Confounding variables, how do we account for them?

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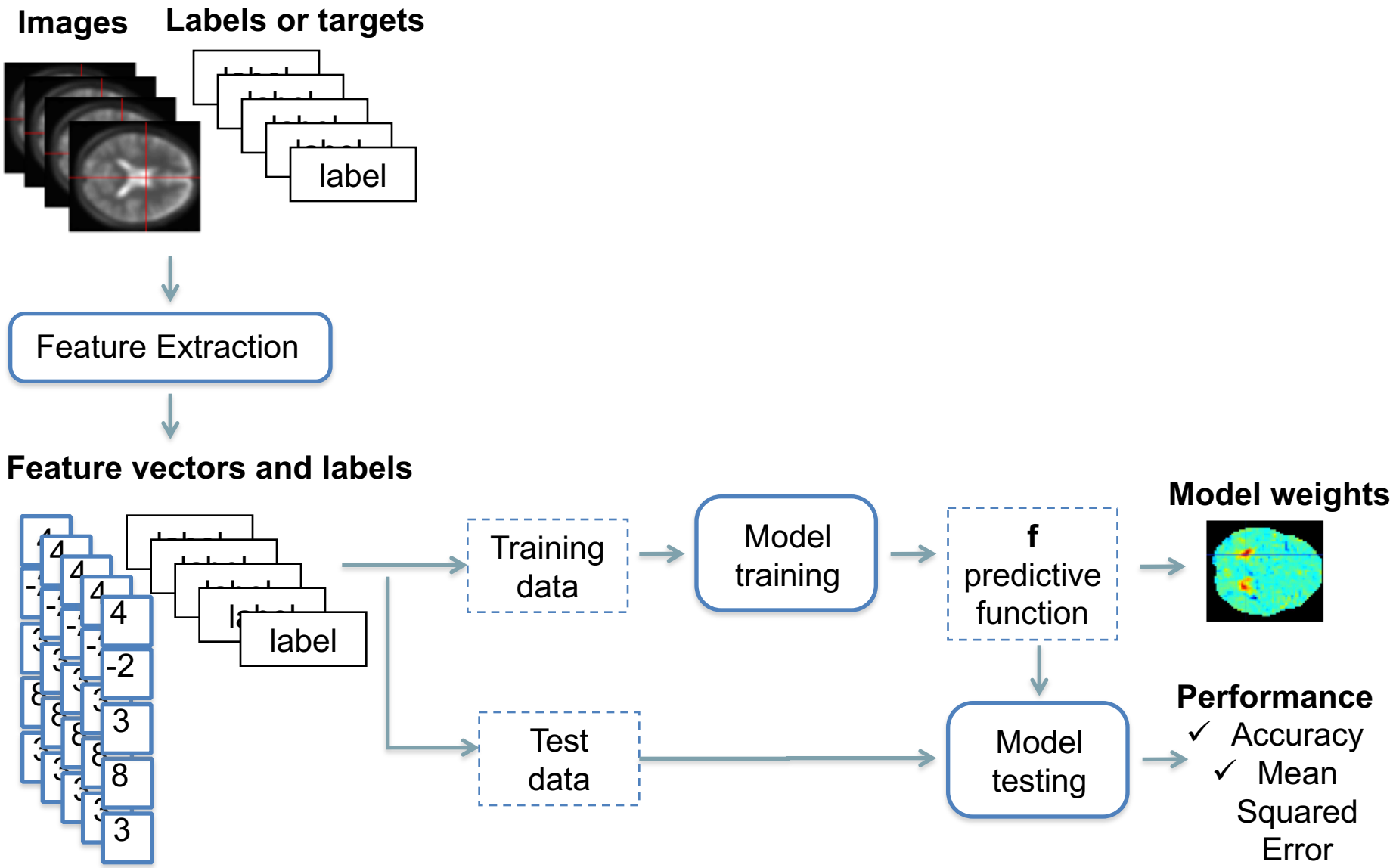
Outline

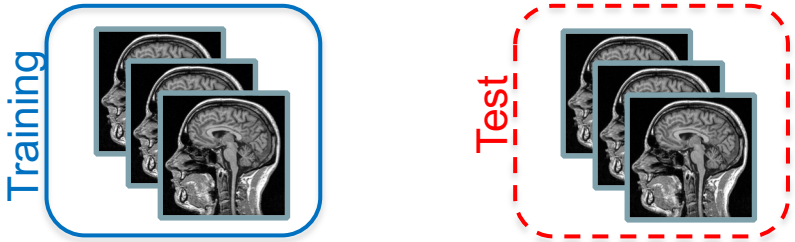
- ✓ Neuroimaging-based predictive models
- ✓ What are confounds in neuroimaging-based predictive models?
- ✓ Common strategies to account for confounds
- ✓ Comparative results
- ✓ A machine learning perspective

