Predicting Alzheimer's Disease Outcomes

Jonathan Ramos

The Problem

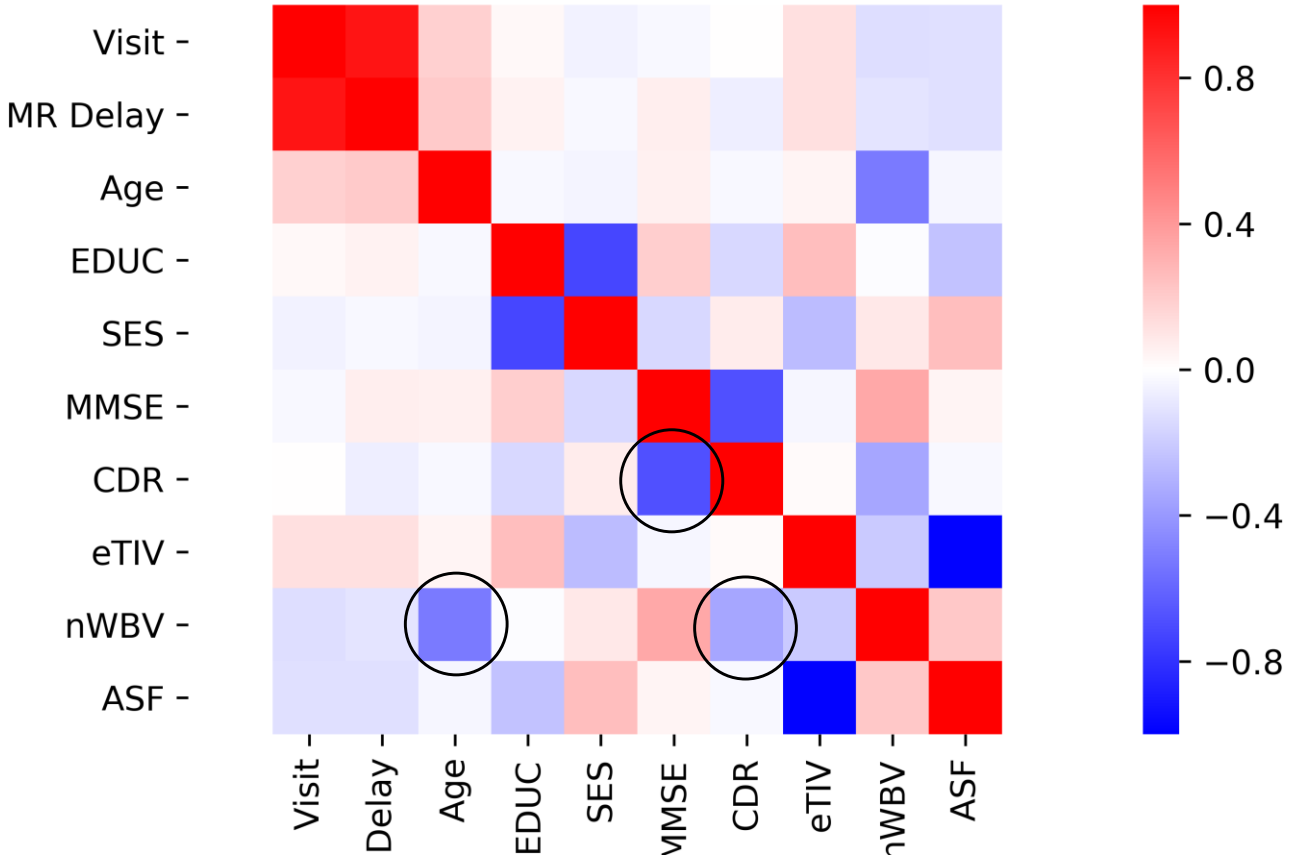
- Alzheimer's Disease (AD) diagnosis confirmation post-mortem
  - Neurofibrillary tracks
  - Abnormal plaque buildup and distribution
- Relevant biomarkers associated with disease outcomes
  - Accessible
  - Sensitive, early detection
  - Correlate with disease outcomes
- AD characterized by atrophy
  - Differences in MRI?

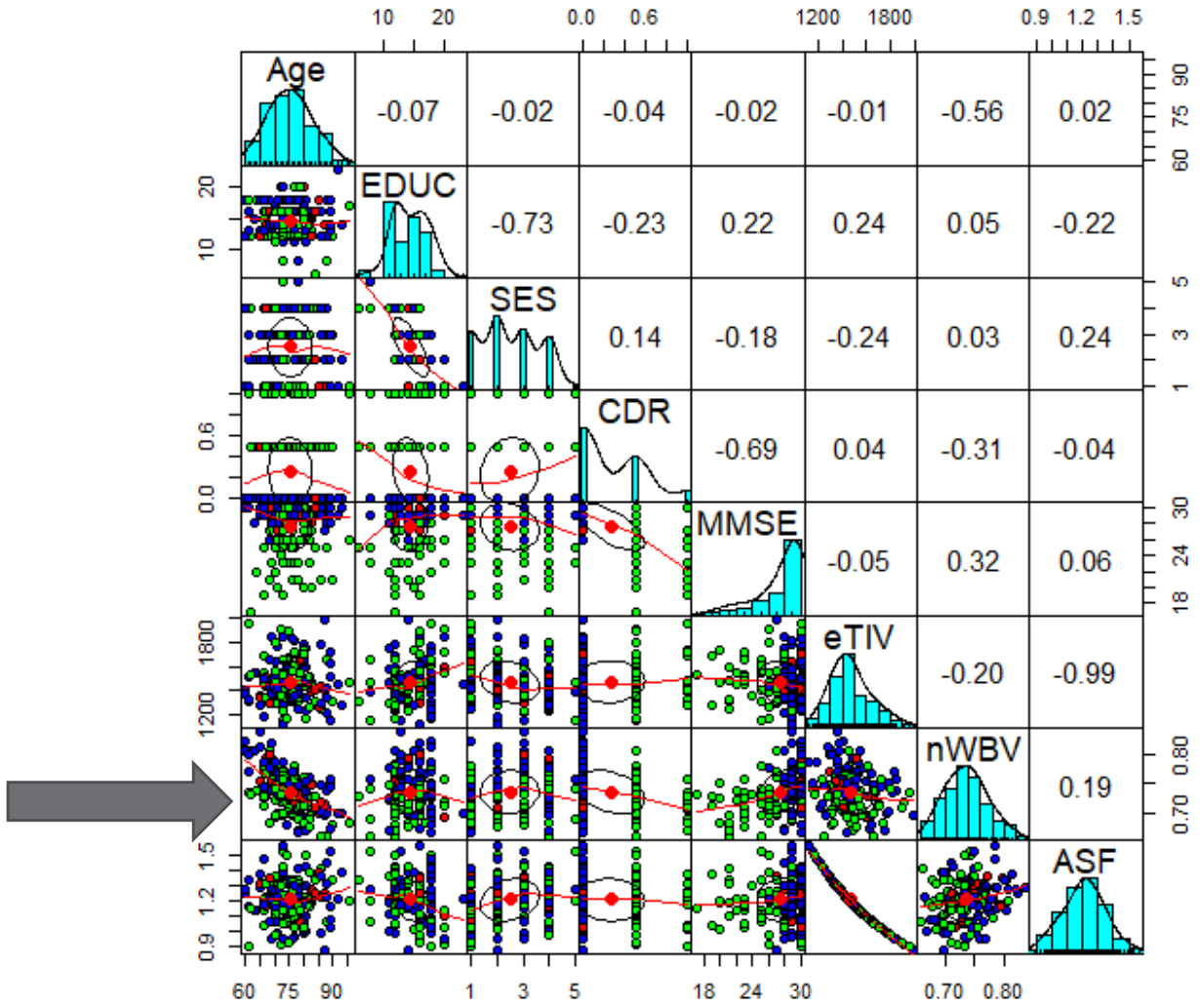
The Questions

- Do participants characterized as demented have a smaller brain volume than participants characterized as nondemented?
- Do participants characterized as demented have a higher atrophy than participants characterized as nondemented?
- Can we use these features to help us build a model to predict disease outcomes?

