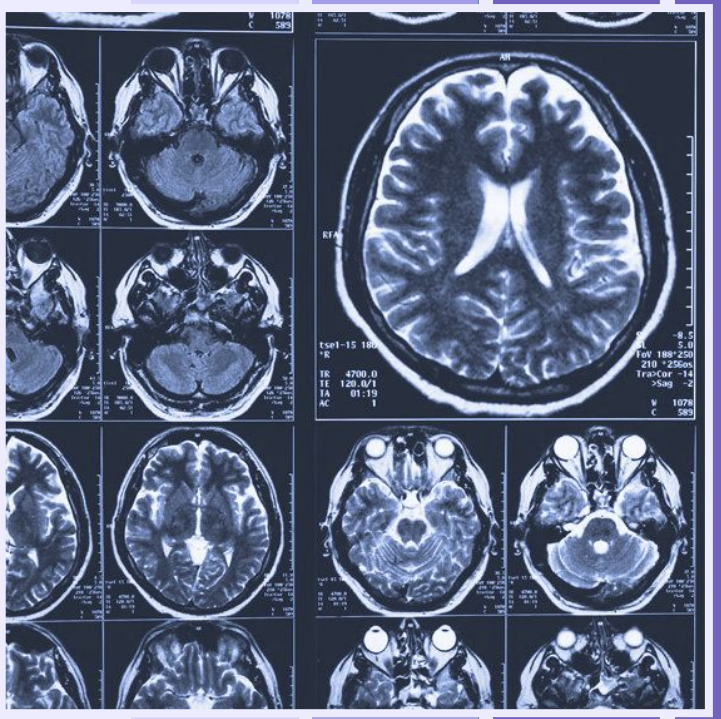
Alzheimer's Progression Digital Twin

Predicting Brain Atrophy Using Machine Learning on MRI Data

By: Evani Menon, Manojna Reddy Kamaram, Diksha Kaushik, Palak, Ishaan Arora, Isobel Kuriyan

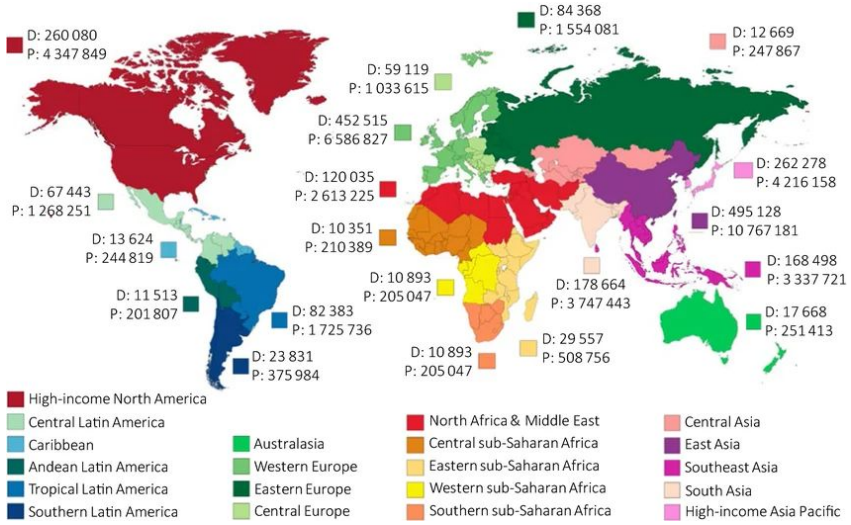


The Alzheimer’s Crisis

- **50-90%** of Alzheimer's cases remain **undiagnosed**
- Disease **progresses silently** for **10-20 years** before symptoms
- Current tools **cannot predict individual patient trajectories**
- By the time diagnosis occurs, interventions are less effective

Why This Matters:

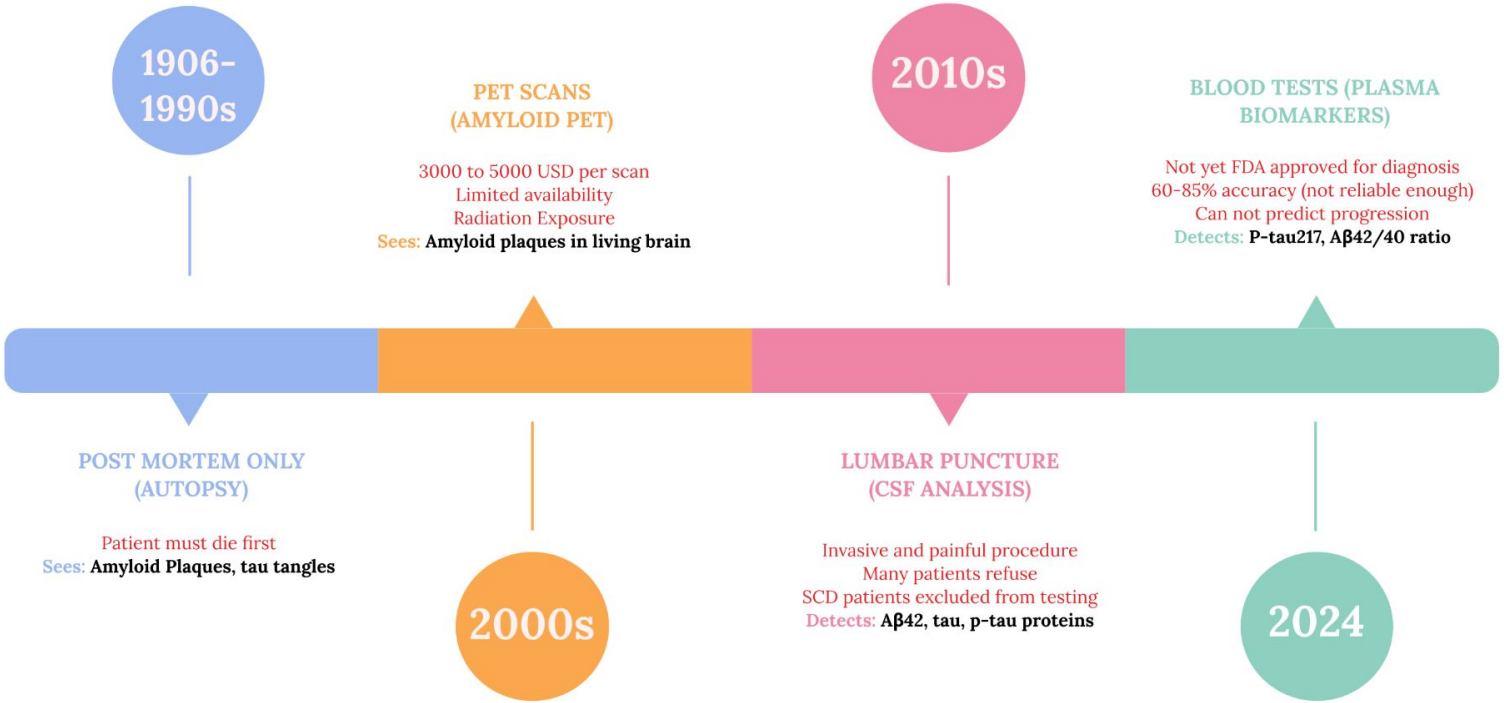
- Over 55 million people worldwide have dementia, **60-70%** being **Alzheimer's** (140M globally by 2050)
- Early diagnosis could reduce number of cases and treatment costs
- Need: **Non-invasive tool to predict who will decline and when**



