Prediction of Autism Treatment Response from Baseline fMRI using Random Forests and Tree Bagging

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Yale University

Autism Spectrum Disorder (ASD)

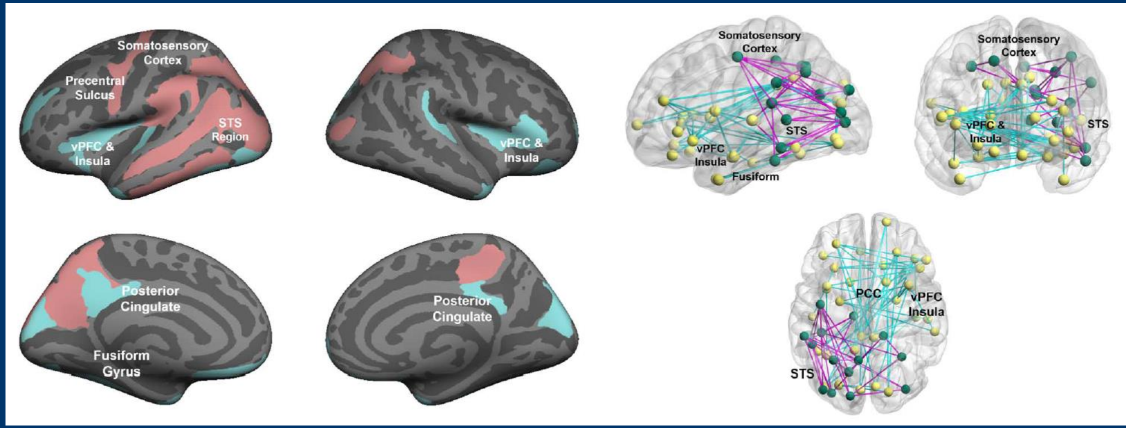
- Neurological developmental disorders characterized by impaired social interactions, difficulties in communication, and repetitive behaviors
- Promising treatment: Intensive behavioral therapies
  - e.g., Pivotal Response Therapy
  - Large commitment from patient and families
  - Early intervention is important
- However, ASD is complex!
  - No "one size fits all" treatment
  - Currently, choose therapy by trial and error

→ Need for *precision medicine*

www.autismspeaks.org

Goal: Predict Autism Treatment Outcome from Baseline fMRI

- fMRI has aided understanding of ASD pathophysiology

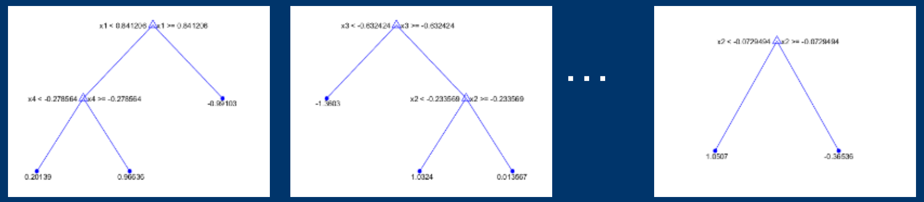


Venkataraman et al., TMI 2016

- fMRI for prediction
  - Changes in autistic traits [Plitt et al., PNAS 2015]
  - Treatment outcomes in other brain disorders [Ball et al., Neuropsych 2014]
  - →We propose first use of fMRI for predicting ASD treatment response

Goal: Predict Autism Treatment Outcome from Baseline fMRI

- Challenge: “large *p*, small *n*”
  - Large number of possible fMRI-derived inputs
  - Small number of subjects in autism studies
- Good candidate for Random Forests



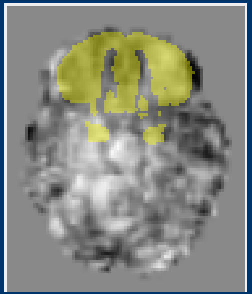
Random Forest

$\longrightarrow Y_{\text{ens}}$

- However…
  - Very noisy inputs degrade prediction accuracy
  - Small samples reduce strength of each tree

Learning Pipeline Overview

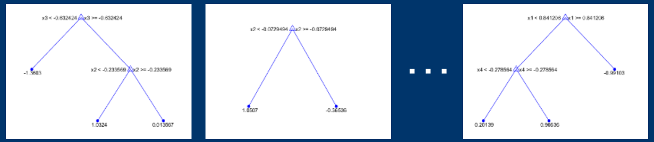
Inputs: fMRI Biomarkers



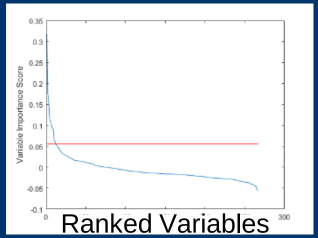
Outputs: Behavioral Treatment Response

Proposed Learning Pipeline

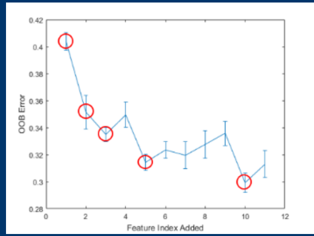
Candidate Variable Selection

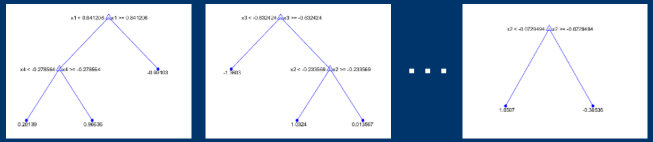


Random Forest



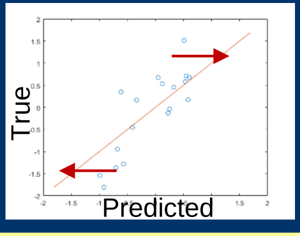
Stepwise Variable Refinement

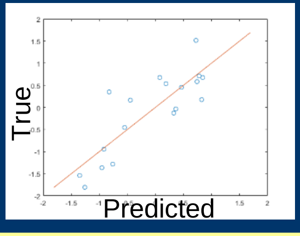




Bagged Ensemble

Bias Correction





Learned Predictive Model

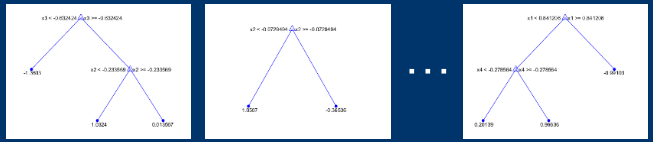
Learning Pipeline Overview

Inputs: fMRI Biomarkers

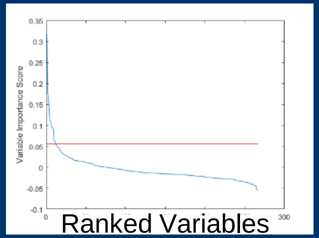
Outputs: Behavioral Treatment Response

Proposed Learning Pipeline

Candidate Variable Selection

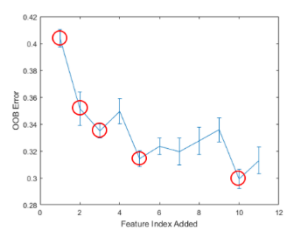


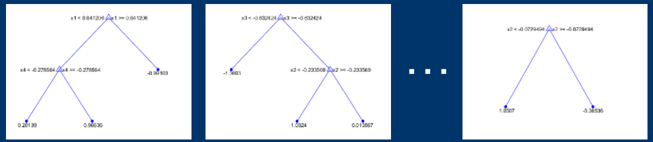
Random Forest



Ranked Variables

Stepwise Variable Refinement





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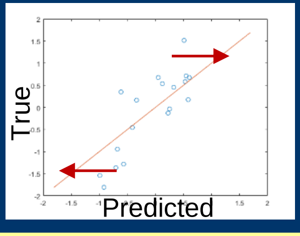
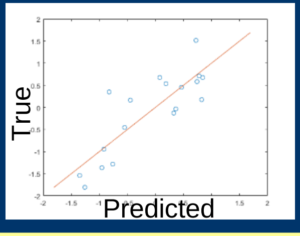
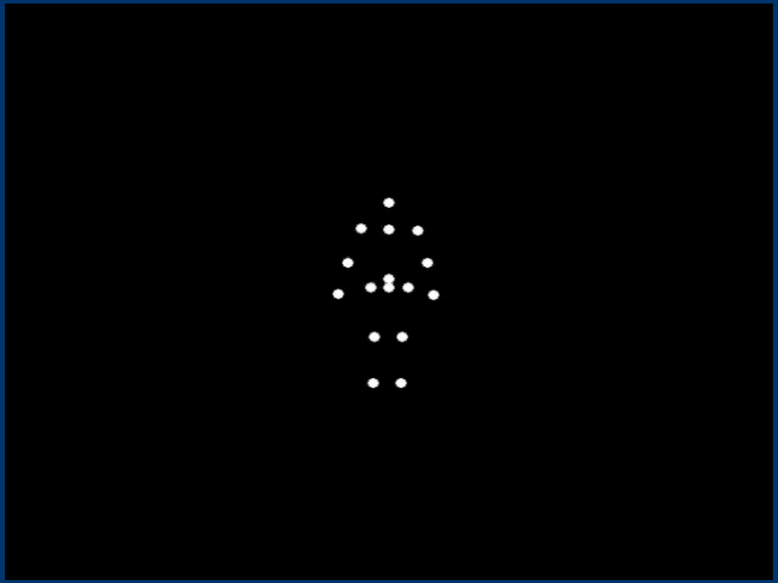