The Data

- 150 participants aged 60-96 were scanned 2 or more times with each visit separated by at least one year.
  - 72 characterized as nondemented for the duration of the study
  - 64 characterized as demented for the duration of the study
  - 14 characterized as nondemented at the beginning of the study, then demented later
- CDR: Clinical Dementia Rating
- nWBV: Normalized Whole Brain Volume



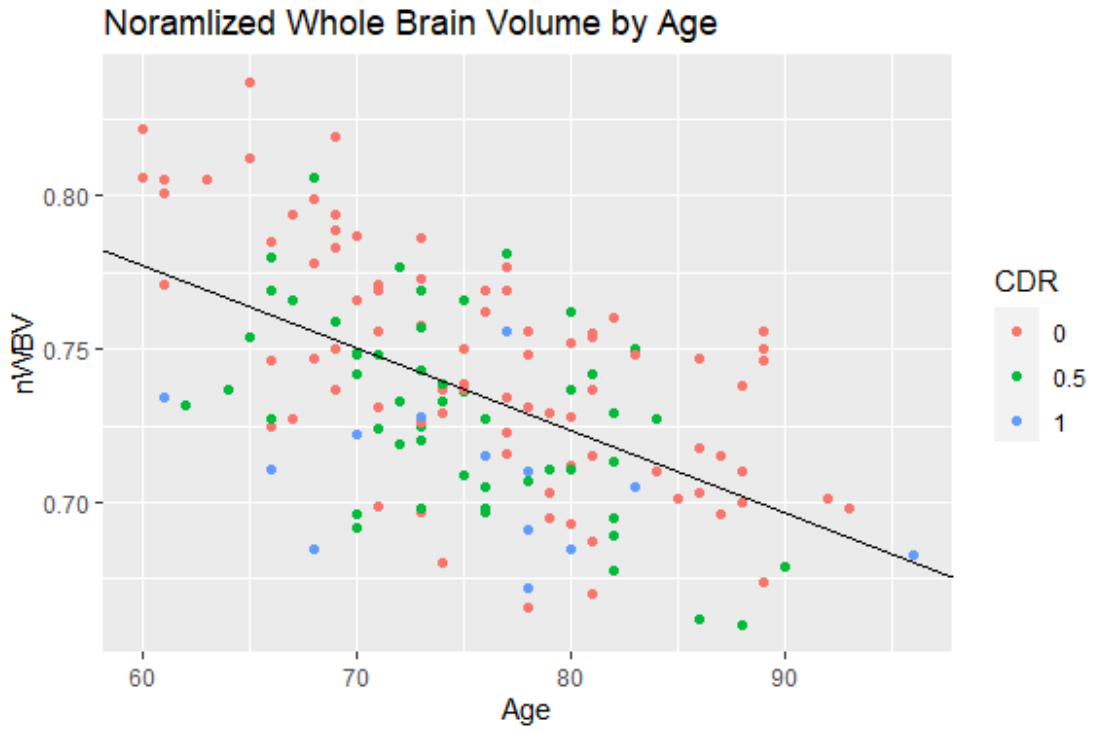


- Green: Nondemented
  - CDR remained 0
- Blue: Demented
  - CDR of at least 0.5
- Red: Converted (early AD stages)
  - CDR was initially 0 but changed to 0.5 or greater

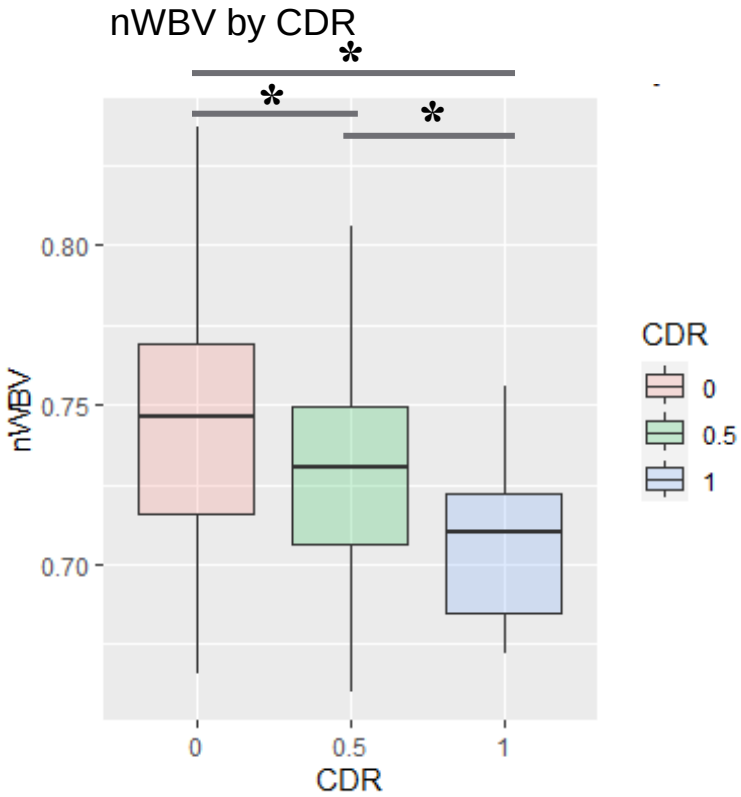
Data Cleaning and Preparation

- Dropped unnecessary columns
  - Label columns, Visit, Handedness, ASF (multicollinearity)
- Dealing with NaNs
  - NaNs only observed in SES and MMSE
  - Exploratory analyses suggest:
    - SES is well correlated with EDUC
    - MMSE is well correlated with CDR
  - Median replacement:
    - NaN in SES replaced with median SES based on EDUC level
    - NaN in MMSE replaced with median MMSE based on CDR score

Question 1:
Do brain volumes differ?



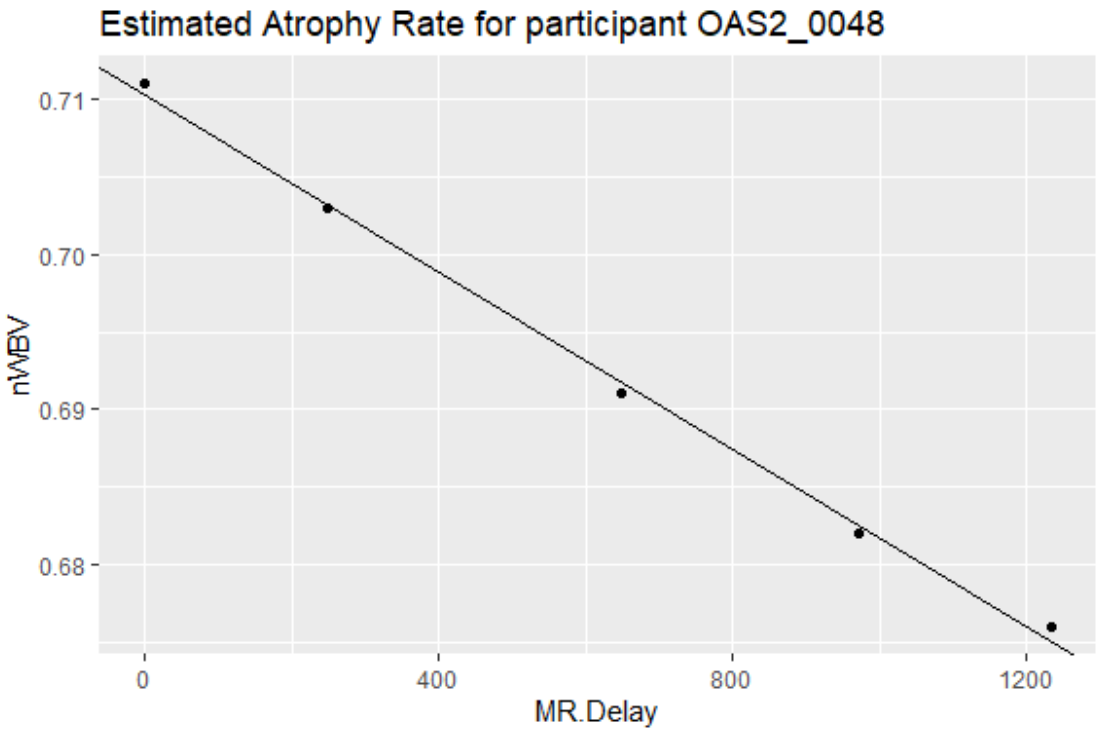
Pearson's r, p=1.18e-13



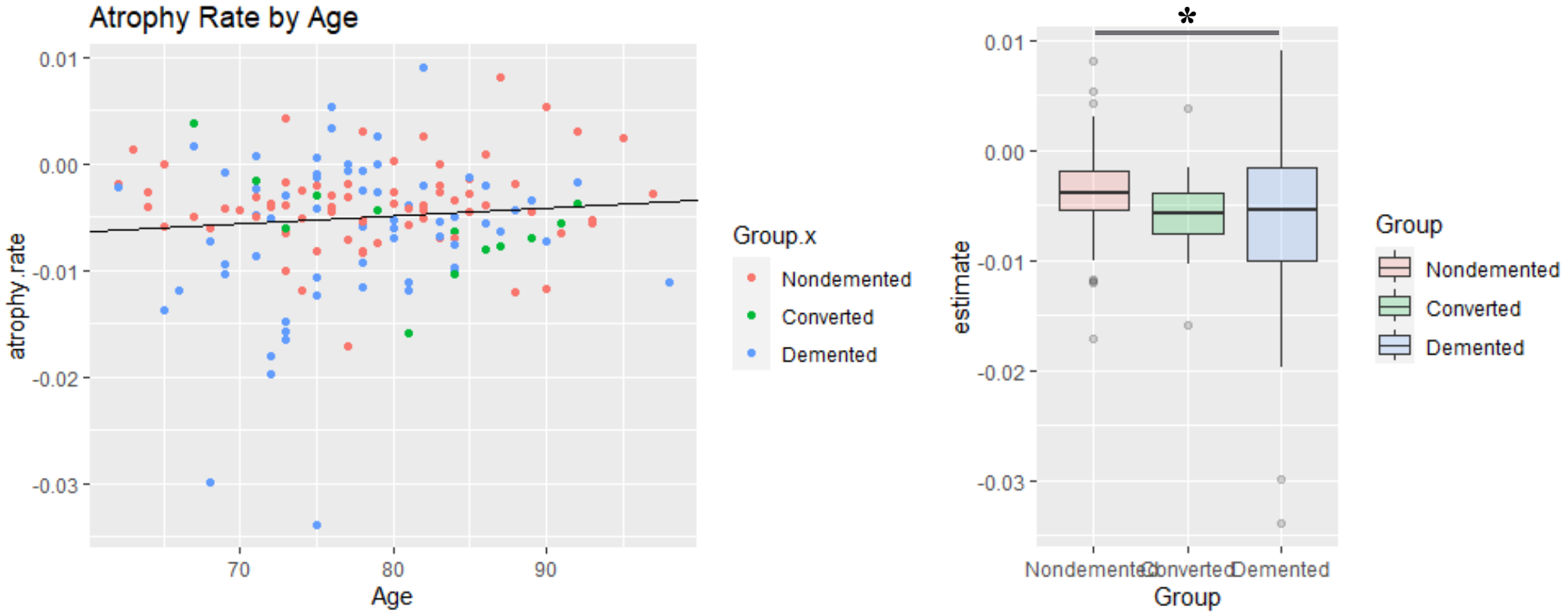
One way ANOVA, p=0.00012
Post-hoc t-tests: (alpha set to Bonferroni corrected p=0.016667)
0 vs 0.5 p=0.011,
0.5 vs 1 p=0.012,
0 vs 1 p=9.12e-5