Global deaths (D) and prevalence (P) for Alzheimer’s disease and other dementias in 2016. Data are n (95% UI). UI = uncertainty interval.

Data extracted from the Global Burden of Disease Study of Alzheimer’s disease and other dementias 2016

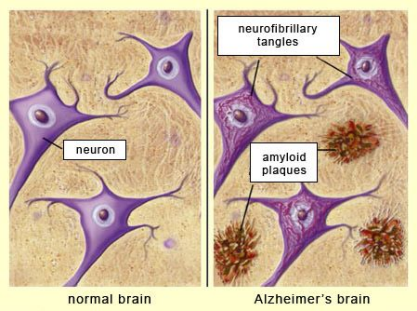
The Evolution of Alzheimer's Diagnosis:



What these Tests Look for:

Amyloid-β Plaques

• Sticky protein clumps between neurons
• Disrupt cell communication
• Detected by: PET scan, CSF, blood test



Neuroinflammation

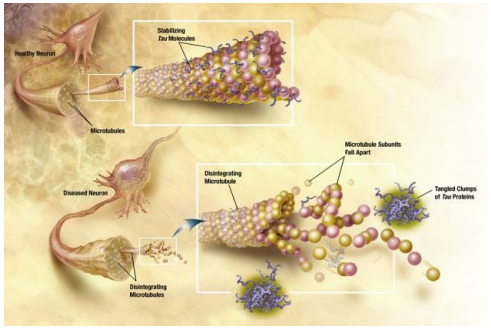
• Brain's immune response
• Causes further damage
• Detected by: PET scan, CSF

Metabolic Changes

• Reduced glucose use in brain
• Neurons can't produce energy
• Detected by: FDG-PET scan

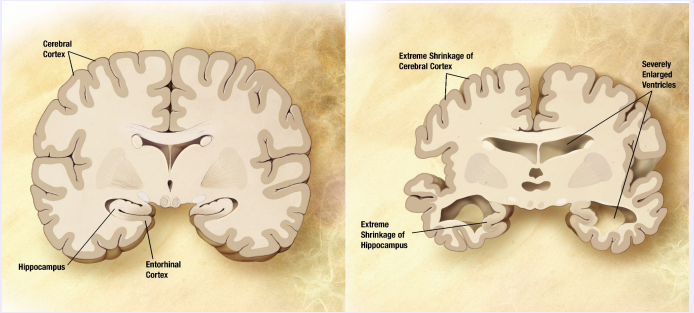
Tau Tangles (Neurofibrillary Tangles)

• Twisted protein fibers inside neurons that kill brain cells
• Detected by: CSF, blood test (p-tau)



Brain Atrophy (Shrinkage)

• Hippocampus shrinks first (memory center)
• Ventricles expand (fluid-filled spaces)
• Cortex thins (outer brain layer)
• Detected by: MRI, PET scan



Digital Twin Concept

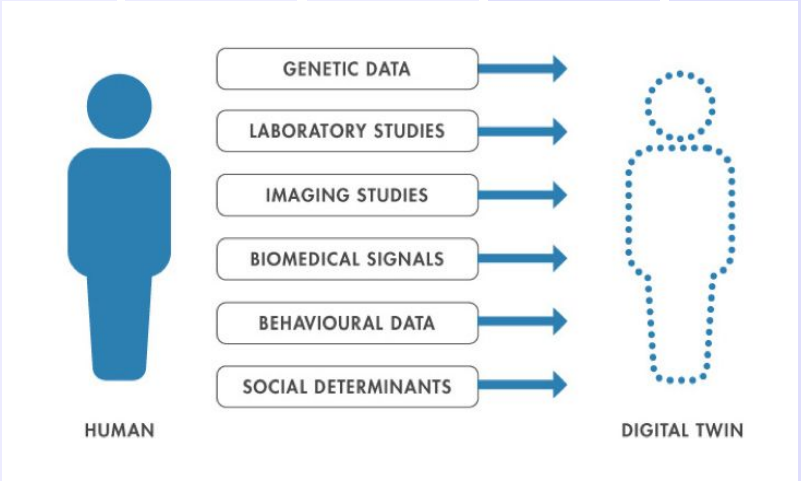
A Digital Twin is a virtual representation that predicts how a real-world system will change over time