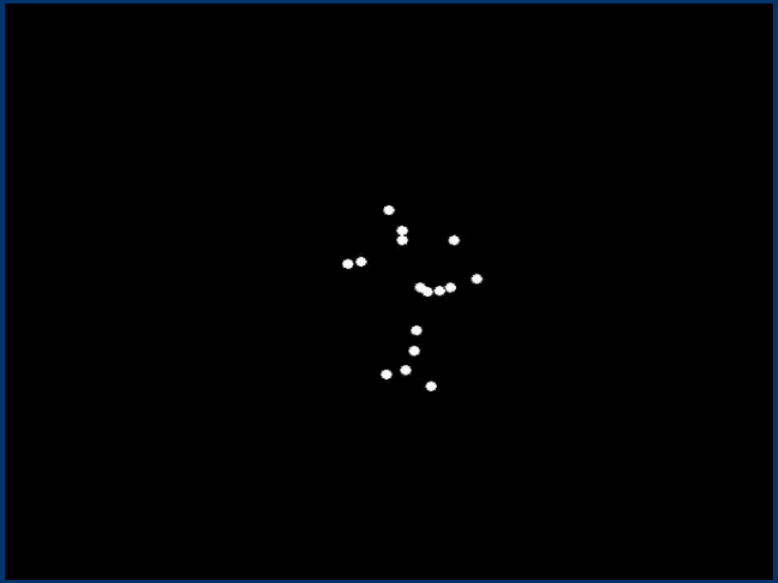


Learned Predictive Model

Inputs: Baseline fMRI-Derived Parameters

- Biopoint: Biological motion perception paradigm





- Focus on brain regions associated with social motivation: Orbitofrontal cortex, ventromedial prefrontal cortex, amygdala, and ventral striatum

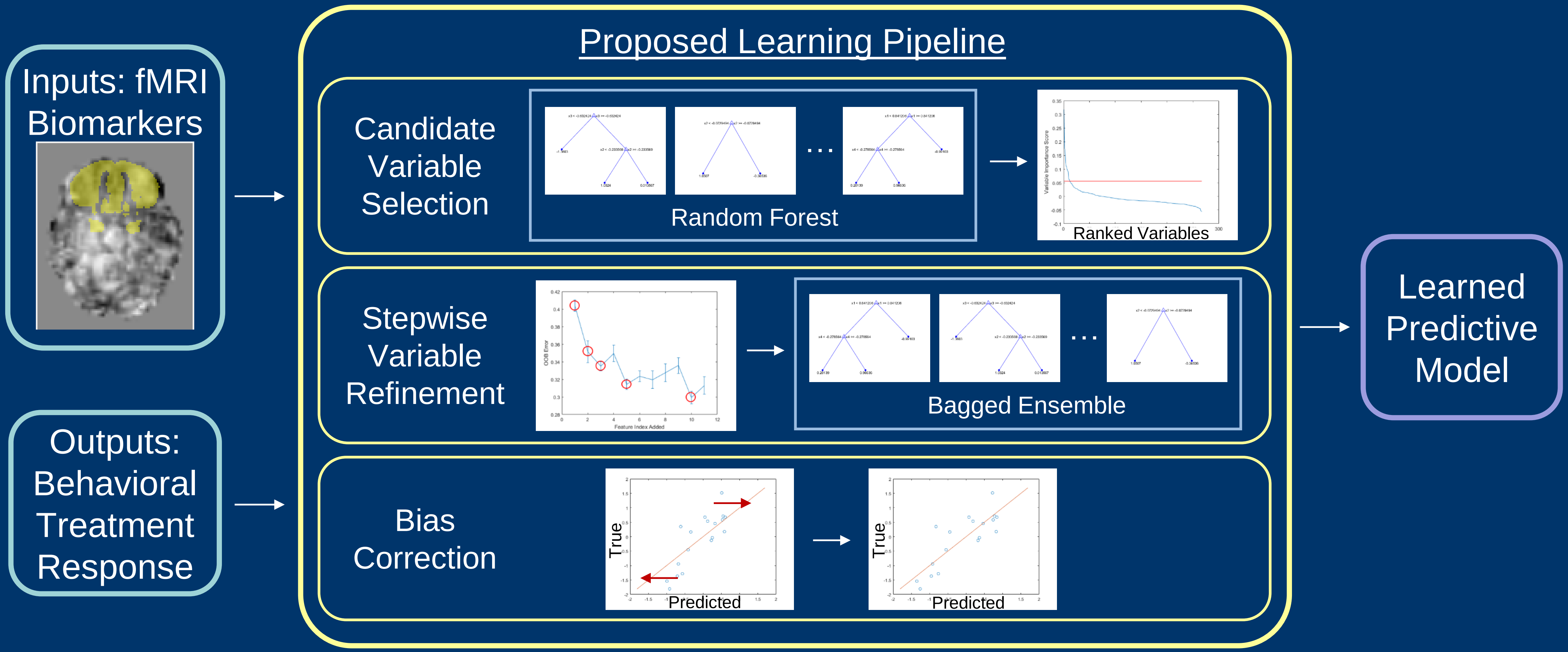
→ Inputs: t-statistics for biological motion > scrambled motion contrast

Outputs: Behavioral Treatment Outcome

- Social Responsiveness Scale, Second Edition (SRS) Score
  - Measures severity of social impairment in ASD
  - Lower SRS score → Better function
- Measure SRS score at baseline and post-treatment

→ Outputs: Normalized change in SRS Score (ΔSRS)

Learning Pipeline Overview



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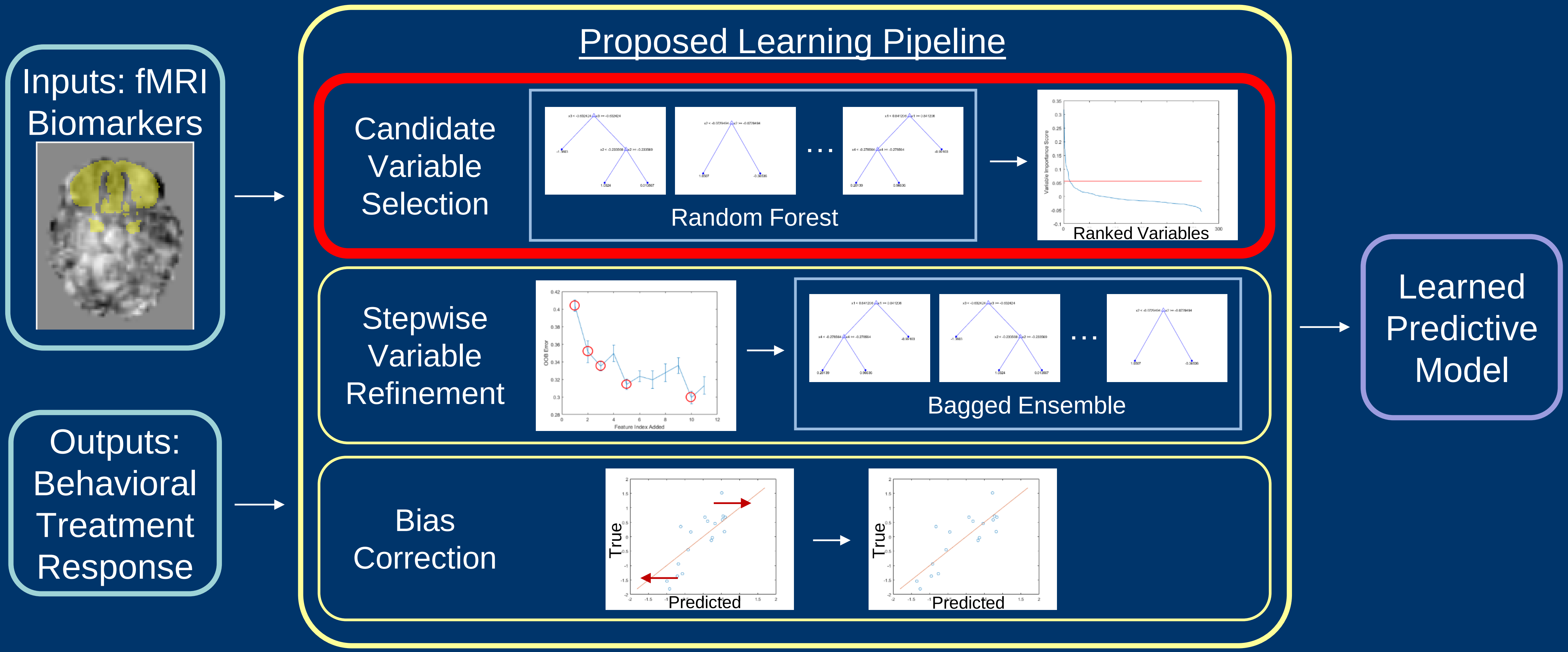
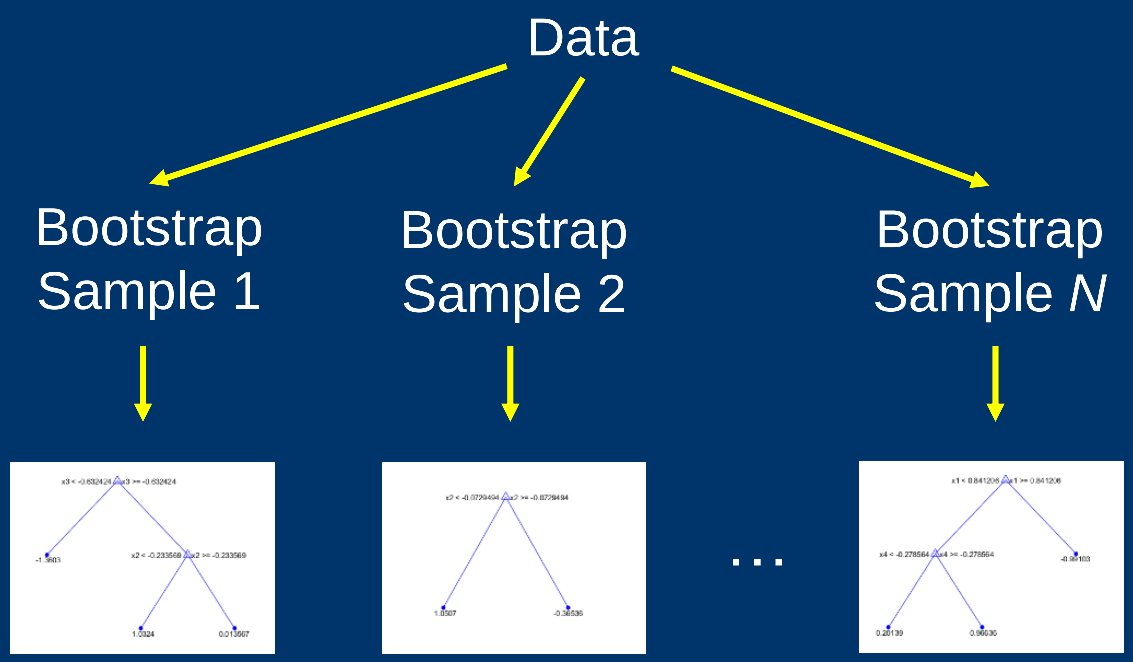