Question 2:
Do atrophy rates differ?

- Estimate atrophy rate via linear regression
  - Take the nWBV measurements over MR.Delay (unit in days)
  - Take the slope from linear regression
  - Repeat for each participant
- Stitch together a new data frame containing
  - A new atrophy.rate column
  - Only the most recent data per participant



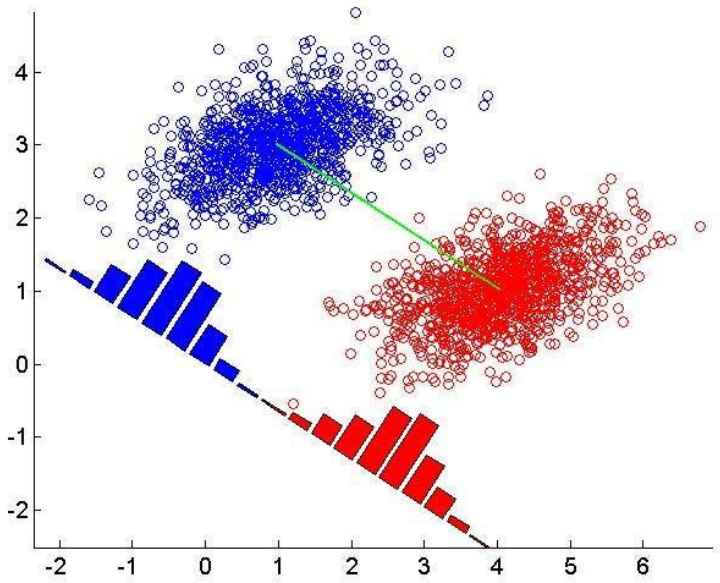
Question 2:
Do atrophy rates differ?



Pearson's r, p=0.2419

one-way ANOVA p=0.02407
Nondemented vs Convertd p=0.1308
Converted vs Demented p=0.6438
Demented vs Nondemtned p=0.009001

Question 3:
Predicting AD outcomes

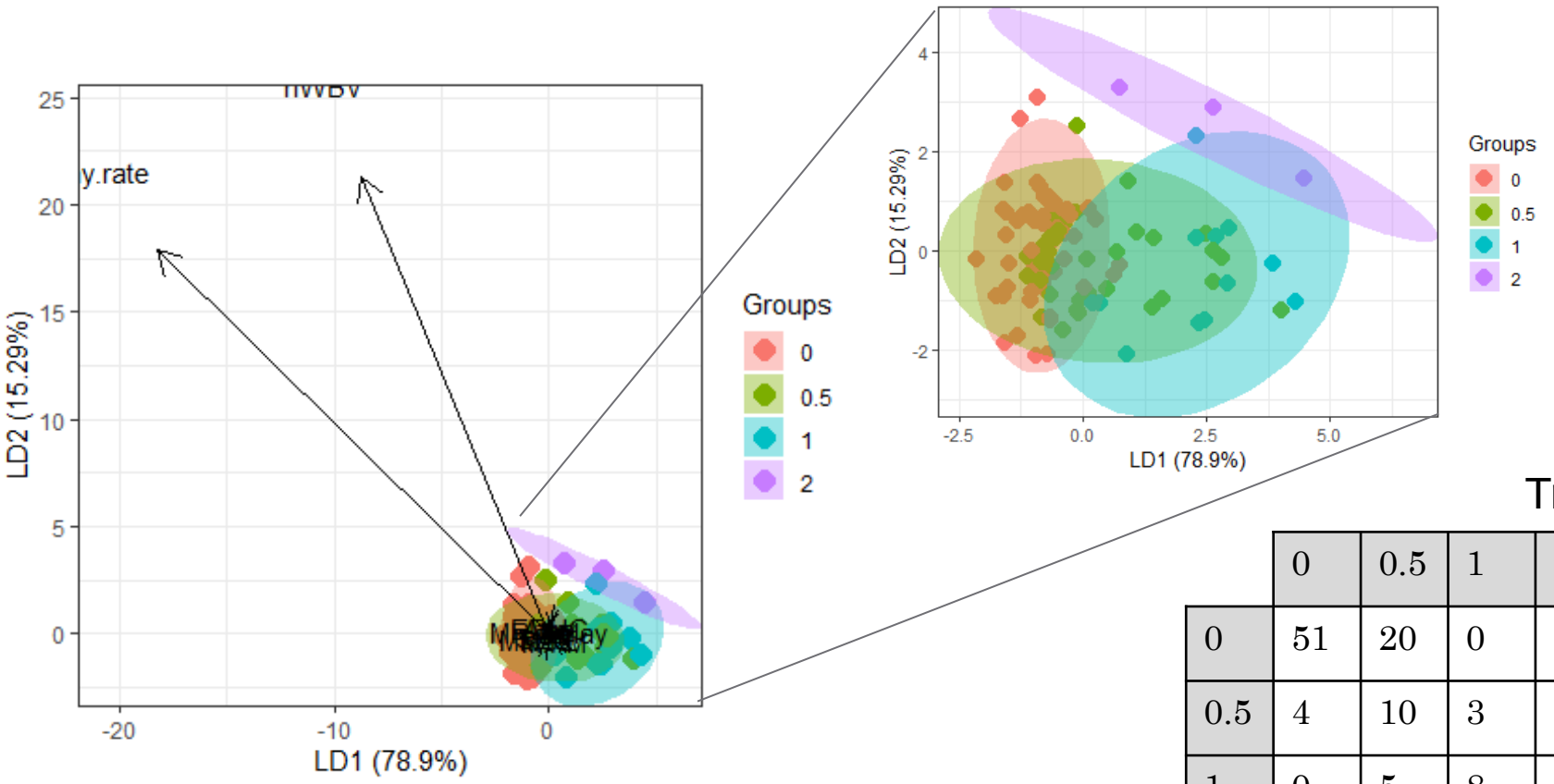


- Linear Discriminant Analysis
  - Supervised learning
  - Dimensionality Reduction
    - k-1 components
  - Maximizing class separability
    - Maximize the distance between means
    - Minimize variance of each class

$$\max_{v:\|v\|=1} \frac{(\mu_1 - \mu_2)^2}{{s_1}^2 + {s_2}^2}$$

$$\mu_j = \boldsymbol{v}^T \boldsymbol{m}_j, \qquad j = 1,2$$

Question 3:
Linear Discriminant Analysis



Train accuracy: 68.57%

Test accuracy: 64.44%

P-value = 0.0007966, (Acc > No information rate)