We're building a machine learning model that:

- Analyzed longitudinal MRI + clinical data
- Learns from historical patterns and predicts future disease progression (personalized prediction)
- Forecasts cognitive decline 12-24 months ahead
- Visualizes personal model of atrophy patterns in patient's brain
- Simulates "what-if" scenarios

The gap our project fills:

- Non-invasive (just MRI- already standard)
- Predicts future progression (not just diagnosis)
- Shows WHERE brain will atrophy
- Accessible and affordable



Digital Twins in Alzheimer’s Research

PREVIOUS WORK

RECENT BREAKTHROUGH **(January 2025) Amato et al.**
(Proves digital twins work for Alzheimer's and why our project is relevant)

- **EEG-based Digital Twin** (https://pmc.ncbi.nlm.nih.gov/articles/PMC12125947/)
- Uses brainwave recordings (EEG)
- Predicts CSF biomarkers
- Functional brain activity analysis

OUR WORK AND HOW IT’S DIFFERENT

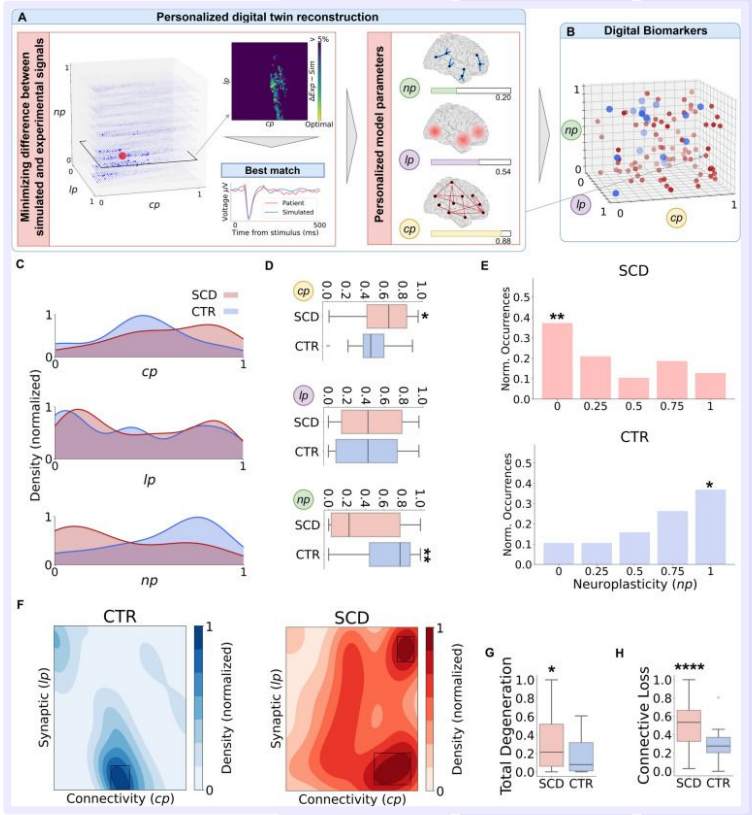
MRI-based Structural Digital Twin

- Uses brain imaging (MRI)
- Predicts brain atrophy patterns
- Structural anatomy analysis

Complementary approach - predicts **WHERE** brain will shrink

COMBINED FUTURE

Recent work showed EEG-based twins can predict disease markers. We're tackling the structural side - predicting actual brain anatomy changes. These approaches complement each other.



RID	VISCODE	MMSE	DX	Hippocampus	Gender	Education	APOE4	visit_num
4.0	m12	26.0	MCI	6166.0	Male	10.0	0.0	2.0
4.0	m18	27.0	MCI	6057.0	Male	10.0	0.0	3.0
4.0	m36	25.0	MCI	5986.0	Male	10.0	0.0	5.0
5.0	bl	29.0	CN	6546.0	Male	16.0	0.0	0.0
5.0	m06	29.0	CN	6356.0	Male	16.0	0.0	1.0
5.0	m12	30.0	CN	6454.0	Male	16.0	0.0	2.0
5.0	m24	29.0	CN	6203.0	Male	16.0	0.0	4.0
5.0	m36	30.0	CN	6038.0	Male	16.0	0.0	5.0
6.0	bl	25.0	MCI	5004.0	Female	13.0	0.0	0.0
6.0	m06	21.0	MCI	4995.0	Female	13.0	0.0	1.0
6.0	m12	26.0	MCI	4930.0	Female	13.0	0.0	2.0
6.0	m18	24.0	MCI	4831.0	Female	13.0	0.0	3.0
6.0	m24	26.0	MCI		Female	13.0	0.0	4.0
6.0	m36	22.0	MCI	4627.0	Female	13.0	0.0	5.0
7.0	bl	20.0	Dementia	6357.0	Male	10.0	1.0	0.0
7.0	m06	23.0	Dementia	6397.0	Male	10.0	1.0	1.0
7.0	m12	20.0	Dementia		Male	10.0	1.0	2.0
7.0	m24	20.0	Dementia	5889.0	Male	10.0	1.0	4.0
8.0	bl	28.0	CN	5511.0	Female	18.0	0.0	0.0
8.0	m06	29.0	CN	5549.0	Female	18.0	0.0	1.0
8.0	m12	28.0	CN		Female	18.0	0.0	2.0
8.0	m36	29.0	CN		Female	18.0	0.0	5.0
8.0	m48	30.0	CN		Female	18.0	0.0	6.0
8.0	m60	28.0	CN		Female	18.0	0.0	7.0

Hippocampus values available for ~500 ADNI1 subjects"

Data Sources

PRIMARY DATASET: ADNI
(Alzheimer's Disease Neuroimaging Initiative)

