and Prevention of AD

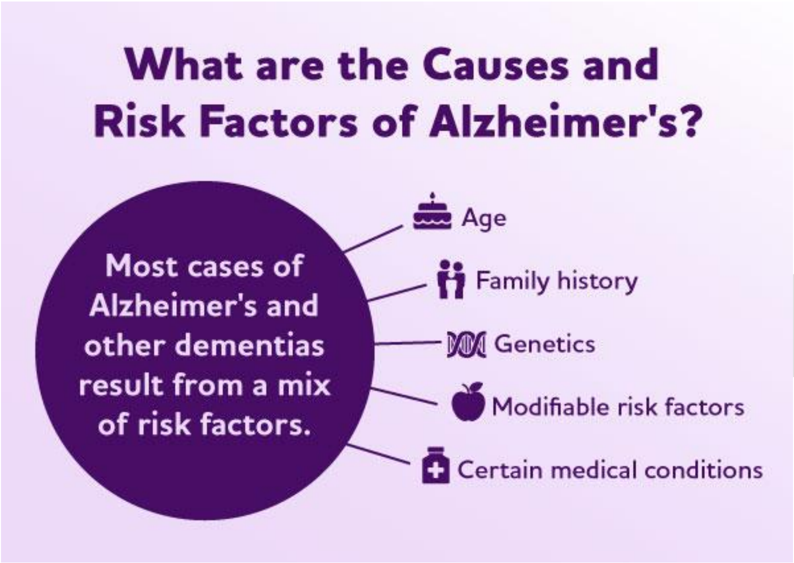
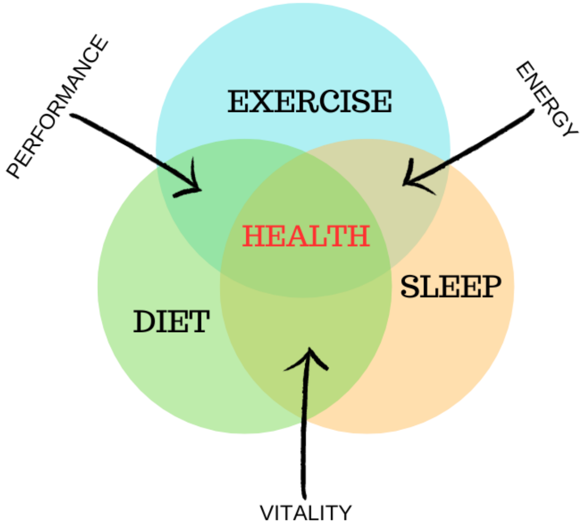


Image source: Alzheimer's Association



Lifestyle Strategies for Slowing Alzheimer’s. Image source: Thrivology

Challenges Faced

- Clinica and Heudiconv tool for automating image preprocessing
- Limited data
- IndexError during volume extraction

(a) (b)

Comparison of a discarded scan with a high-quality scan. (a) Defaced scan with missing brain regions. (b) High-quality scan.

Future work

- Exploring other subgroups:
  - Ethnicity and race
  - Socioeconomic status
  - Comorbidity profiles
    - Exploring link between Anxiety and Alzheimer's Disease
      - Potential issue: limited access to comprehensive comorbid dataset
- Integrating deep learning methods with the Random Forest Classifier
  - Potential issue: model complexity and may require more computational resources
- Develop a clinical tool to identify specific regions that drive AD progression in an individual's brain
  - Potential issue: navigating clinical validation and regulatory approval processes

Summary

ADNI preprocessed scans

	N	Sex (F:M)	Age (years)
CN	281	171:110	73.7-81.0
MCI	332	104:228	71.6-83.0
AD	202	108:94	69.4-83.6
	815	**383:432**	**69.4-83.6**

Brain parcellation

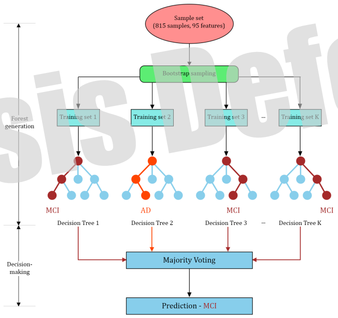
Measure: volume	Brain region #1	Brain region #2	Brain region #...	Brain region #95
subject_1	20442.213	3406.848	##	1471.716
subject_2	20664.388	3490.035	##	1426.638
subject_..	##	##	##	##
subject_815	19909.568	3246.525	##	1321.207