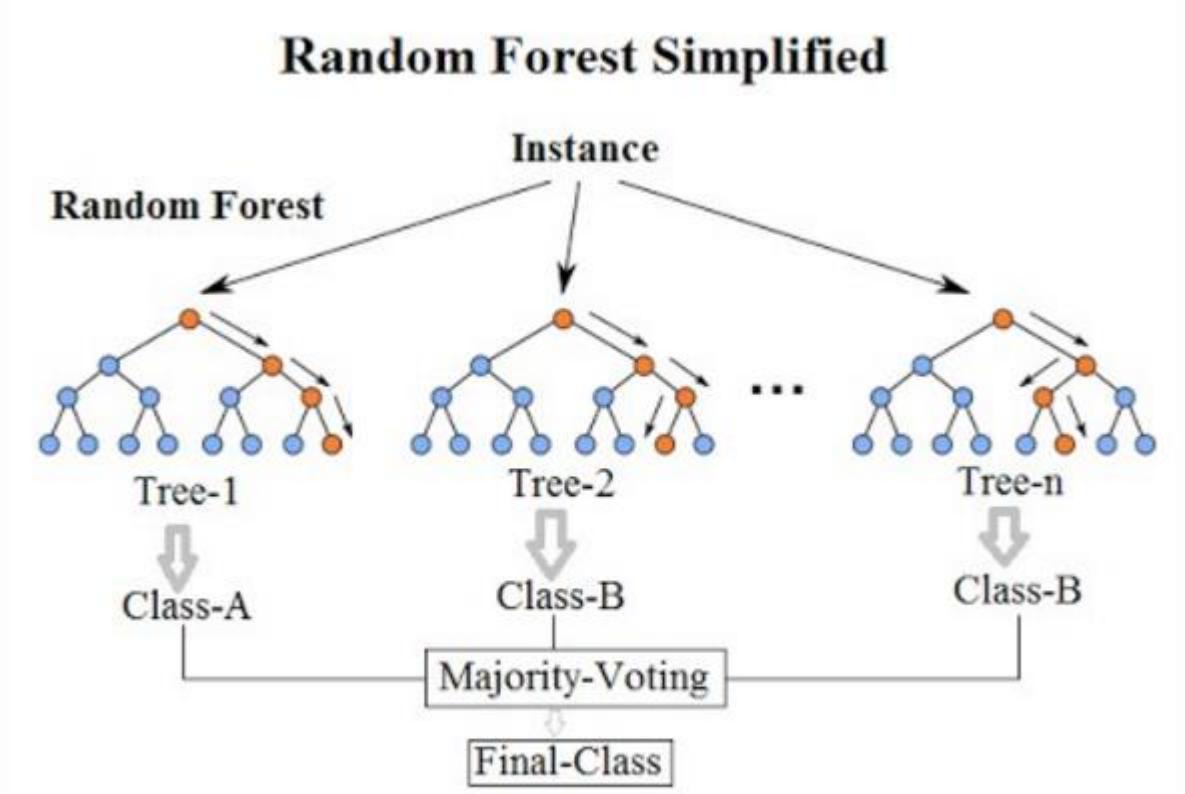
Train

	0	0.5	1	2
0	51	20	0	0
0.5	4	10	3	0
1	0	5	8	0
2	0	0	1	3

Test

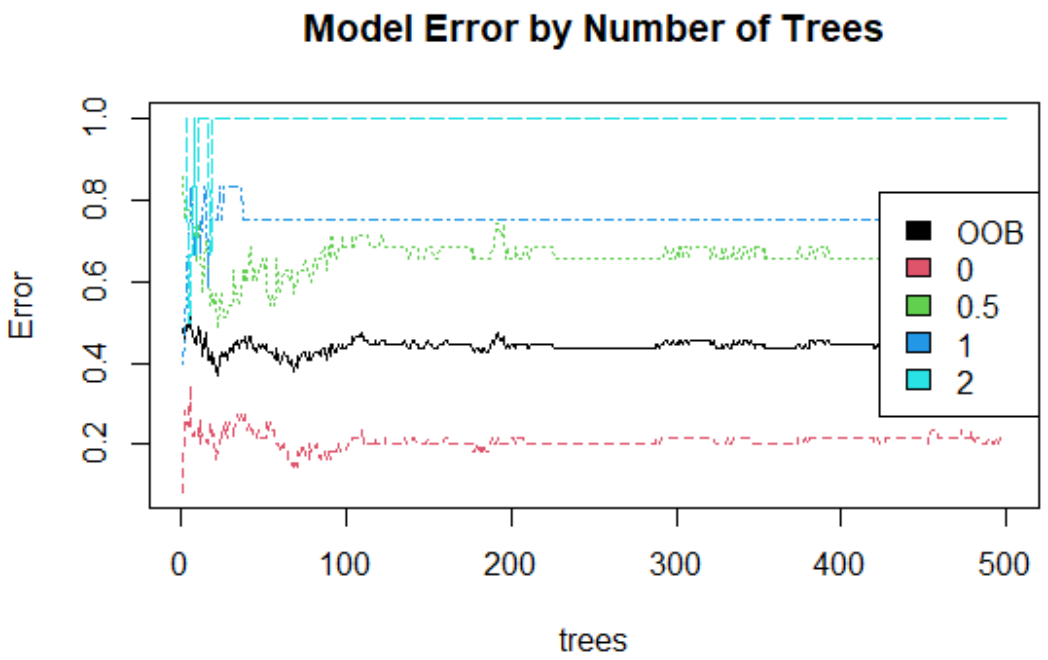
	0	0.5	1	2
0	18	8	1	0
0.5	0	9	2	0
1	0	1	2	0
2	0	0	4	0

Question 3:
Predicting AD outcomes



- Decision trees highly sensitive to training data, might fail to generalize
- So we train many random trees
  - Bootstrap data
    - Many new datasets are generated by random row selection with replacement
    - Reduces sensitivity to original data
  - Random feature subset selection to train
    - Reduces correlation between trees
- Majority vote of all trees
- Bootstrapping + Aggregating = Bagging

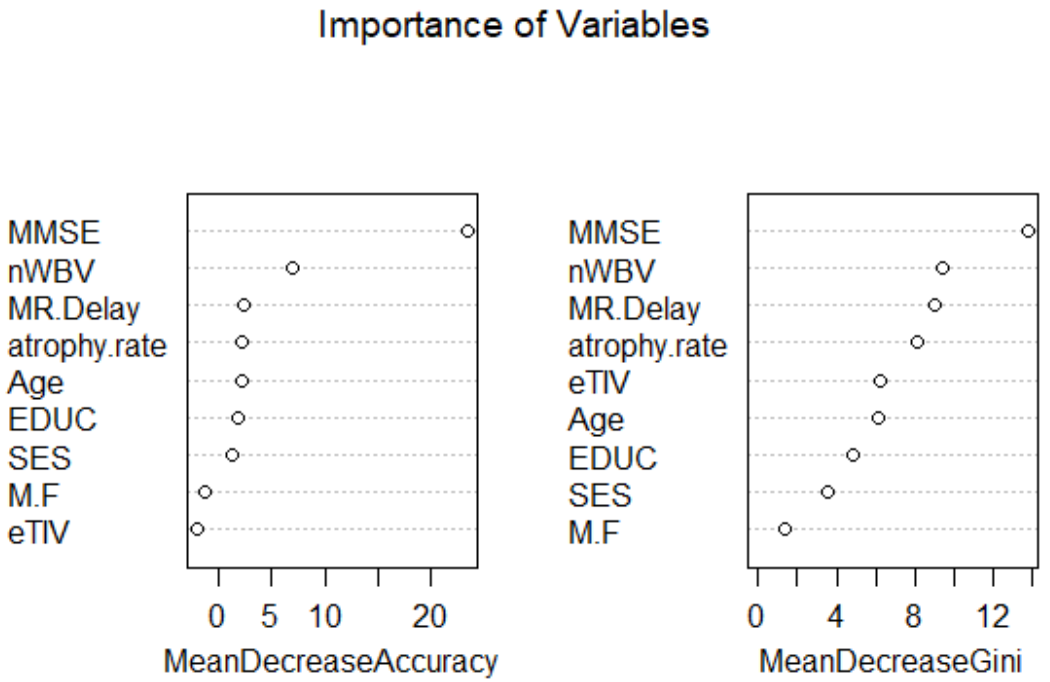
Question 3: Random Forest



Train accuracy: 54.29%

Test accuracy: 64.44%

P-value = 0.0007966,
(Acc > No information rate)



Train

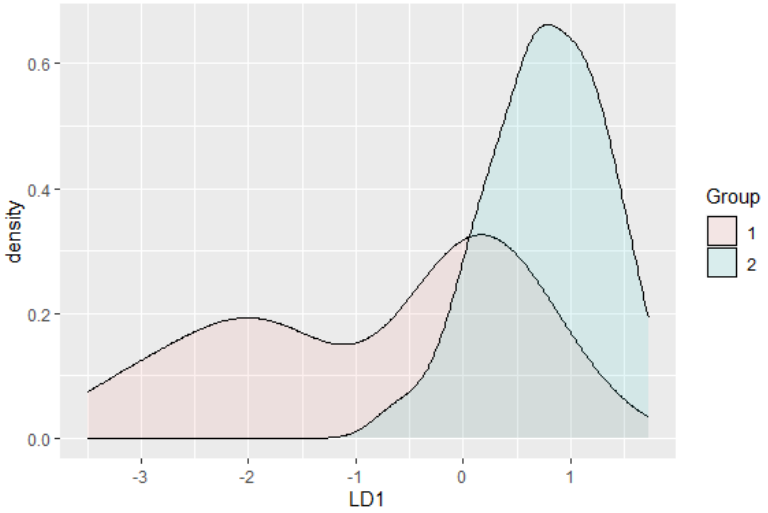
	0	0.5	1	2
0	44	11	0	0
0.5	18	10	7	0
1	0	9	3	0
2	0	2	1	0