WHAT WE ARE USING:

1) **MRI Scans (ADNI1 Collection)**
   Type: T1-weighted structural brain imaging
   Format: NIfTI (.nii.gz)
   Subjects: 200-300 patients (our target subjects out of ~5k) and 5 demo patients selected
   Timepoints: Baseline, 12mo, 24mo
   Size: ~50 GB (for 200-300 subjects x 3 timepoints)

2) **Clinical Data (ADNIMERGE.csv)**
   MMSE cognitive test scores
   Demographics (age, gender, education)
   APOE4 genetic risk factors
   Brain volume measurements
   Diagnosis labels (CN, MCI, AD)

DATA ACCESS:
Access approved for ADNI usage
Download via ADNI portal: adni.loni.usc.edu
All data is de-identified (HIPAA compliant)

Understanding our Data

MMSE score

Mini Mental State Exam. A 30-point cognitive test. A patient scoring 28 today might score 22 in a year.

This is the **primary prediction target** that the LSTM is trying to forecast.

Diagnosis (CN/MCI/Dementia)

CN = Cognitively Normal
MCI = Mild Cognitive Impairment
Dementia = Alzheimer's
This is used for classification tasks and for picking demo patients

Hippocampus Volume

The hippocampus is the first brain region to physically shrink in Alzheimer's. A healthy adult has ~6,000mm^3 total. AD patients can drop to ~4,000mm^3.

This is the biomarker that we will **visualize shrinking in 3D.**

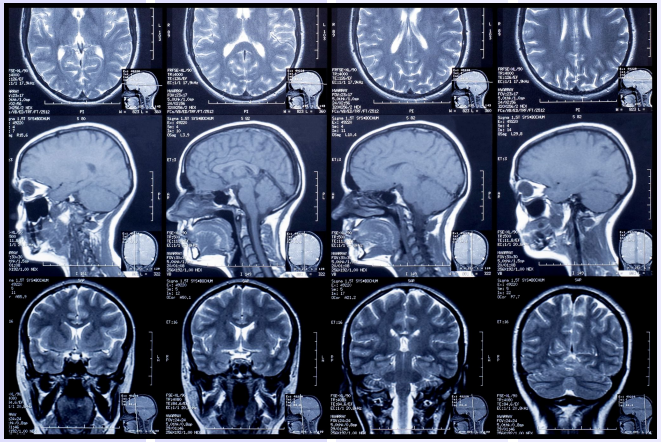
It's also a powerful model feature because physical atrophy often predicts cognitive decline before the patient even notices symptoms.

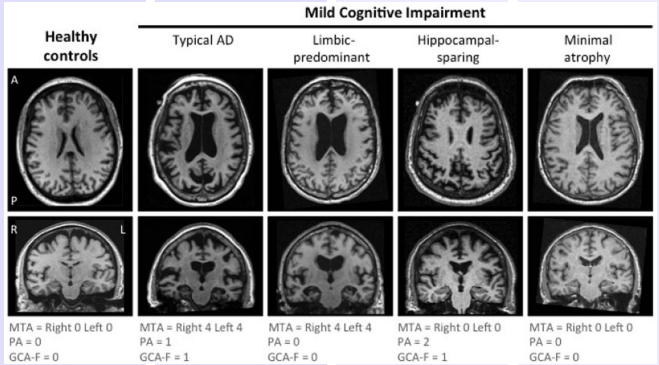
Gender & Education

Both affect baseline cognitive scores. Highly educated patients often "mask" early decline better, so their MMSE stays artificially high longer. Gender affects disease progression rate. Without these, the model could make systematically wrong predictions for certain subgroups.

APOE4

The strongest known **genetic risk factor** for Alzheimer's. Carrying one copy of the ε4 allele doubles your risk; two copies increases it 8–12x. It's a 0/1/2 number per patient that never changes. Including it lets our model adjust trajectory predictions based on genetic risk. A patient with APOE4=2 and MCI is very likely to convert to dementia; APOE4=0 is much less likely.





Project Impact

CLINICAL IMPACT:

- Early Detection Window: Predict 12-24 months ahead
- Enables intervention when treatments work best
- Could reduce AD cases

Non-Invasive Alternative to Lumbar Puncture

- 67% of clinics refuse CSF testing for SCD patients
- Our approach: Just MRI (already standard imaging)

Personalized Precision Medicine

- Not "you have Alzheimer's" but "here's YOUR timeline"
- Visualize WHERE your brain will atrophy
- Enables targeted intervention strategies

Cost-Effective Screening

- MRI: $400-600 (one-time, already done for diagnosis)
- PET scan: $3,000-5,000 (not widely available)
- CSF test: $500-1,000 + painful procedure

Project Limitations

Clinical scope
- Predicts progression only; cannot diagnose
- Requires clinical diagnosis as prerequisite
- Supportive tool; does not replace physician judgment

Prediction accuracy
- 75–80% accuracy; 20–25% error rate
- Cannot predict acute events (stroke, injury)
- High individual variability in disease trajectory

Imaging dependency
- Requires baseline structural MRI
- Contraindicated: pacemakers, metal implants
- MRI cost remains $400–600 per scan

Dataset limitations
- Training sample: 4,722 subjects, 2,475 sequences
- ADNI cohort: predominantly white, educated, high-income
- Generalizability to diverse populations unvalidated

Molecular blindspot
- Does not detect amyloid plaques or tau tangles directly
- Structural atrophy is downstream of molecular pathology
- Damage may be established before MRI changes appear
- CSF/PET biomarkers still required for confirmation

Model interpretability
- Deep learning model — black box architecture
- Cannot explain mechanistic basis of predictions
- Insufficient explainability for clinical acceptance