Random Forests for Regression Review

- Ensemble learning method that uses
  - Bagging



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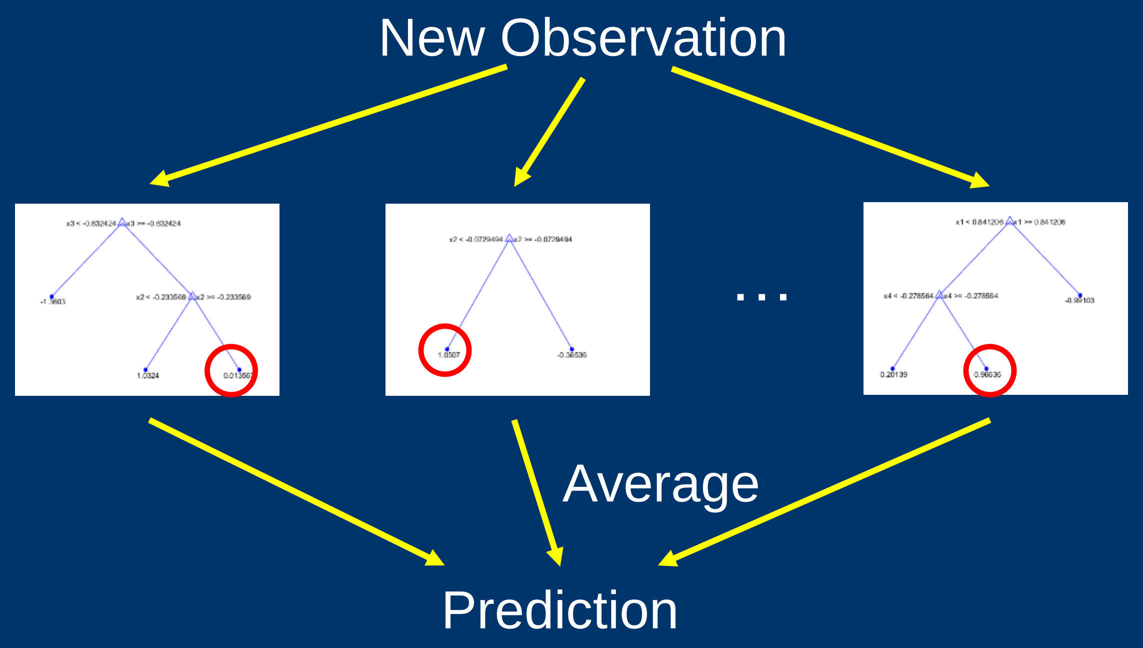
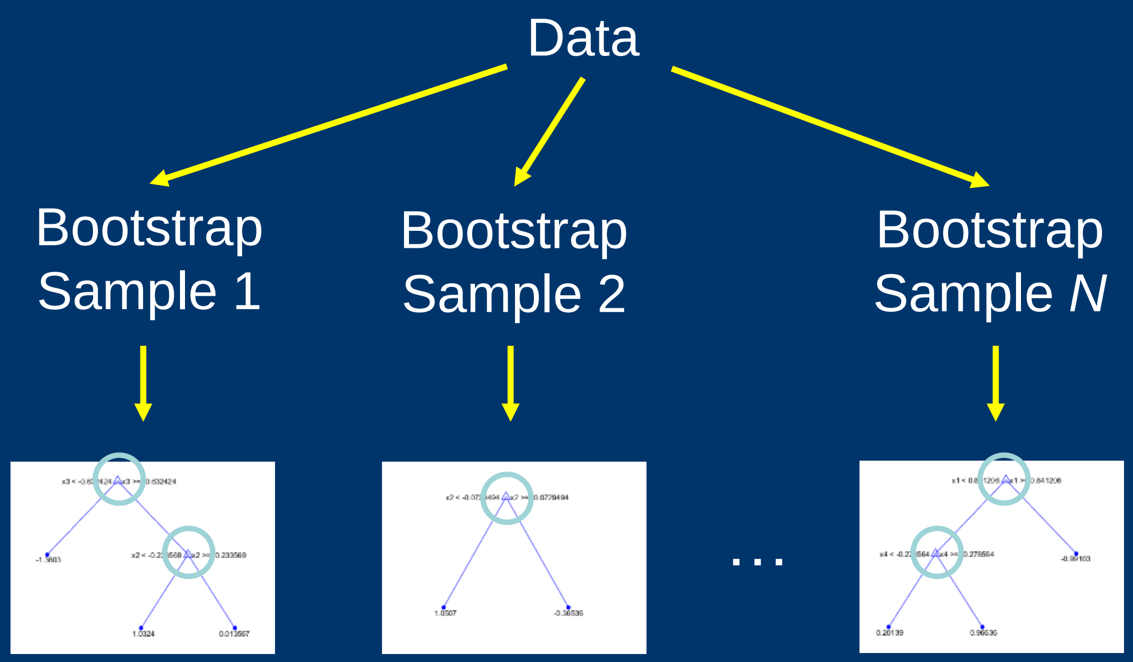


Random Forests for Regression Review

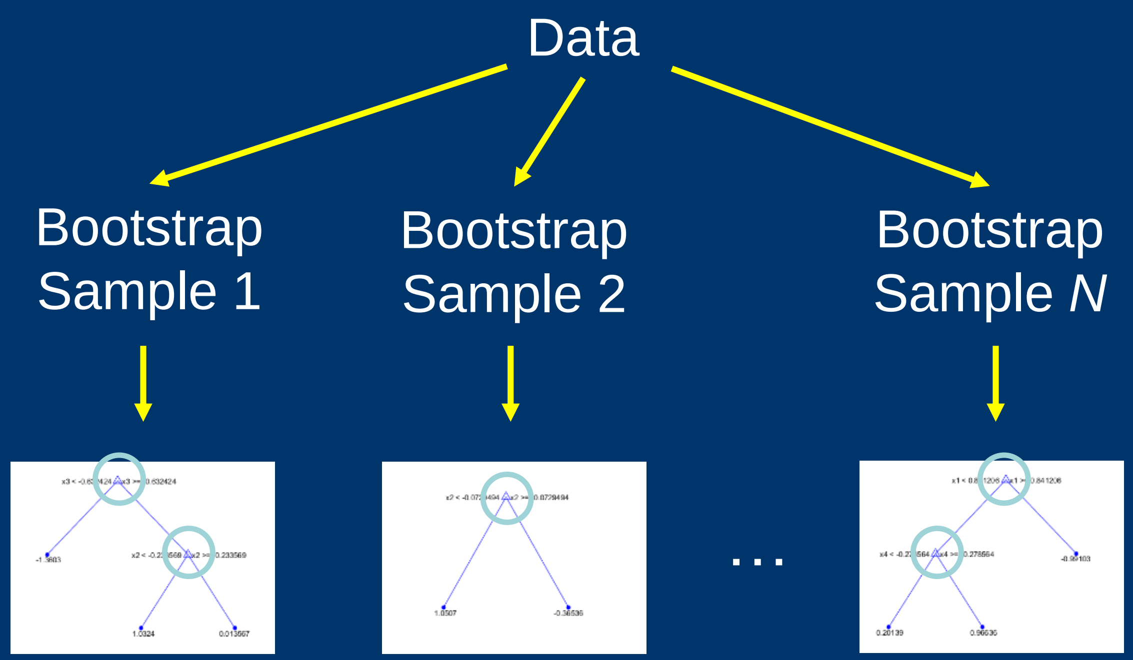
- Ensemble learning method that uses
  - Bagging
  - Random subset sampling of predictors



Best split variable chosen from *m* randomly selected predictors

Random Forests for Regression Advantages

- Reduced correlation of trees → Reduced variance of estimate
- Efficient exploration of high dimensional inputs



Best split variable chosen from *m* randomly selected predictors

Random Forests for Regression
Out-of-bag (OOB) Error

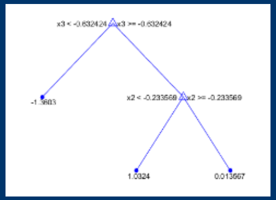
- Internal estimate of test error rate estimated by out-of-bag (OOB) error
- $E = \sum_{i}(Y_{i,oob} - Y_{i,true})^2$

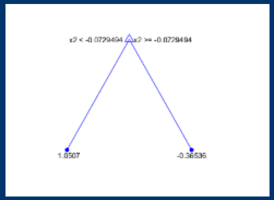
Observation *i*

OOB Sample 1

Not OOB Sample 2

OOB Sample N





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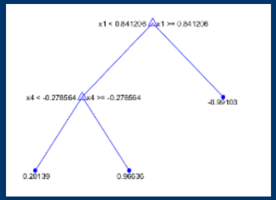