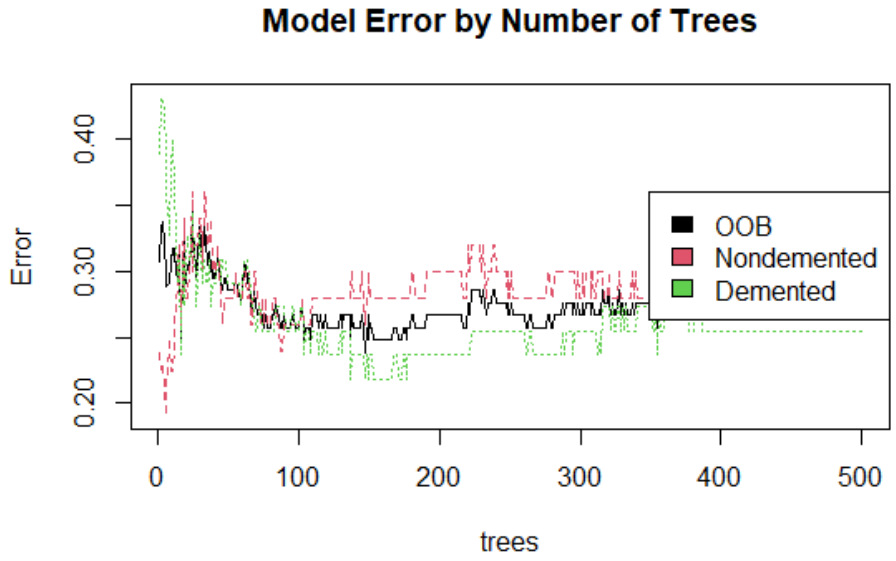
Test

	0	0.5	1	2
0	14	5	2	0
0.5	4	13	5	1
1	0	0	2	0
2	0	0	0	0

Question 3:
Can we Improve the model?

Let's consider just trying to classify if a patient had Dementia at all, a binary model where nondemented = 2, demented =1 (positive class is1)





	Train	Test
Sensitivity	60.00%	74.07%
Specificity	94.55%	100.0%
Accuracy	78.1%	84.44%

Train

	1	2
1	30	3
2	20	52

Test

	1	2
1	20	0
2	7	18

	Train	Test
Sensitivity	60.00%	81.48%
Specificity	74.55%	72.22%
Accuracy	73.33%	77.78%

Train

	1	2
1	36	14
2	14	41

Test

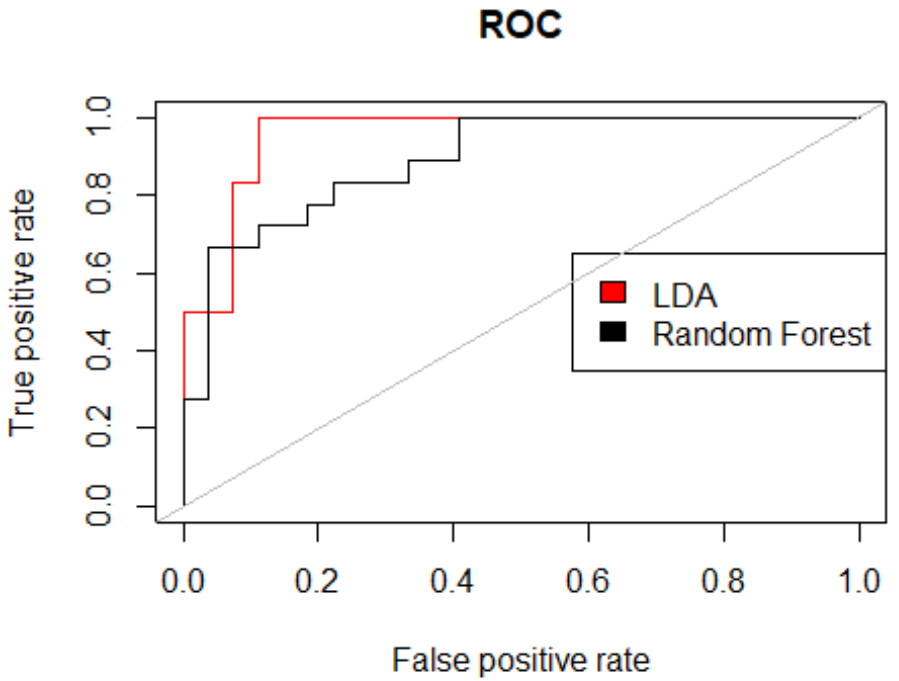
	1	2
1	22	5
2	5	13

Area under the Curve

- Receiver operating characteristic (ROC), plots TPR and FPR for various threshold values.
- True Positive Rate (TPR) = $Sensitivity = \frac{TP}{TP+FN}$
- False Positive Rate (FPR)

$$= 1 - Specificity = \frac{FP}{TN + FP}$$

- Prefer model with larger area under the ROC curve
  - Models with larger AUC have higher sensitivity and specificity over more thresholds overall
  - Diagonal line shows random class assignment (AUC=0.5)



LDA AUC: 0.957
RF AUC: 0.893

Conclusion

- Participants characterized as demented have a smaller nWBV
- Participants characterized as demented do not have the same atrophy rate as participants characterized as non demented.
  - Participants determined to be in early stages of AD fall in between
- Both models struggle to differentiate between more subtle differences in CDR (nondemented vs slight vs mild vs moderate dementia CDR = 0, 0.5, 1, 2 respectively).
- When classifying whether or not a participant had any dementia at all, LDA gives the best results at 89.47% accuracy

Overall AD is a very complex disease that depends on many different factors, notably MMSE, nWBV and estimated atrophy rate. We cannot fully rely on models to deliver accurate diagnoses, but these studies demonstrate that derived metrics from MRI may be an informative component when considering diagnoses.

Data Source

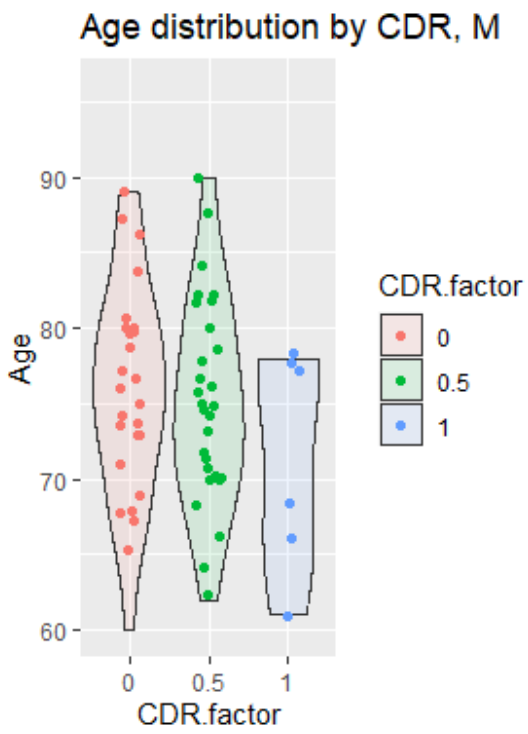
Marcus DS, Fotenos AF, Csernansky JG, Morris JC, Buckner RL. Open access series of imaging studies: longitudinal MRI data in nondemented and demented older adults. J Cogn Neurosci. 2010 Dec;22(12):2677-84. doi: 10.1162/jocn.2009.21407. PMID: 19929323; PMCID: PMC2895005.