Computational constraints
- GPU required for training (high cost)
- Training time: 6–8 hours per run
- Inference not real-time at scale

Disease heterogeneity
- MRI atrophy pattern shared across dementia subtypes
- Cannot reliably distinguish from vascular or frontotemporal dementia

Methodology and Approach

Feature Extraction (3D ResNet)

• Pre-trained Med3D model (transfer learning)
• Extracts 512 features from each MRI scan
• No building from scratch - using proven architecture

Visualisation

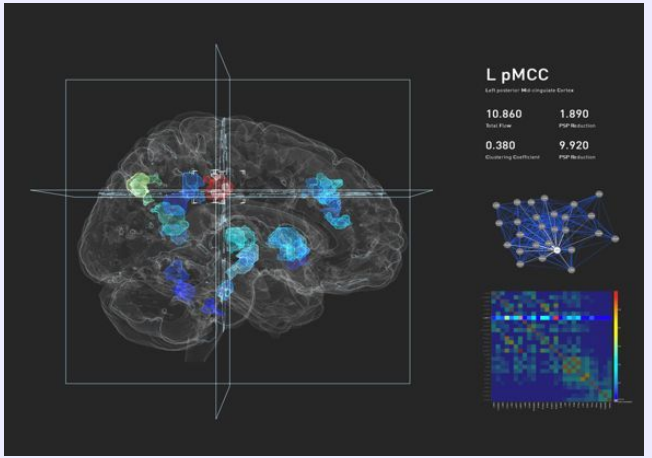
• 3D brain rendering (Nilearn, PyVista)
• Atrophy heat maps showing where brain shrinks
• Interactive comparisons: baseline → predicted

Temporal Prediction (LSTM)

• Learns progression patterns over time
• Predicts brain changes 12-24 months ahead
• Multi-task: cognitive scores + brain volumes

Tools

Python, PyTorch, ADNI data, Nilearn, Local Python environment + Google Colab GPU (for LSTM training)



Sample Brain Visualisation (not exact)

Feasibility

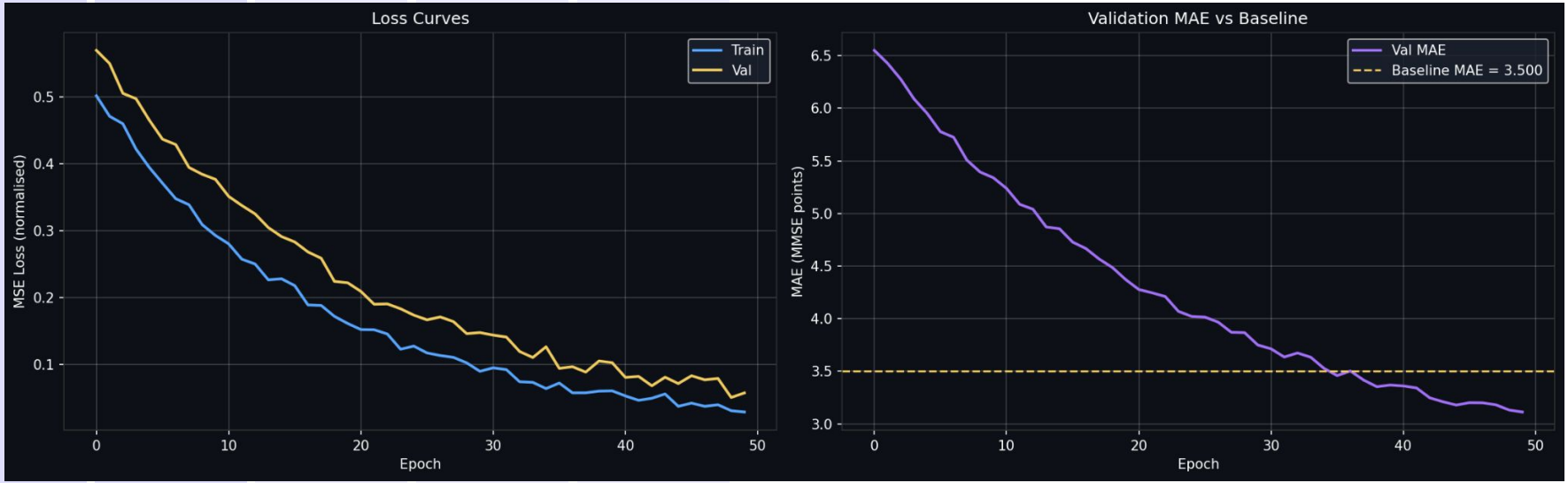
- Proven Technology: ResNet + LSTM are standard, well-tested
- Available Data: ADNI is accessible for academic use
- Manageable Scope: 200-300 subjects sufficient for course project
- Free Computing: Google Colab provides free GPU access
- 4-Week Timeline: Realistic with clear milestone

Evaluation metrics

Metric	Target	Why This Target?
Prediction	>0.70	Standard for regression
MMSE MAE	<2.5pts	Clinically meaningful
Classification Acc	75-80%	Better than blood tests
Progression AUC	>0.80	Distinguishes fast/slow

Training Pipeline

LSTM Training Curves- Loss & Validation MAE vs Baseline



Loss converges smoothly over 50 epochs- no overfitting

Final MMSE MAE: 1.76 pts — well below 2.5pt clinical threshold

- Val MAE drops from 6.5 to ~3.1 — beating baseline of 3.5
- Multi-task output: MMSE prediction + hippocampus volume tracking