Average

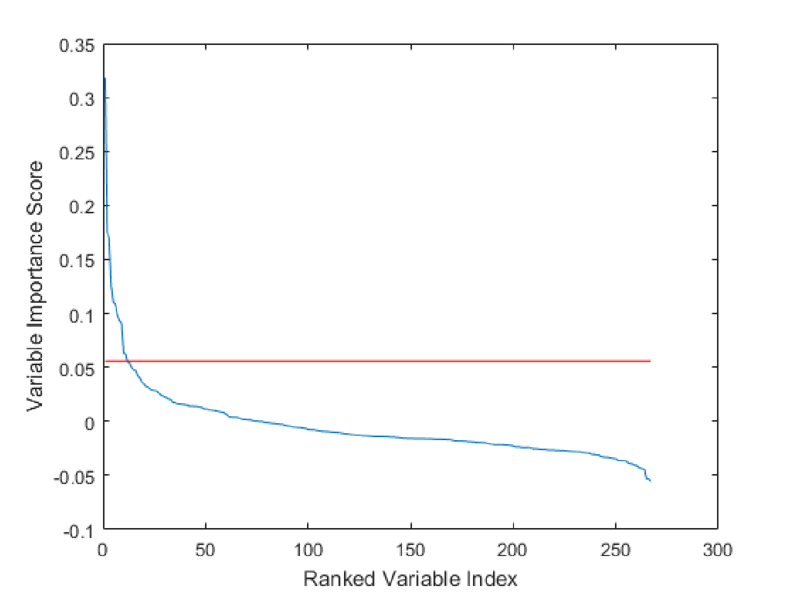
$Y_{i,oob}$

Random Forests for Regression Variable Importance

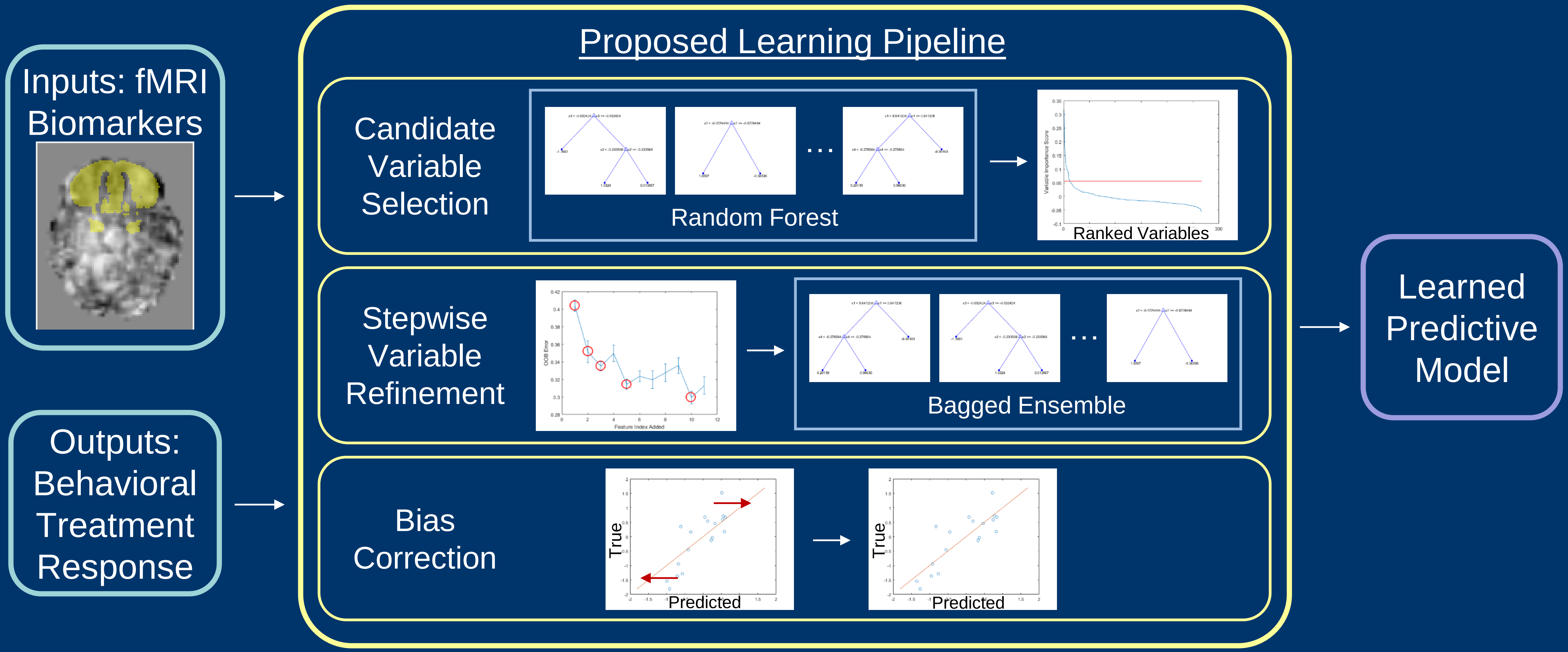
- For each tree and variable
  - Randomly permute values for the OOB samples
  - Calculate change in prediction error
- Importance score: Average change in error over all trees
- Bigger increase in error → higher variable importance
- Note: small negative scores possible due to randomness

Candidate Variable Selection Using Variable Importance

- Run random forests to obtain variable importance scores
- Retain voxels with score > absolute value of lowest negative score
  - Intuition: Irrelevant variables have low scores that fluctuate around 0



Learning Pipeline Overview



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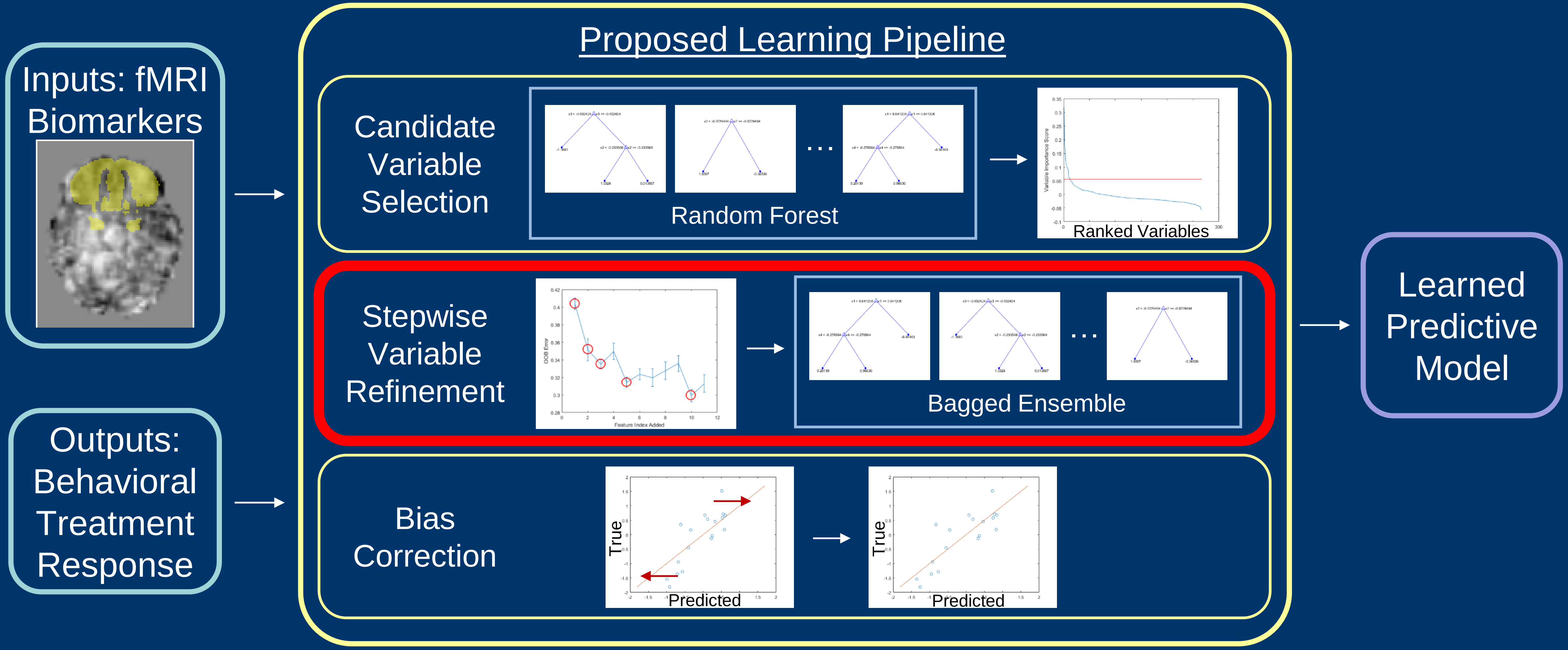
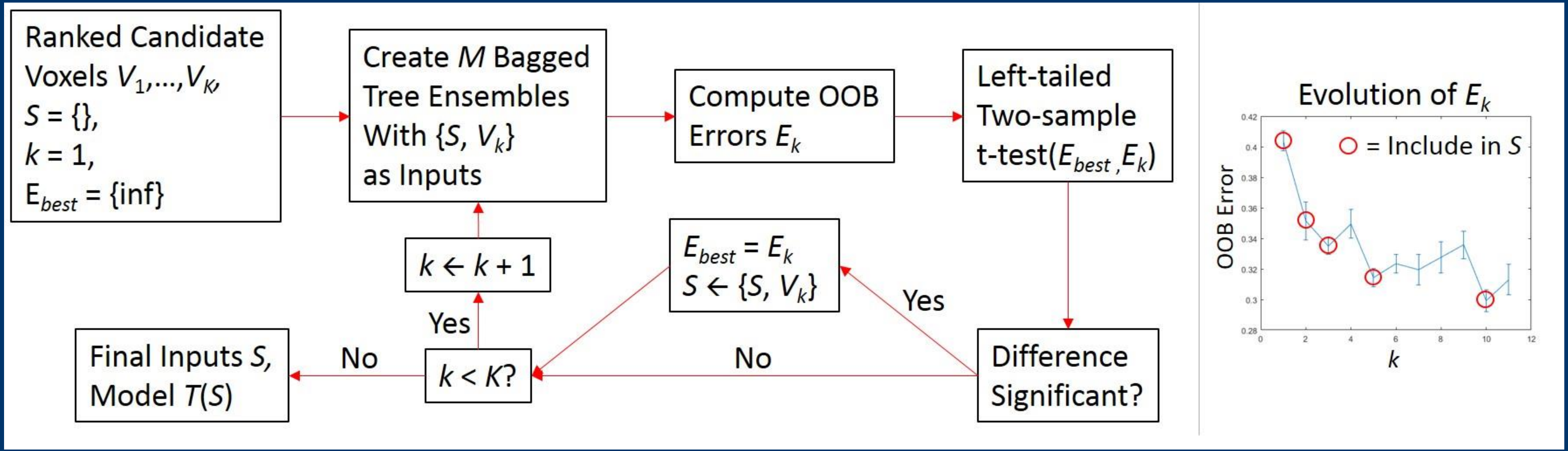