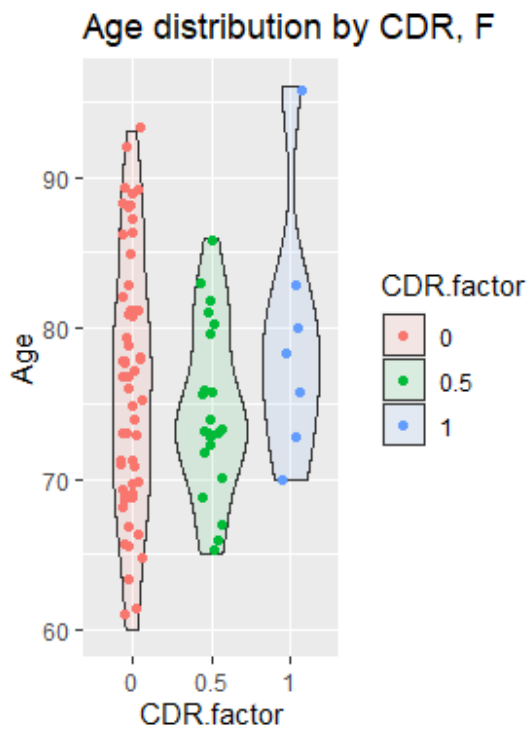
Accessible via Kaggle

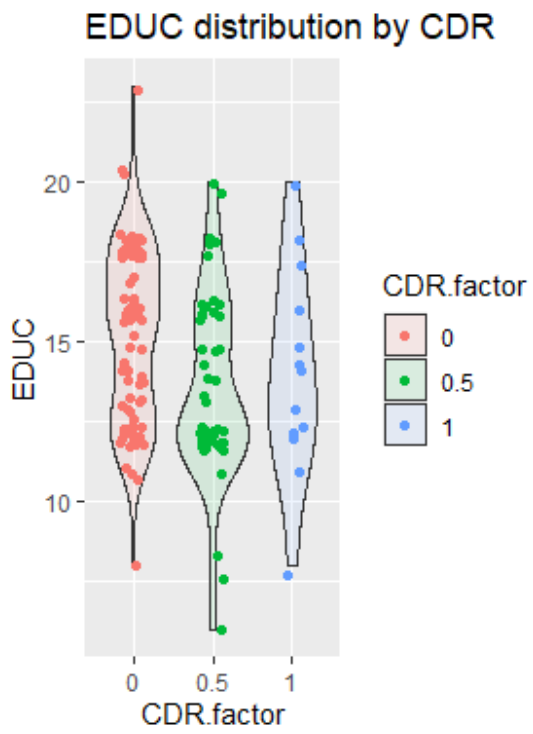
References

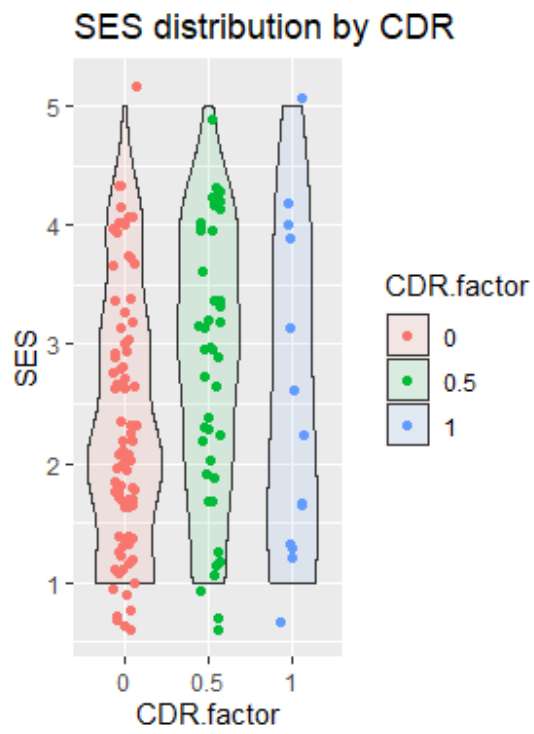
- 1. Gonzalez AE, Jorgensen ET, Ramos JD, Harkness JH, Aadland JA, Brown TE, Sorg BA. Impact of Perineuronal Net Removal in the Rat Medial Prefrontal Cortex on Parvalbumin Interneurons After Reinstatement of Cocaine Conditioned Place Preference. Front Cell Neurosci. 2022 Jul 28;16:932391. doi: 10.3389/fncel.2022.932391. PMID: 35966203; PMCID: PMC9366391.
- 2. Kehoe EG, McNulty JP, Mullins PG, Bokde AL. Advances in MRI biomarkers for the diagnosis of Alzheimer's disease. Biomark Med. 2014;8(9):1151-69. doi: 10.2217/bmm.14.42. PMID: 25402585.
- 3. Marcus DS, Wang TH, Parker J, Csernansky JG, Morris JC, Buckner RL. Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. J Cogn Neurosci. 2007 Sep;19(9):1498-507. doi: 10.1162/jocn.2007.19.9.1498. PMID: 17714011.
- 4. Scarlett JM, Hu SJ, Alonge KM. The "Loss" of Perineuronal Nets in Alzheimer's Disease: Missing or Hiding in Plain Sight? Front Integr Neurosci. 2022 May 25;16:896400. doi: 10.3389/fnint.2022.896400. PMID: 35694184; PMCID: PMC9174696.
- 5. Silbert LC, Quinn JF, Moore MM, Corbridge E, Ball MJ, Murdoch G, Sexton G, Kaye JA. Changes in premorbid brain volume predict Alzheimer's disease pathology. Neurology. 2003 Aug 26;61(4):487-92. doi: 10.1212/01.wnl.0000079053.77227.14. PMID: 12939422.