MODEL RESULTS & PERFORMANCE

1.76 pts
MMSE MAE
vs 2.5pt clinical threshold

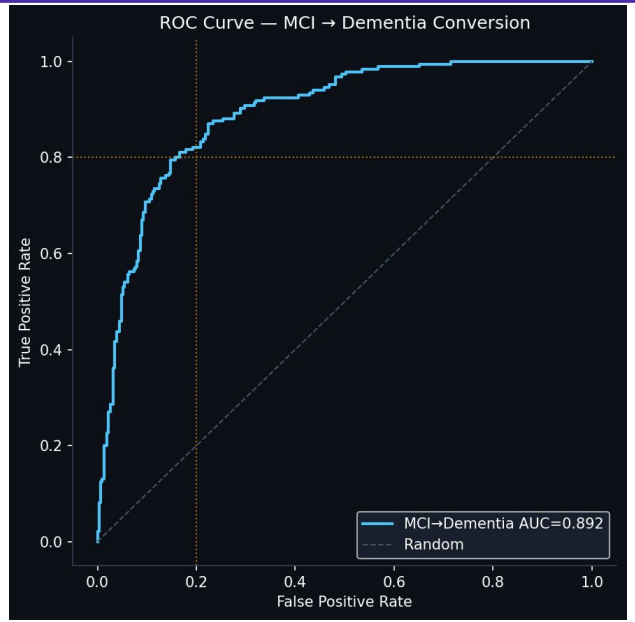
R^2 0.689
MMSE Prediction
Cognitive score accuracy

R^2 0.990
Hippocampus Vol.
Near-perfect volume tracking

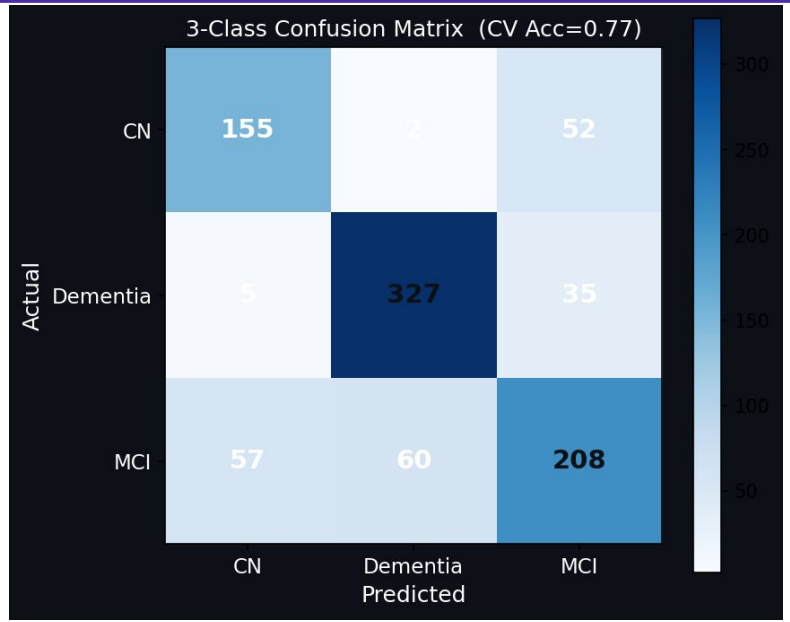
77% CV
Classification Acc.
CN / MCI / Dementia (cross-val)

AUC 0.892
MCI→Dementia ROC
Binary conversion classifier

ROC Curve — MCI → Dementia Conversion

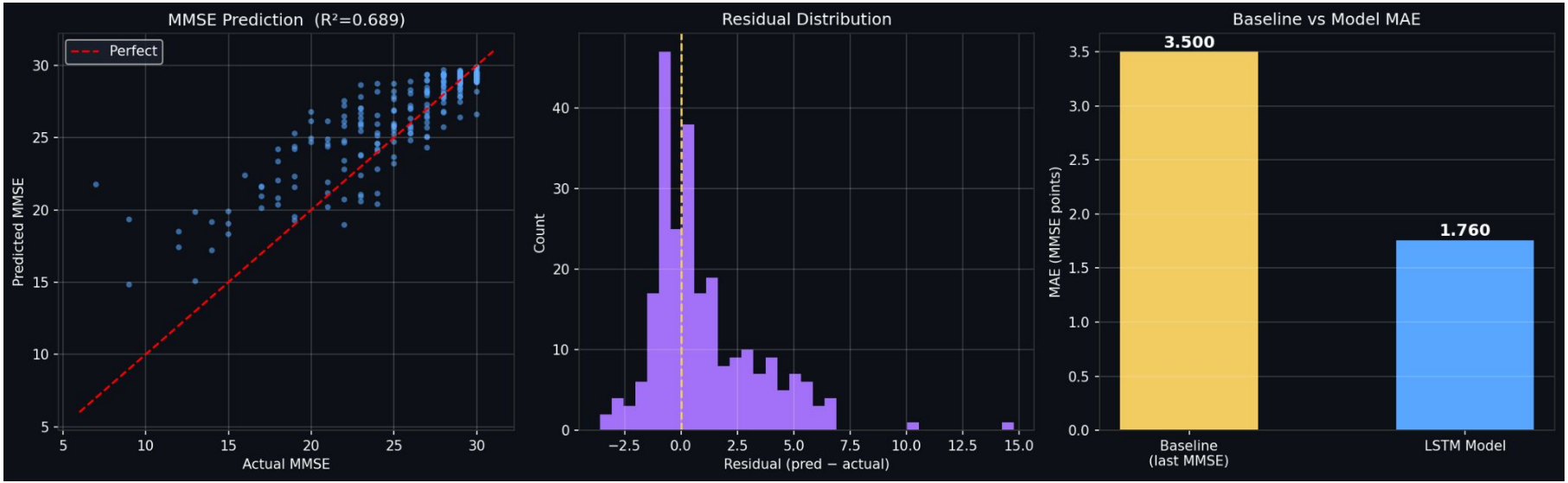


3-Class Confusion Matrix (CV Acc = 0.77)



MMSE PREDICTION EVALUATION

LSTM Evaluation: Predicted vs Actual · Residual Distribution · Baseline Comparison