Stepwise Variable Refinement

- Iteratively refine candidate input variables for bagged tree ensemble
- V_i = *i*th ranked candidate voxel, *S* = Set of best voxel inputs, *E* = OOB Error



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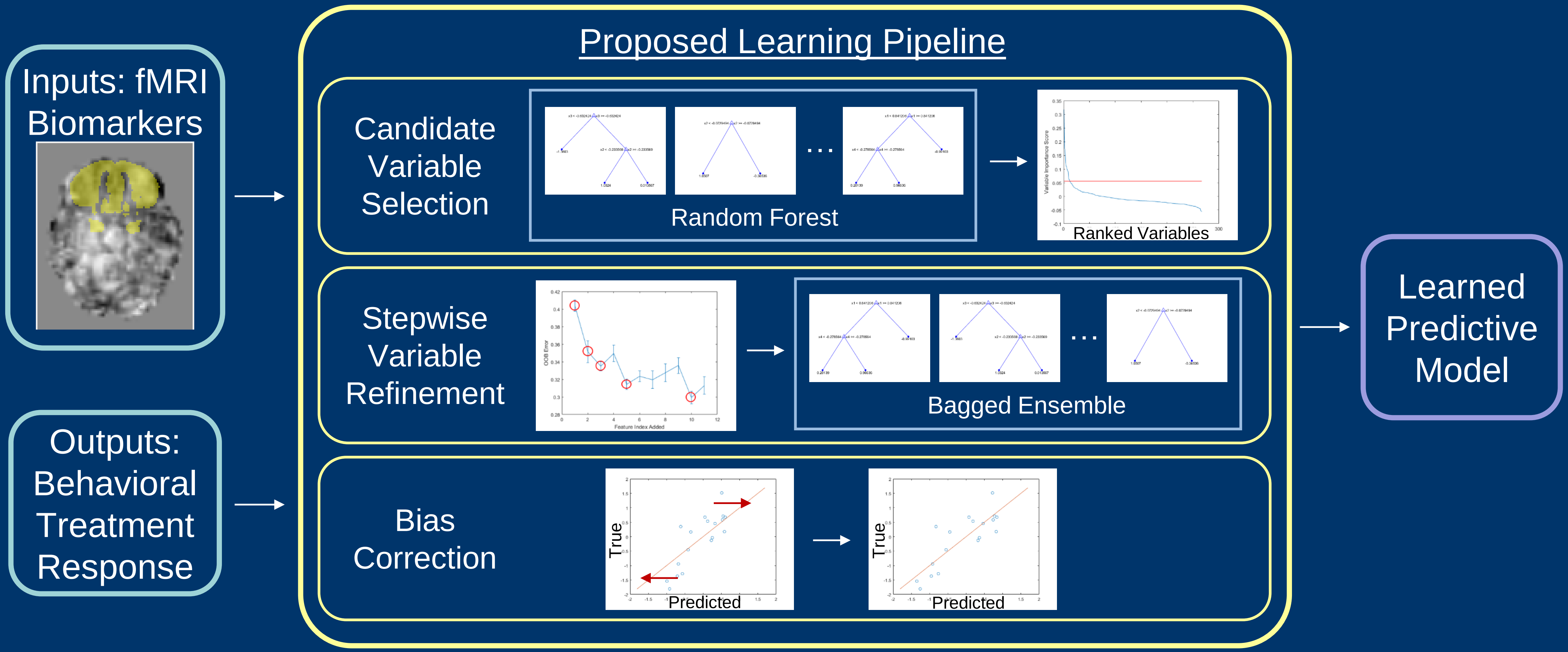

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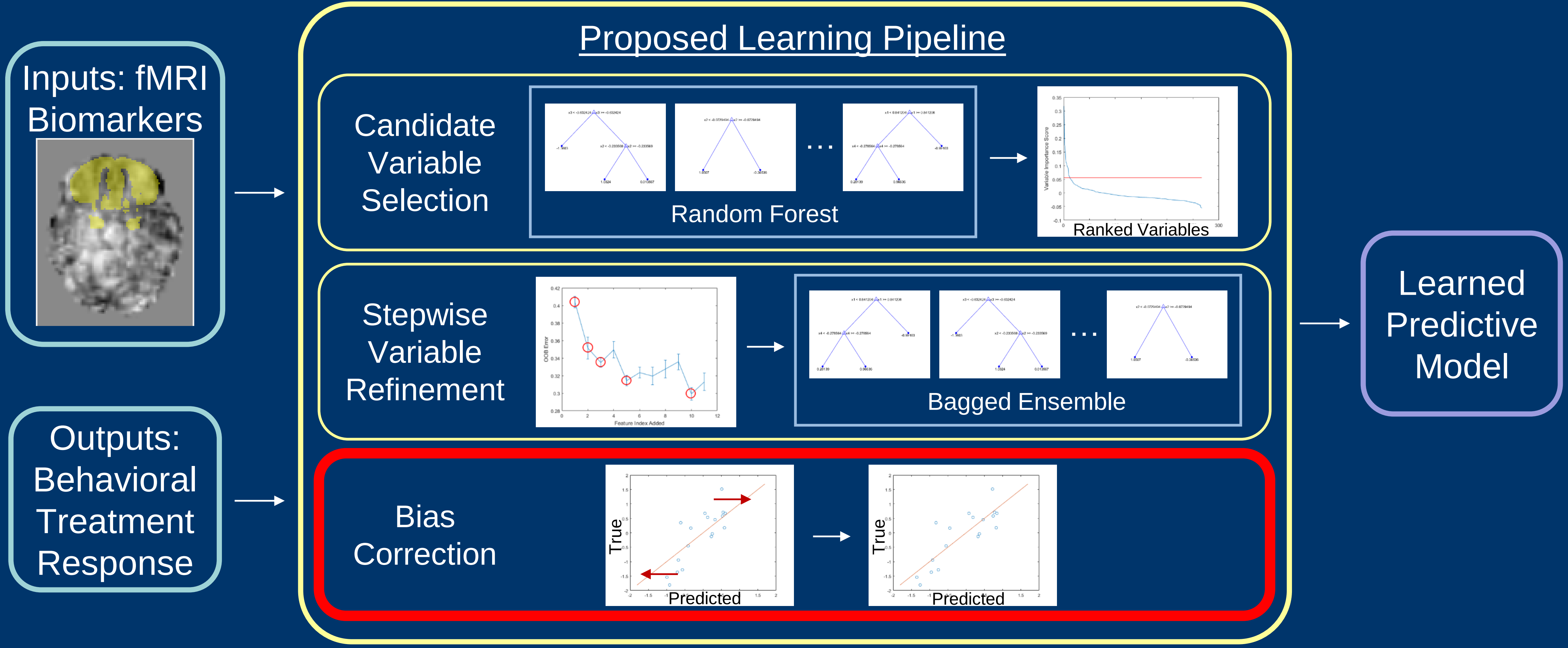
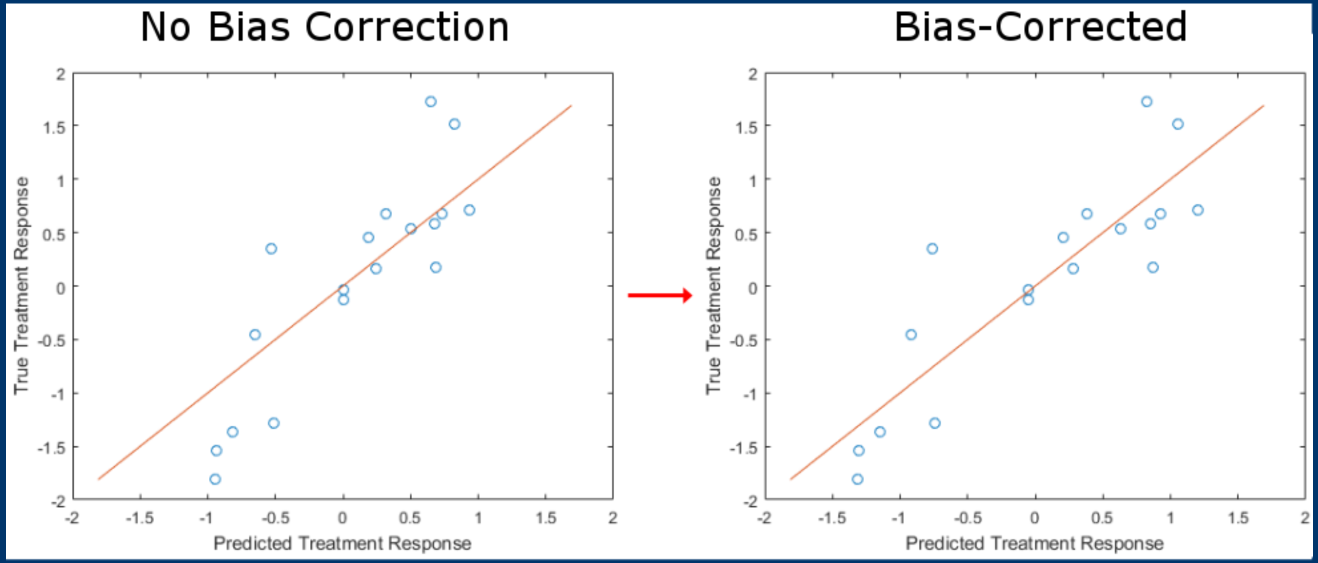