Supplemental Figures

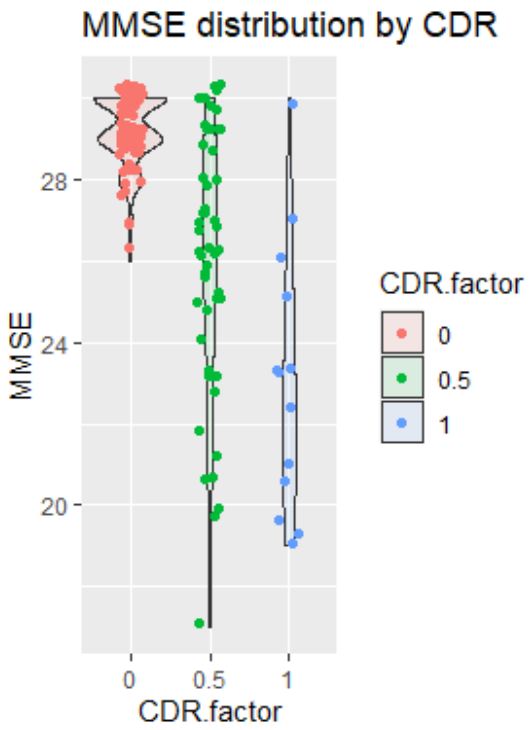


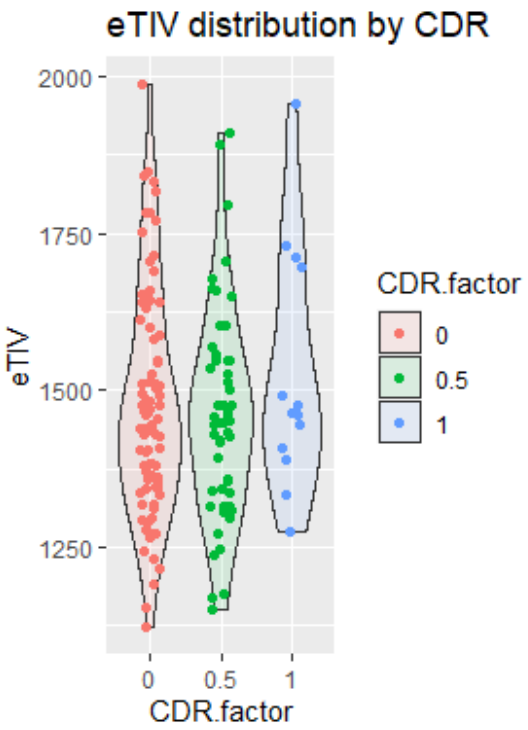


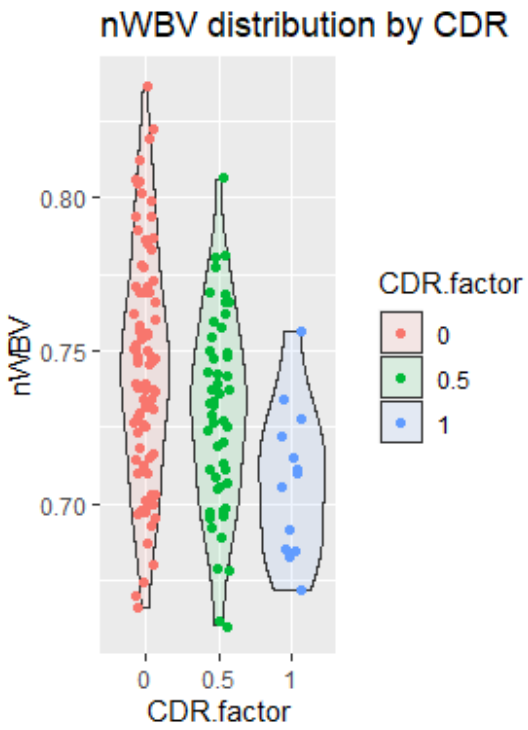


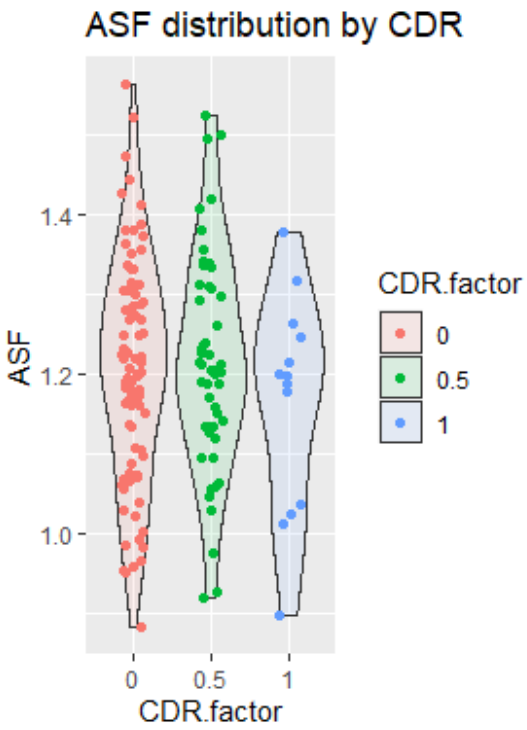


Supplemental Figures





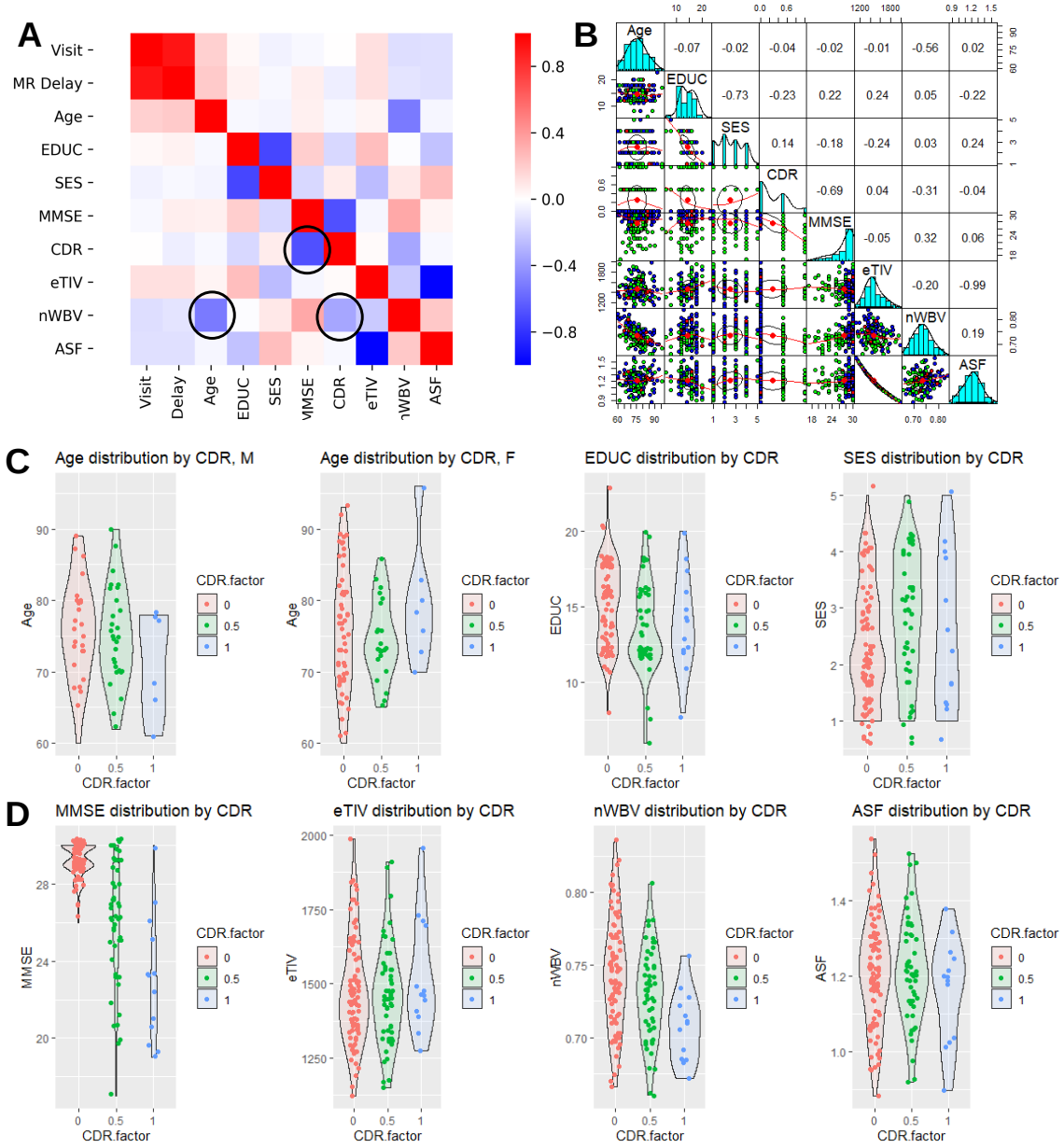




Thank you! Questions?