Volume extraction

Prepared dataset for ML

Normalization
SMOTE
Statistical testing

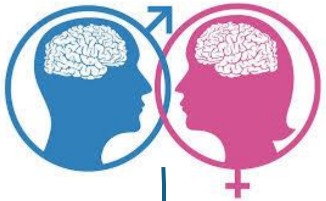
RF based AD prediction



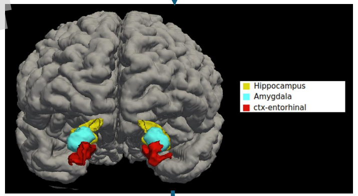
Model performance

Accuracy = 92.87%

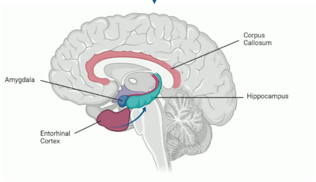
Neuroanatomical trends in AD



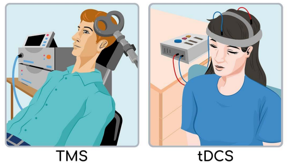
Top ranked Brain regions



Roles of top regions



Treatments for AD



Conclusions

- High-performance Random Forest model
- Top 3 brain regions affected in AD: hippocampus, amygdala, entorhinal cortex
- Potential female-specific influence: left middle temporal cortex
- Potential male-specific impact: right entorhinal cortex
- Age and sex differences could guide future research and treatments

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Thank you for your time!

Neuroanatomical-Based Machine Learning Prediction of Alzheimer's Disease Across Sex and Age

Bhaavin Kishore Jogeshwar

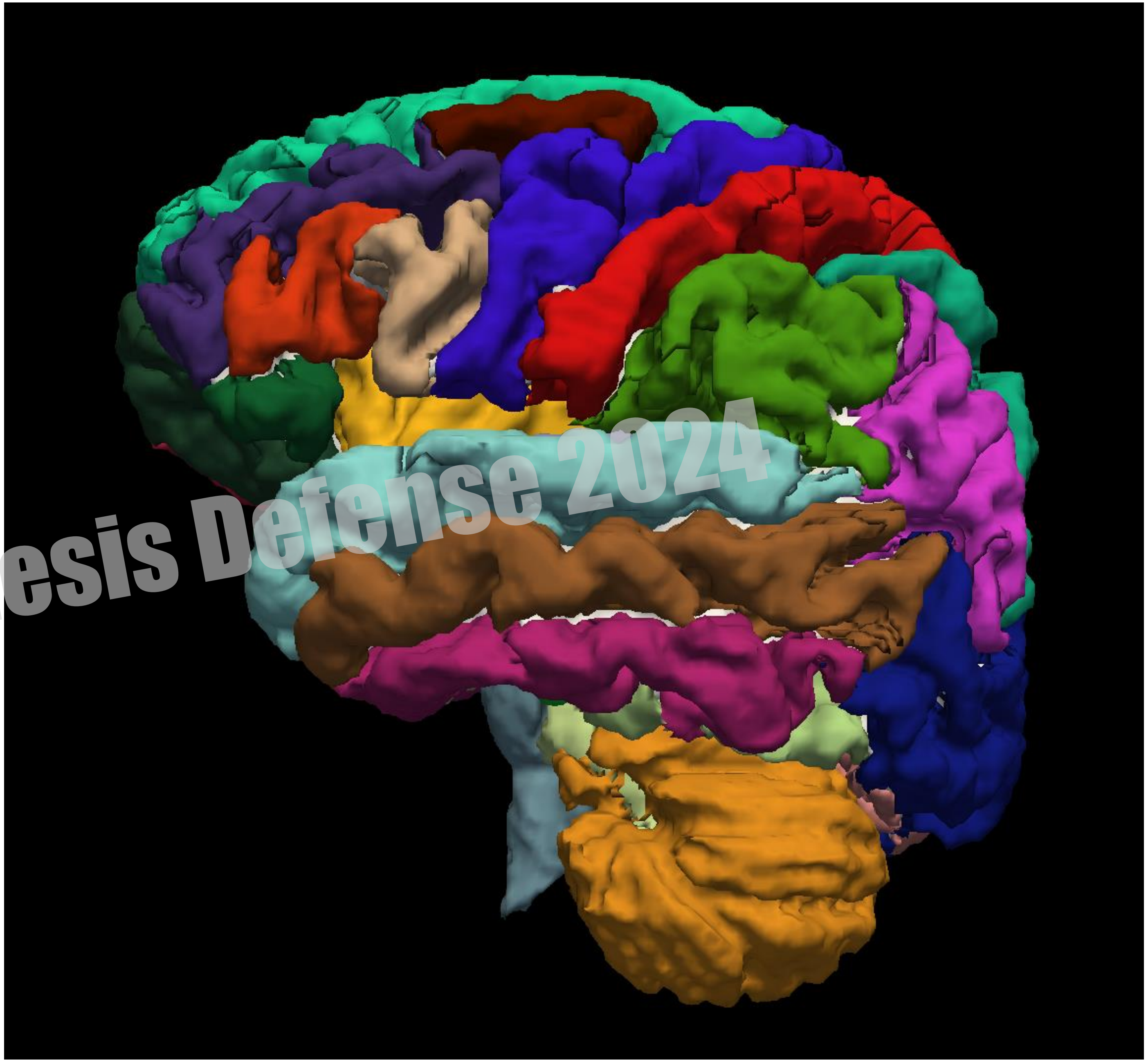
Advised by

Prof. Benjamin Nephew[a]

Prof. Loris Fichera[b]

[a]Biology & Biotechnology Department

[b]Robotics Engineering Department



Lateral view of the brain

WPI