Bias Correction

- Regression tree ensembles underestimate high values and overestimate low values
- Linear model: $Y_{\text{true}} = \beta_1 Y_{\text{ens}} + \beta_0$
- Estimate parameters using OOB predictions



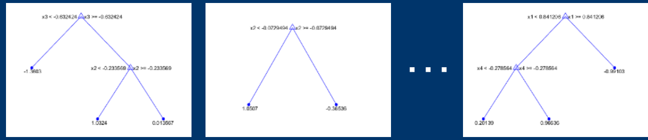
Learning Pipeline Overview

Inputs: fMRI Biomarkers

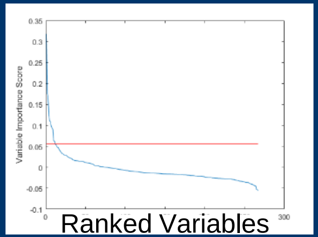
Outputs: Behavioral Treatment Response

Proposed Learning Pipeline

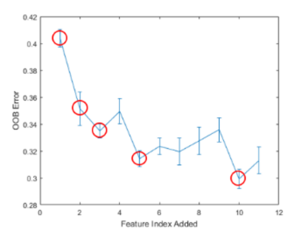
Candidate Variable Selection

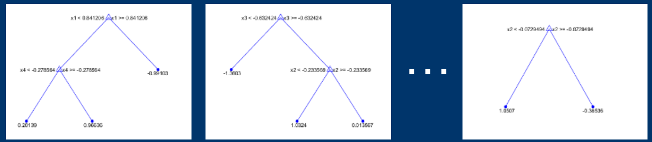


Random Forest



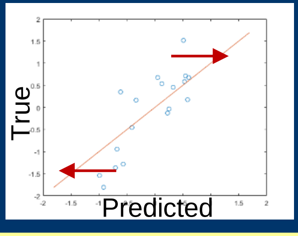
Stepwise Variable Refinement

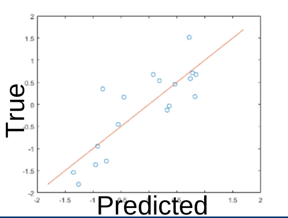




Bagged Ensemble

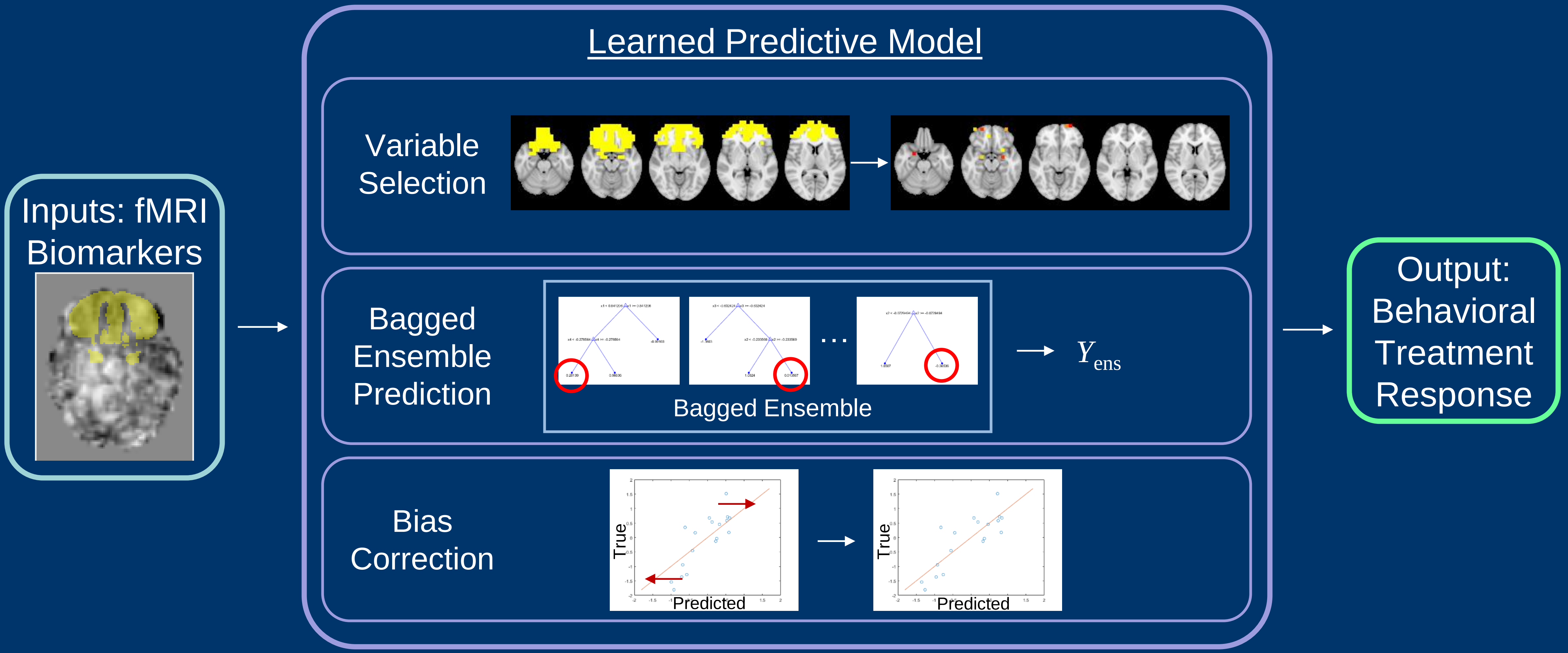
Bias Correction





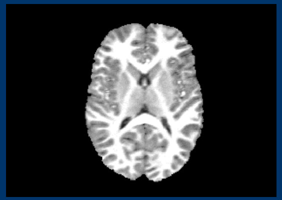
Learned Predictive Model

Predictions from New Data



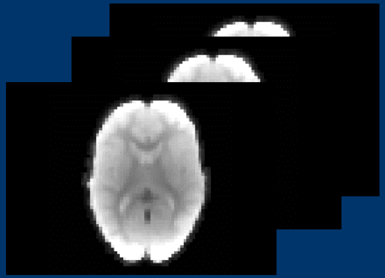
Data

- 19 ASD children underwent 16 weeks Pivotal Response Therapy, 7 hrs/week
- Imaging at baseline:
  - T1-weighted MP-RAGE structural MRI