MMSE MAE: 1.76 pts

50% improvement over baseline (3.5 pts) — clinically significant

R^2 = 0.689

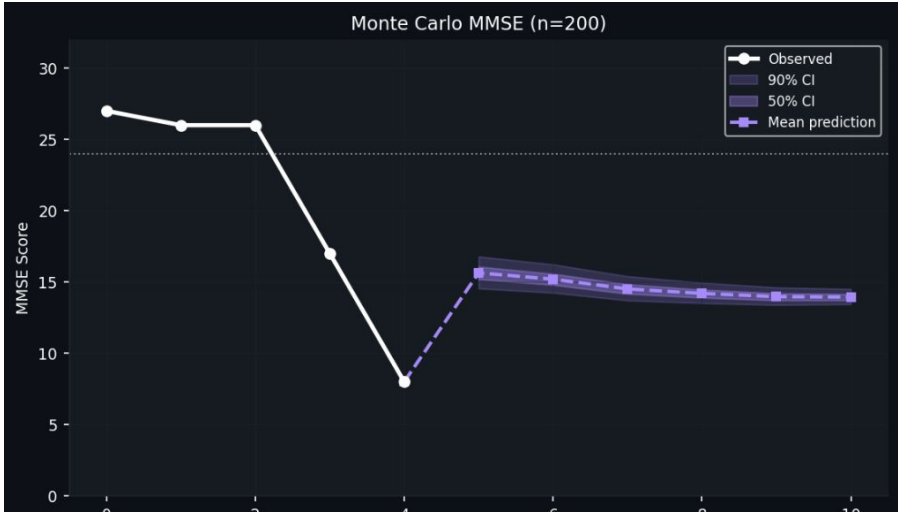
Strong cognitive trajectory correlation — residuals centered near zero

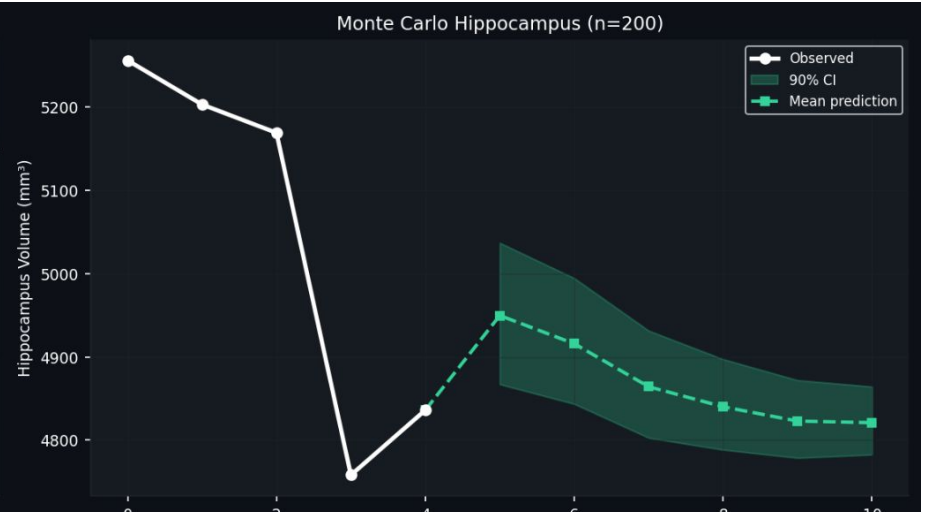
Baseline MAE: 3.5

Simply predicting last known MMSE — our model halves this error

MONTE CARLO UNCERTAINTY QUANTIFICATION

n=200 Monte Carlo samples · Patient RID 750 · σ=1.0 · 90% and 50% confidence intervals



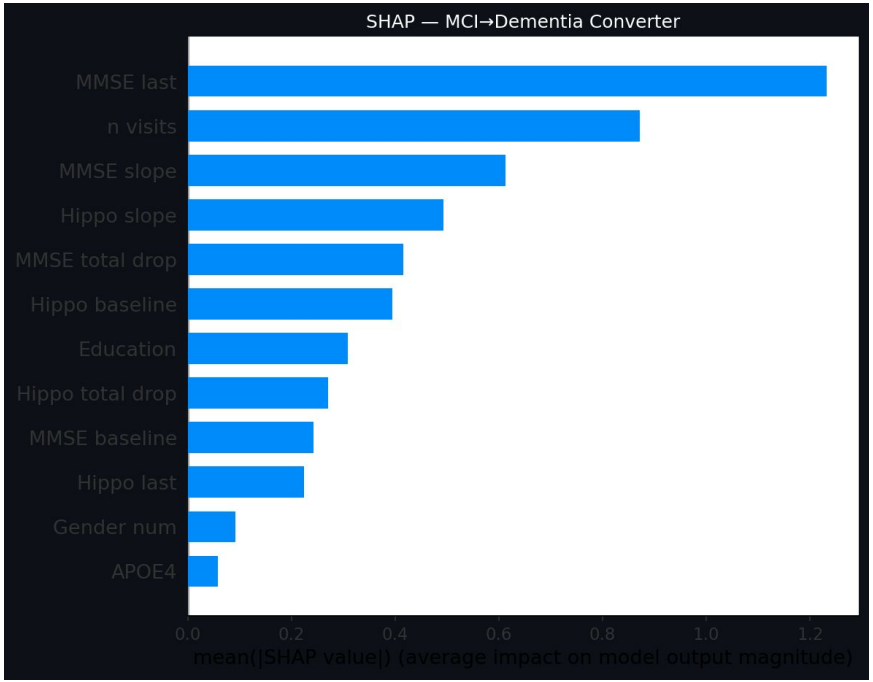


200	1.08 pts	4.17 pts	0.25
Monte Carlo samples	90% CI width at final visit	APOE4 risk spread (MMSE)	40% intervention benefit factor