Formatting figures for paper

Figure 1



Formatting figures for paper

Figure 2

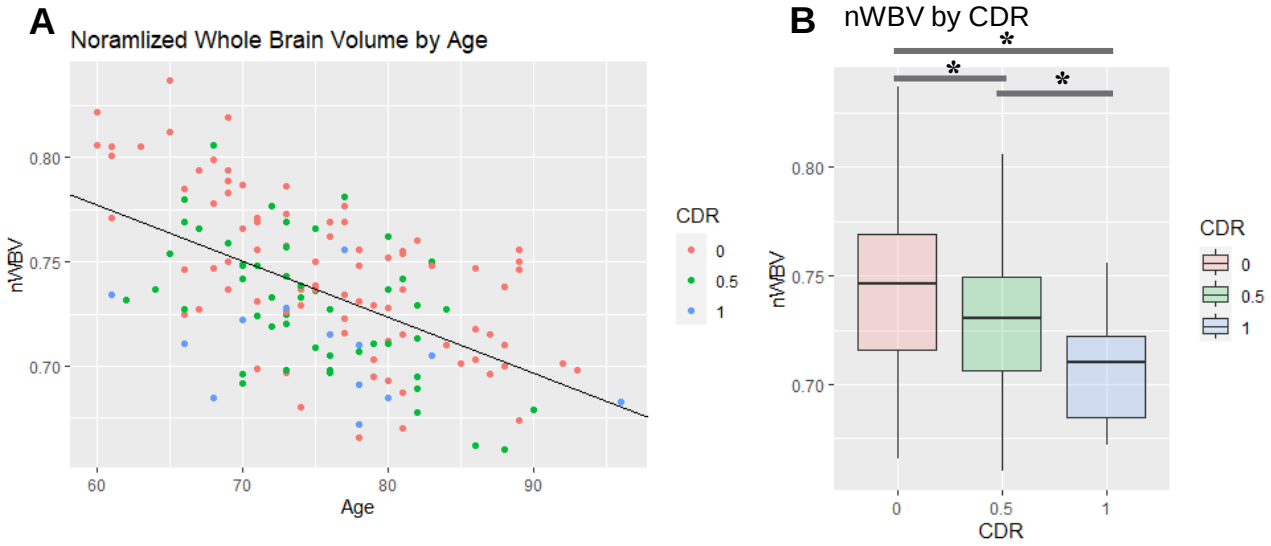


Figure 3

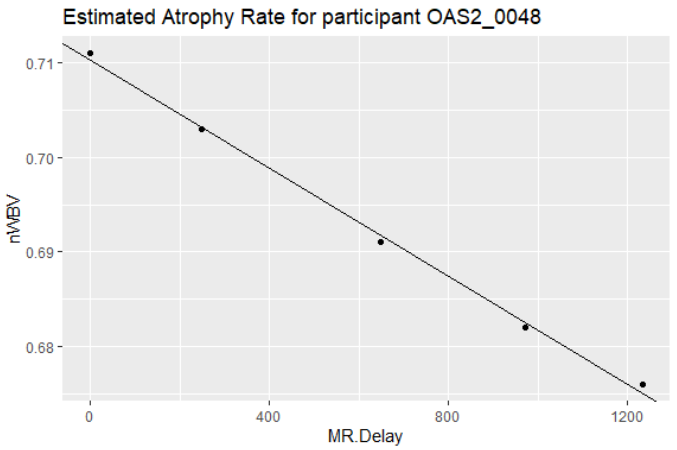
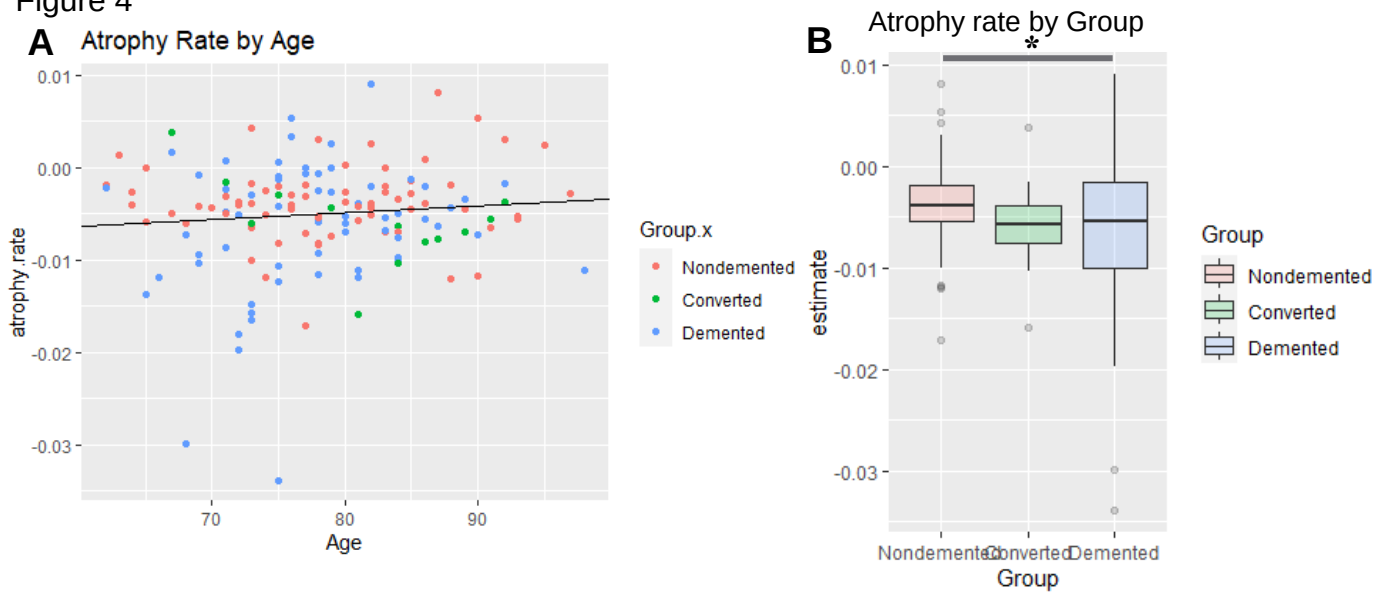
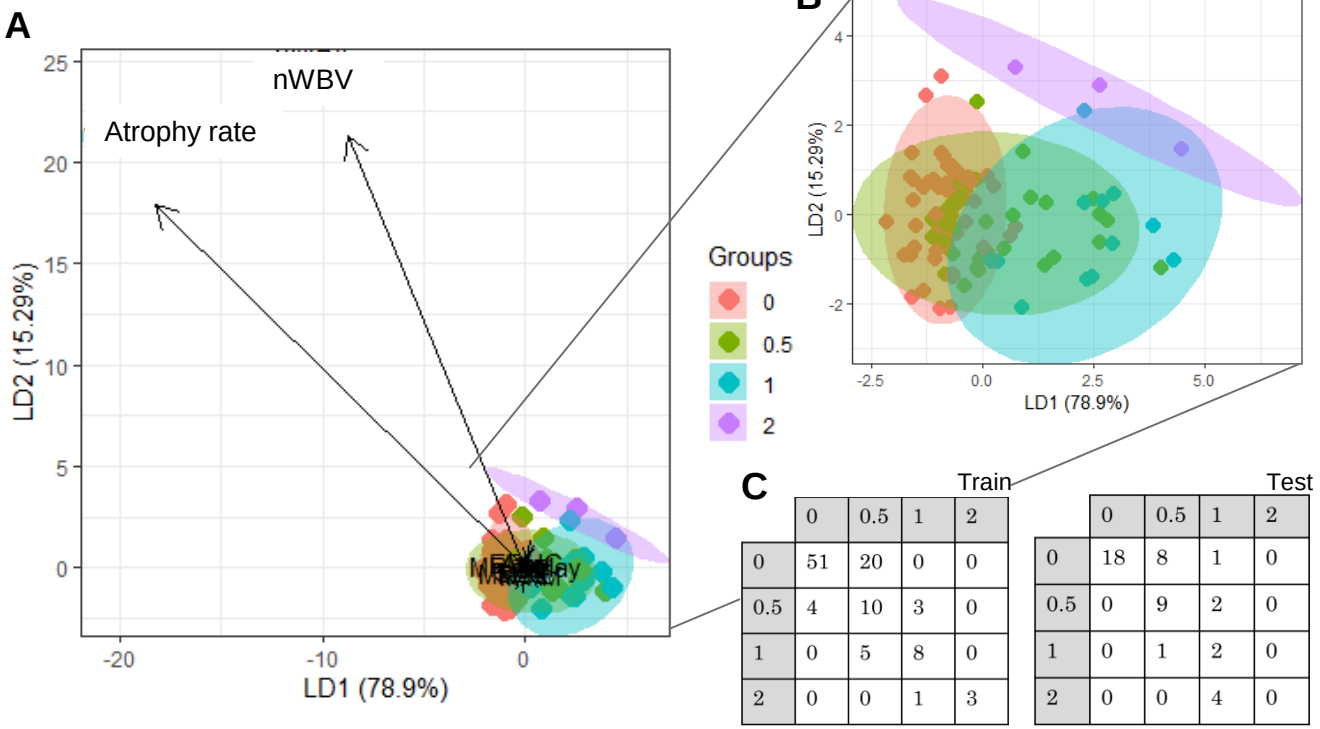


Figure 4



Formatting figures for paper

Figure 5

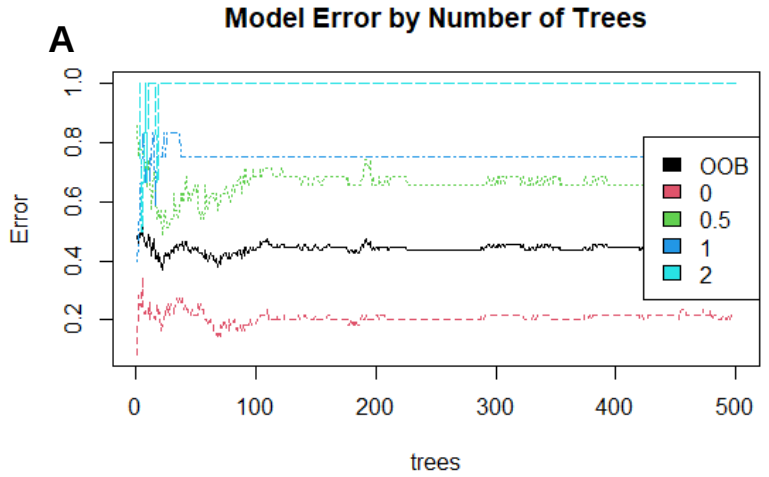


C

Train	0	0.5	1	2
0	51	20	0	0
0.5	4	10	3	0
1	0	5	8	0
2	0	0	1	3

Test	0	0.5	1	2
0	18	8	1	0
0.5	0	9	2	0
1	0	1	2	0
2	0	0	4	0

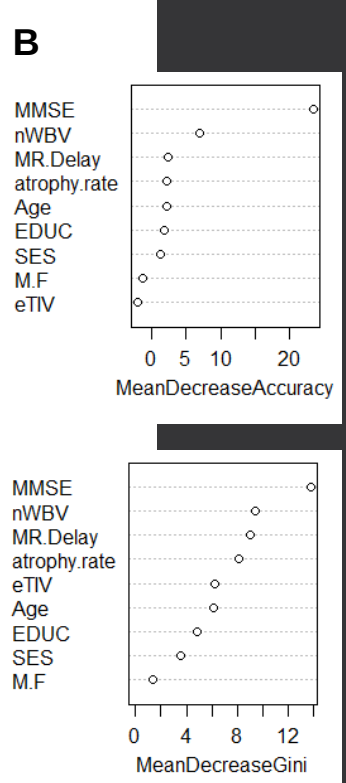
Figure 6



C

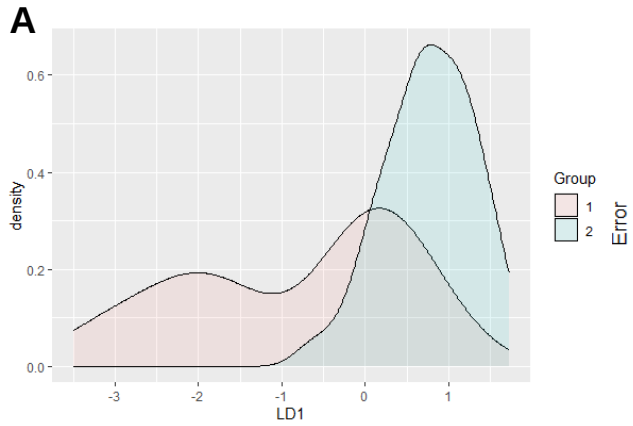
Train	0	0.5	1	2
0	51	20	0	0
0.5	4	10	3	0
1	0	5	8	0
2	0	0	1	3

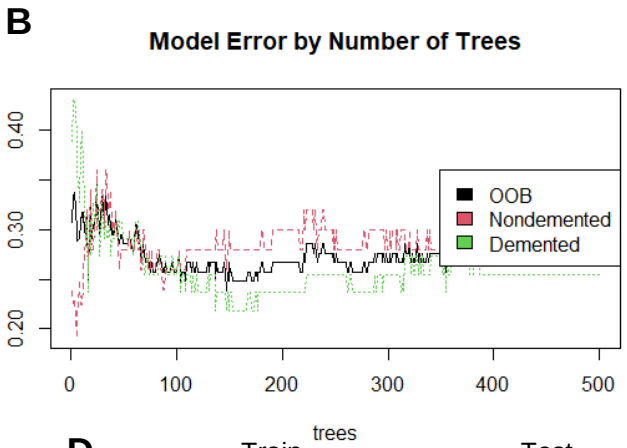
Test	0	0.5	1	2
0	18	8	1	0
0.5	0	9	2	0
1	0	1	2	0
2	0	0	4	0



Formatting figures for paper

Figure 7





C

Train		
	1	2
1	30	3
2	20	52

Test		
	1	2
1	20	0
2	7	18

	Train	Test
Sensitivity	60.00%	74.07%
Specificity	94.55%	100.0%
Accuracy	78.1%	84.44%

D

Train		
	1	2
1	36	14
2	14	41

Test		
	1	2
1	22	5
2	5	13

	Train	Test
Sensitivity	60.00%	81.48%
Specificity	74.55%	72.22%
Accuracy	73.33%	77.78%

Figure 8