1 x 1 x 1 mm^3

  - BOLD T2*-weighted fMRI with Biopoint paradigm

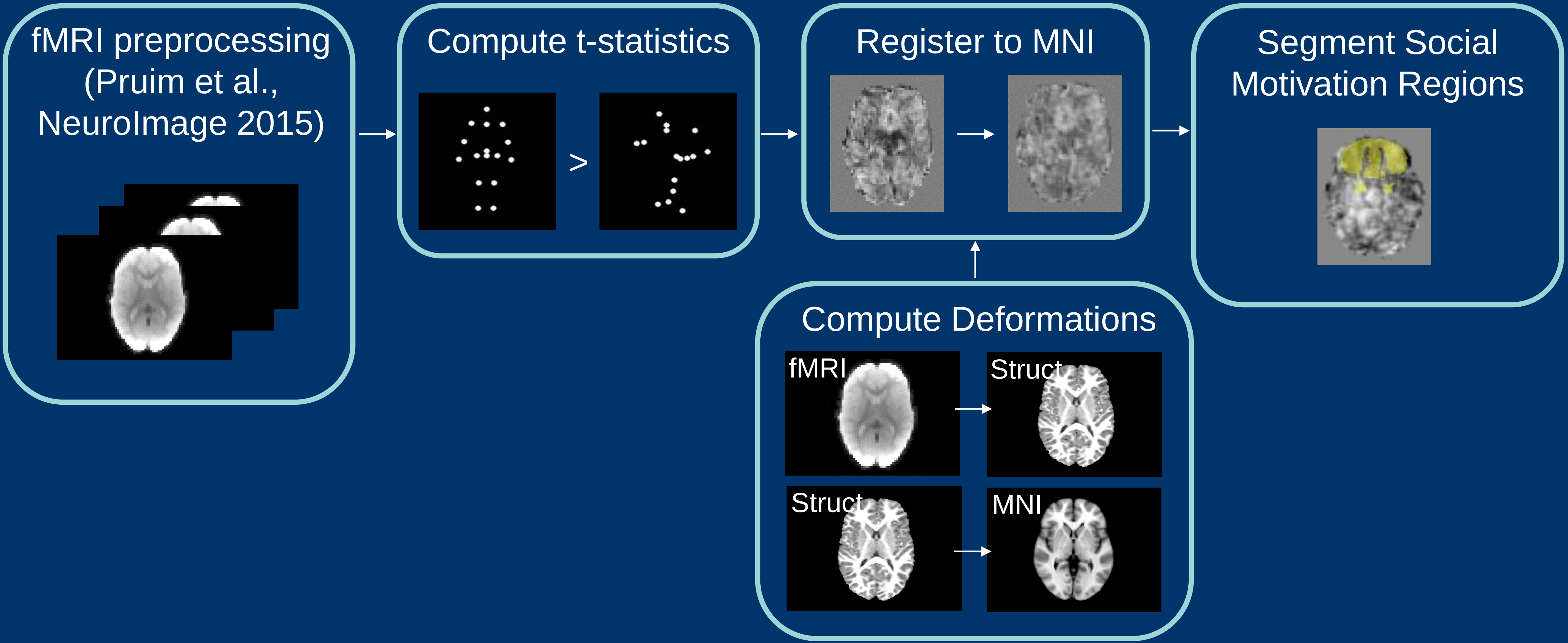


164 volumes

3.44 x 3.44 x 4.00 mm^3

- Note: Data collection involved > 2200 hours

Image Preprocessing



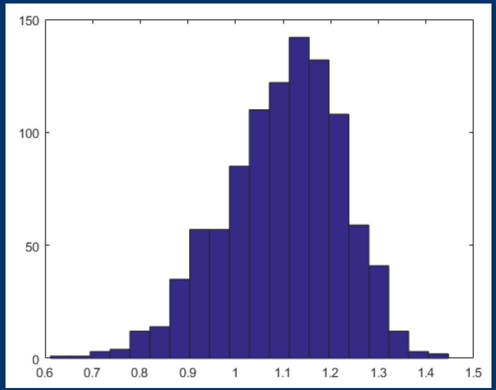
Methods Compared

1. Standard random forest
2. Standard support vector machine with linear kernel
3. Random forest variable selection → random forest
4. Random forest variable selection → bagging
5. Random forest variable selection → stepwise variable refinement
6. Random forest variable selection → stepwise variable refinement → bias correction (Proposed approach)

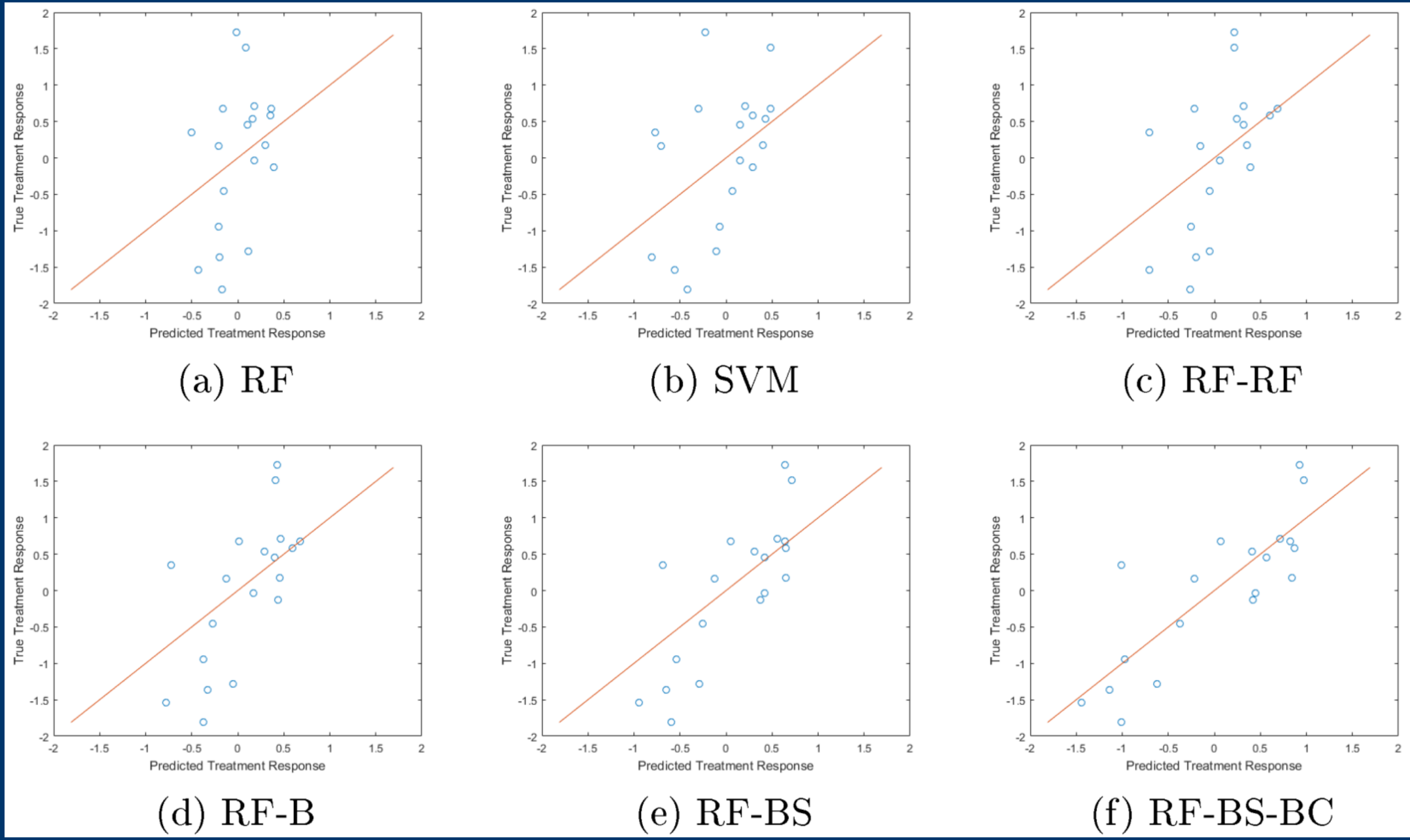
- MATLAB implementation with default parameters, except
  - 5000 trees for variable selection
  - 1000 trees for final models

Evaluation Criteria

- Leave-one-out cross-validation
- Accuracy measures for
  - Outputs (ΔSRS)
    - Mean squared error
    - Pearson's correlation coefficient
  - Predicted outcomes (Post SRS)
    - Relative absolute error
    - Mean absolute percentage error
- Significance assessed using permutation tests
  - p = (# runs with values more extreme than observed statistic) / 1000



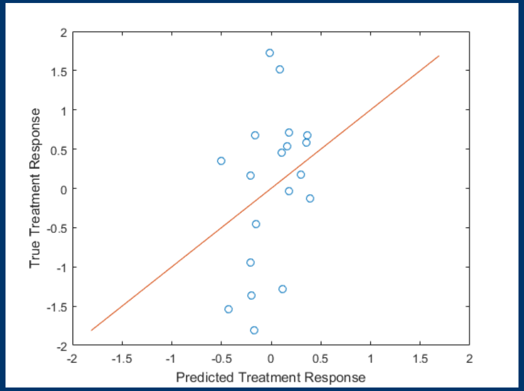
True vs. Predicted Response



Red line: Perfect prediction

Prediction Accuracy

Algorithm	MSE $\pm$ SD	p_{MSE}	r	p_r	RAE	p_{RAE}	MAPE $\pm$ SD	p_{MAPE}
RF	0.82 $\pm$ 0.96	0.019	0.39	0.038	0.63	0.044	0.24 $\pm$ 0.26	0.043
SVM	0.75 $\pm$ 0.93	0.037	0.46	0.040	0.60	0.051	0.22 $\pm$ 0.22	0.051
RF-RF	0.69 $\pm$ 0.80	0.024	0.54	0.023	0.56	0.026	0.21 $\pm$ 0.25	0.030
RF-B	0.57 $\pm$ 0.67	0.012	0.68	0.006	0.50	0.012	0.20 $\pm$ 0.23	0.025
RF-BS	0.40 $\pm$ 0.45	0.001	0.80	0.001	0.44	0.005	0.17 $\pm$ 0.19	0.013
RF-BS-BC	0.29 $\pm$ 0.43	0.001	0.83	0.001	0.35	0.001	0.13 $\pm$ 0.15	0.001



Random forest:
Worst prediction accuracy

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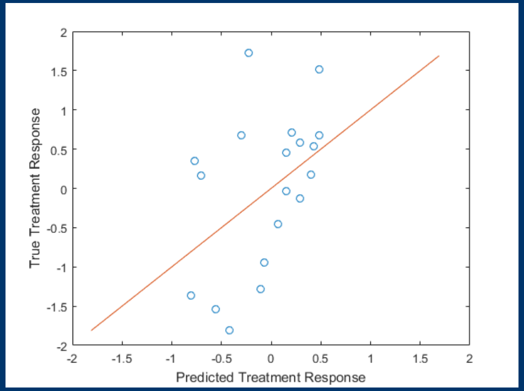

Support vector machine:
Similar errors as random forest

Prediction Accuracy

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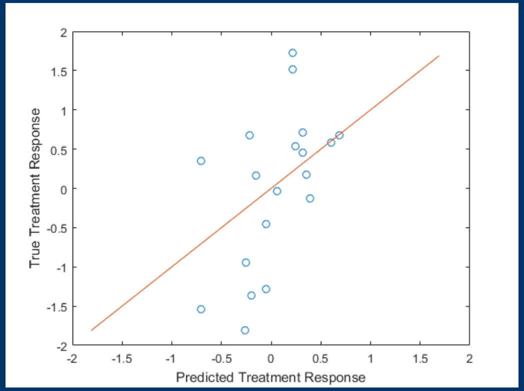