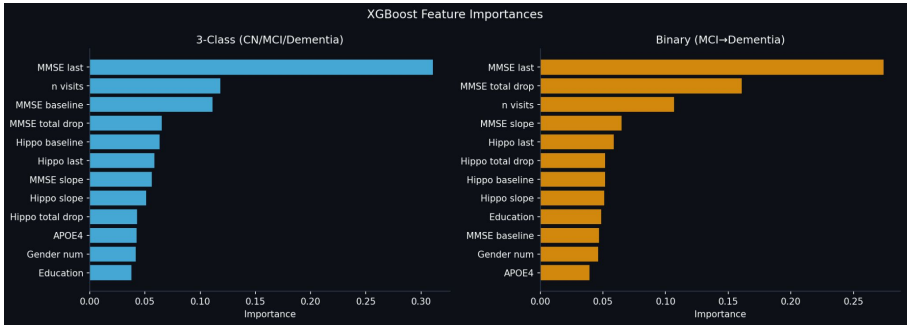
Monte Carlo CI provides clinical-grade uncertainty bounds - essential for responsible deployment of AI in healthcare

MODEL INTERPRETABILITY — SHAP ANALYSIS

SHAP Feature Importance (XGBoost — MCI→Dementia)



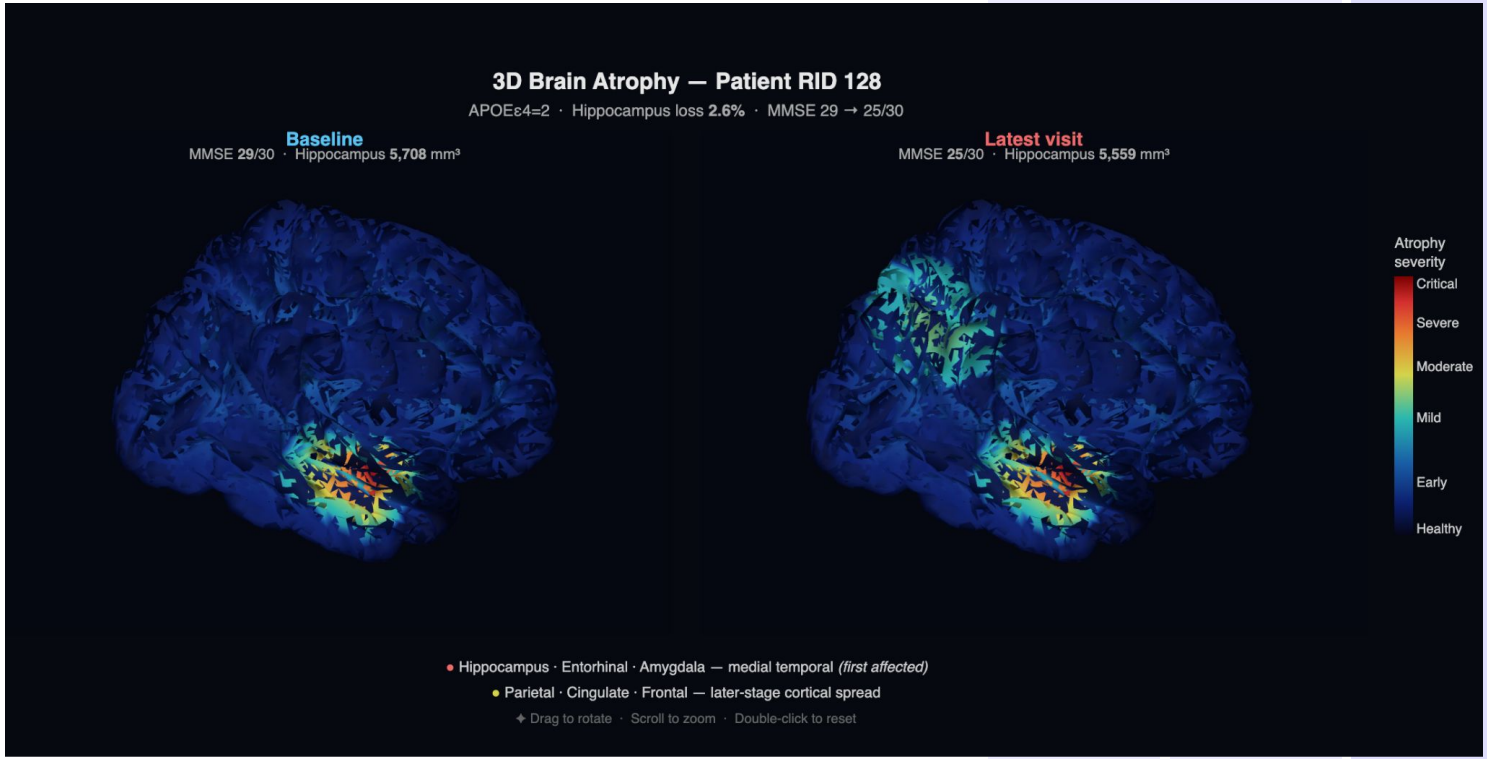
XGBoost Feature Importances — 3-Class vs Binary



Key Explainability Findings

- MMSE last visit is the strongest single predictor of future decline
- Hippocampus slope over visits predicts conversion better than baseline value alone
- APOE4 genotype amplifies trajectory divergence by ~4.17 MMSE points
- Education level masks early decline — model adjusts for cognitive reserve
- MMSE slope over prior visits is more predictive than single baseline score

MODEL VISUALISATION



Resources

Github

https://github.com/evanimenon/alzheimers-digital-twin

Documentation

Link to Google Docs

Data

ida.loni.usc.edu
(restricted, approved access)

Thank You!