Select top variables → random forest:
Variable selection improves prediction

Prediction Accuracy

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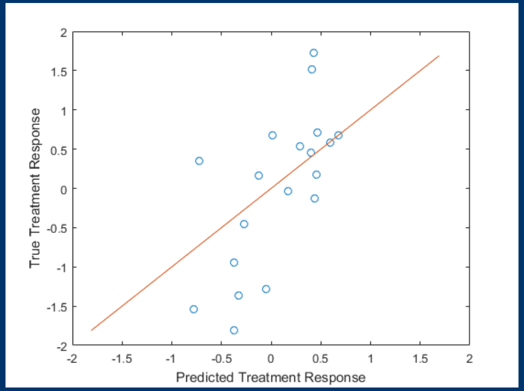

Select top variables → bagging: Stronger trees reduce errors

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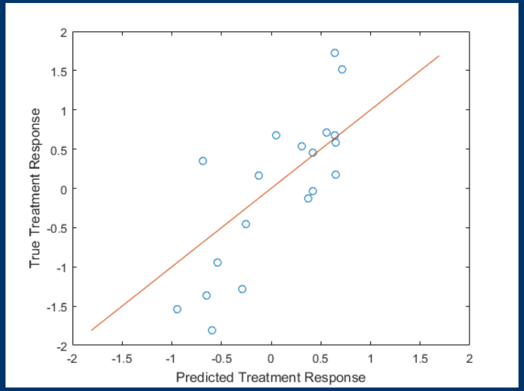
Algorithm	MSE ± SD	p_{MSE}	r	p_r	RAE	p_{RAE}	MAPE ± SD	p_{MAPE}
RF	0.82 ± 0.96	0.019	0.39	0.038	0.63	0.044	0.24 ± 0.26	0.043
SVM	0.75 ± 0.93	0.037	0.46	0.040	0.60	0.051	0.22 ± 0.22	0.051
RF-RF	0.69 ± 0.80	0.024	0.54	0.023	0.56	0.026	0.21 ± 0.25	0.030
RF-B	0.57 ± 0.67	0.012	0.68	0.006	0.50	0.012	0.20 ± 0.23	0.025
RF-BS	0.40 ± 0.45	0.001	0.80	0.001	0.44	0.005	0.17 ± 0.19	0.013
RF-BS-BC	0.29 ± 0.43	0.001	0.83	0.001	0.35	0.001	0.13 ± 0.15	0.001



Stepwise variable refinement:
Improved over bagging top variables

Prediction Accuracy

Algorithm	MSE ± SD	p_{MSE}	r	p_r	RAE	p_{RAE}	MAPE ± SD	p_{MAPE}
RF	0.82 ± 0.96	0.019	0.39	0.038	0.63	0.044	0.24 ± 0.26	0.043
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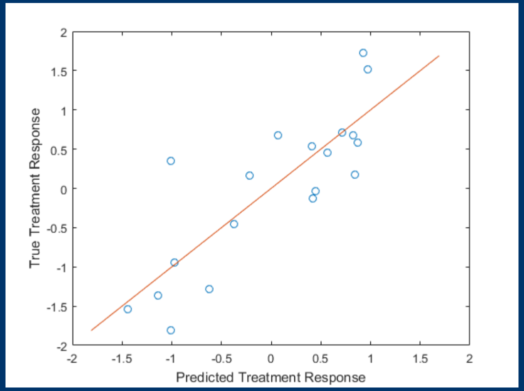


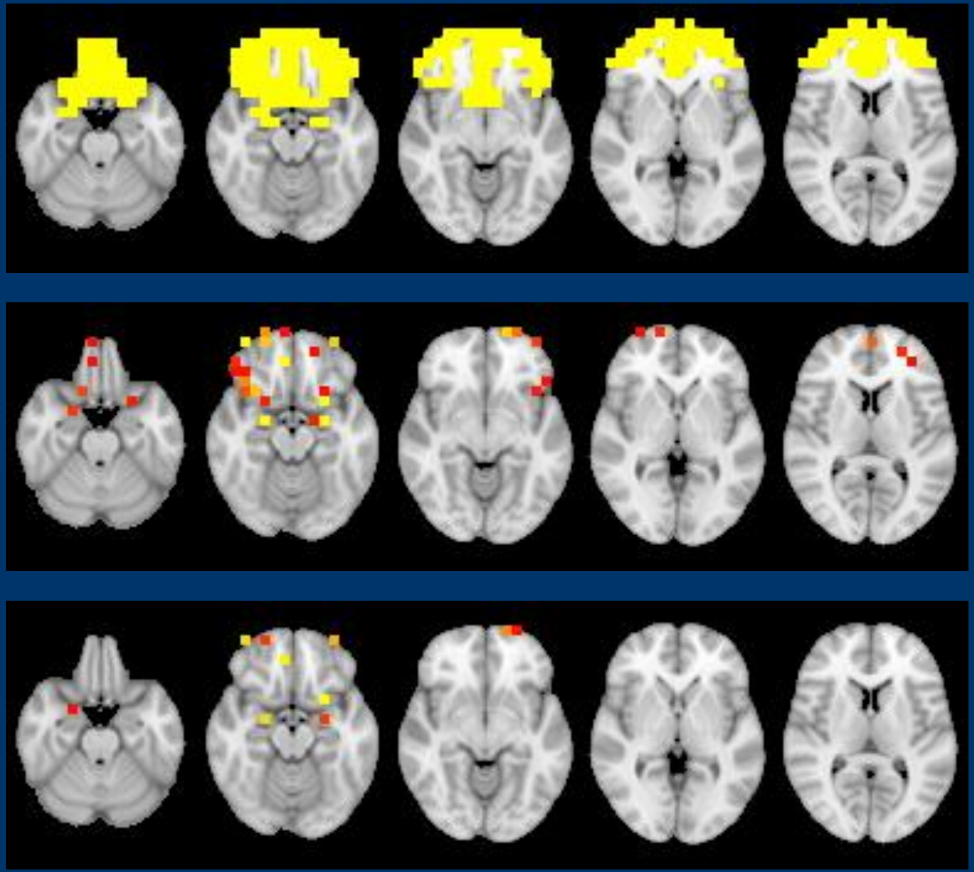
Proposed approach:
Highest prediction accuracy

Variable Selection Results

Social motivation regions (original inputs): Orbitofrontal cortex, ventromedial prefrontal cortex, amygdala, ventral striatum

Random forest candidate variable selection

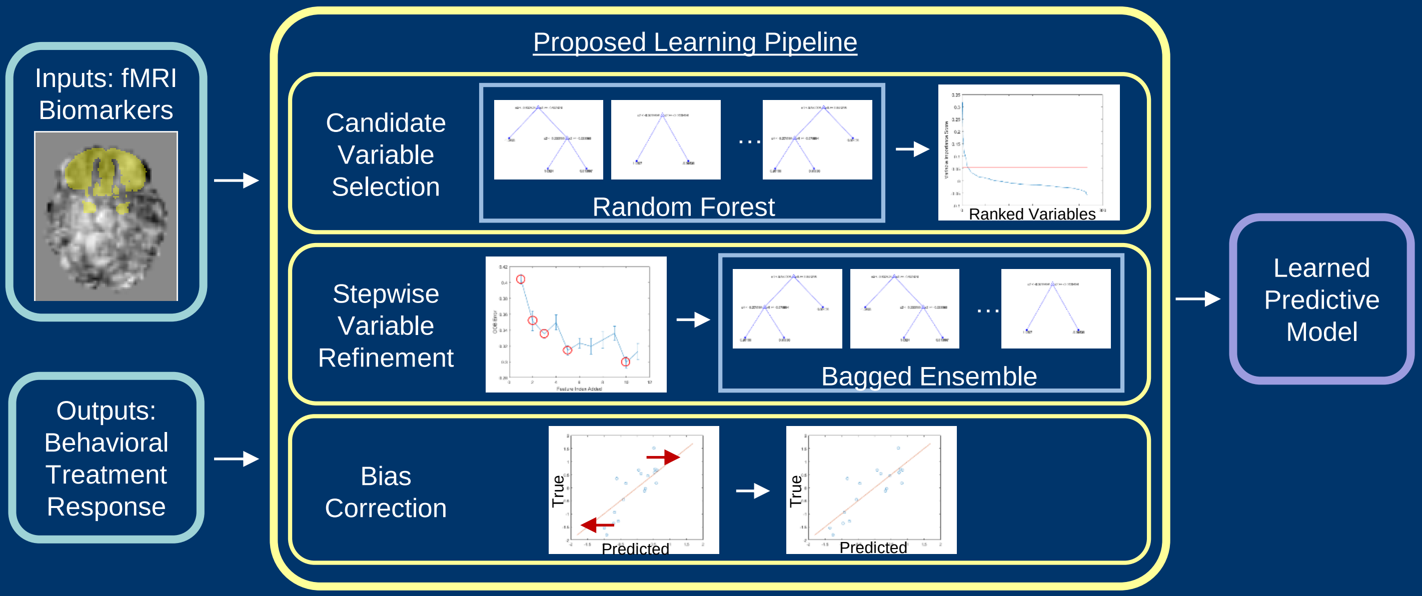
Stepwise variable refinement (final inputs)



Red → Yellow: More frequently selected across trials

Conclusions

- Developed learning pipeline to predict response to autism behavior therapy from baseline fMRI
- Move toward personalized treatment



- Future work
  - Explore other biomarkers for prediction, e.g., functional connectivity
  - More data, assess generalization

Thank You!

- Dr. Pamela Ventola (Data collection)
- Dr. Daniel Yang (fMRI preprocessing)
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