Neuroimaging-based predictive models

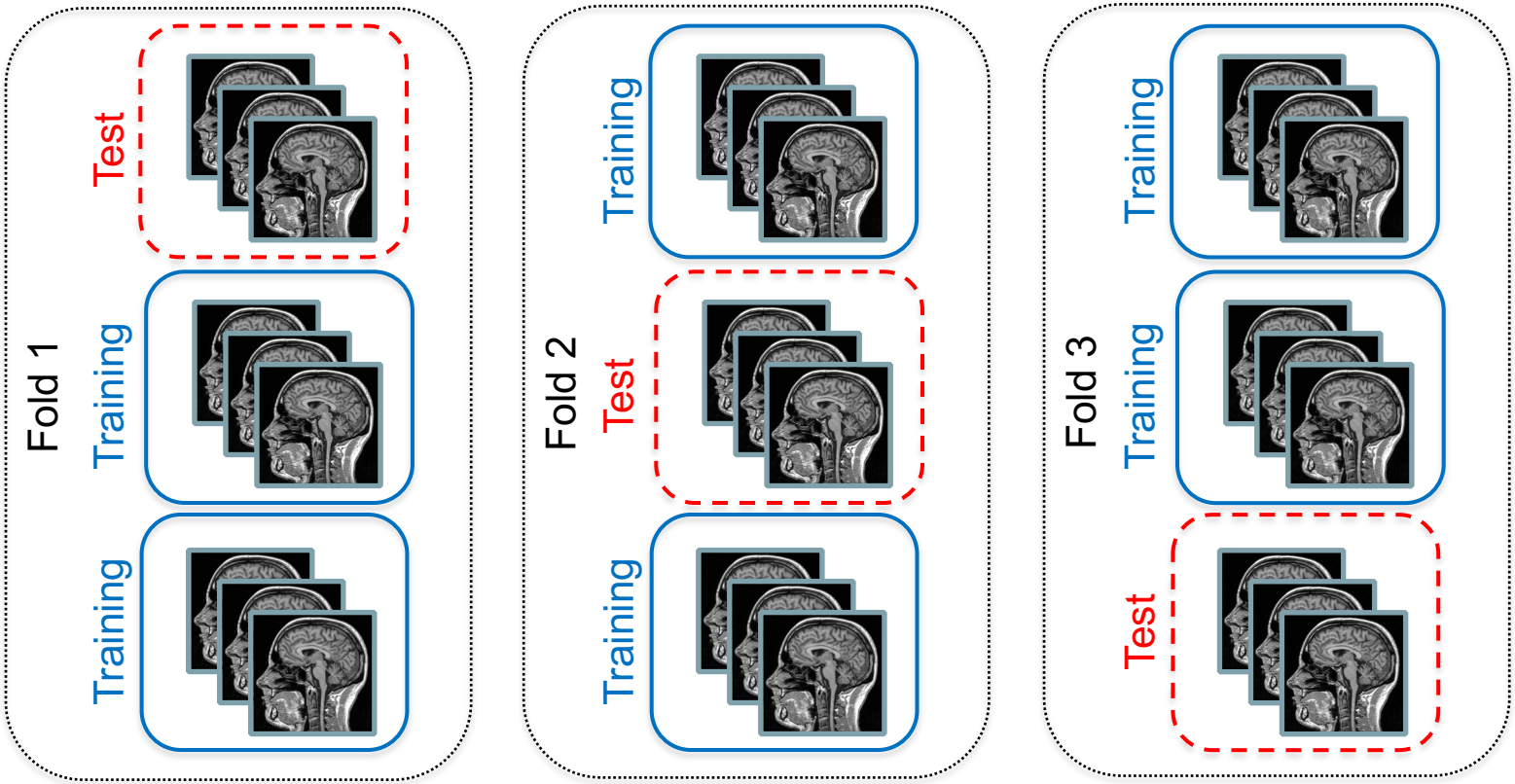


How do we split the data into training/test?

- Half split



- K-fold cross-validation strategy (e.g. k=3, 5, 10)



What are confounds in neuroimaging-based predictive models?

Definition 1: "***variable*** *that affects the* ***neuroimaging data*** *and/or the* ***targets*** *but is not of interest from a neuroscience or clinical perspective.*"

Definition 2: "***variable*** *that is not of primary interest, correlates with the* ***to-be-decoded variable*** *(the target), and is encoded in the* ***neuroimaging data***" (Snoek et al. 2019).

Definition 3: "***variable*** *which affects the* ***imaging data*** *and has an association with the* ***target*** *variable in the sample that differs from that in the* ***population-of-interest***" (Rao et al., 2017).

Example of confounds in neuroimaging-based predictive models

Example 1: Predicting ***age*** from structural MRI data considering ***site/scanner*** as confound.

Example 2: Predicting ***cognitive decline*** in demented patients from structural MRI data considering ***age*** and **sex** as confounds.

Example 3: Predicting ***object category*** from fMRI activity patterns considering ***luminance*** and ***spatial frequency*** as confounds.

What are the reasons to account for confounds?

- ✓ **Improve the generalizability of the models:**
  - Account for scanner related noise in the images to improve the performance of the model.

- ✓ **Improve the interpretability of the models:**
  - Account for total brain volume in order to identify predictive brain features that are not influenced by overall brain size.

Common strategies to account for confounds

1. **Matching / Counter-balancing**
2. **Image adjustment by confounds or regressing-out**
3. Incorporating confounds as predictors
4. Instance-based weighting

Notation

X: features

y: labels

C: confounds

Subject 1	x_{11}	…	x_{1j}	…	x_{1J}	y_1	c_{11}	…	c_{iK}
⋮	…	…	…		…				
Subject *i*	x_{i1}		x_{ij}		x_{iJ}	y_i	c_{i1}	…	c_{iK}
⋮	…	…	…		…				
Subject N	x_{N1}		x_{Nj}		x_{NJ}	y_N	c_{N1}	…	c_{NK}

Feature vector

$\mathbf{x}_i = (x_{i1}, x_{i2}, \dots x_{iJ})$

Vector for feature *j*

$\mathbf{x}_j = (x_{1j}, x_{2j}, \dots x_{Nj})^{\mathsf{T}}$

Label or target for $\mathbf{x}_i$

y_i

Confounds for $\mathbf{x}_i$

$\mathbf{c}_i = (c_{i1}, c_{i2}, \dots, c_{iK})$

1. Matching / Counterbalancing

- The sample is chosen so that there is no significant correlation between the confound variables ($\mathbf{c}$) and the target ($\mathbf{y}$).

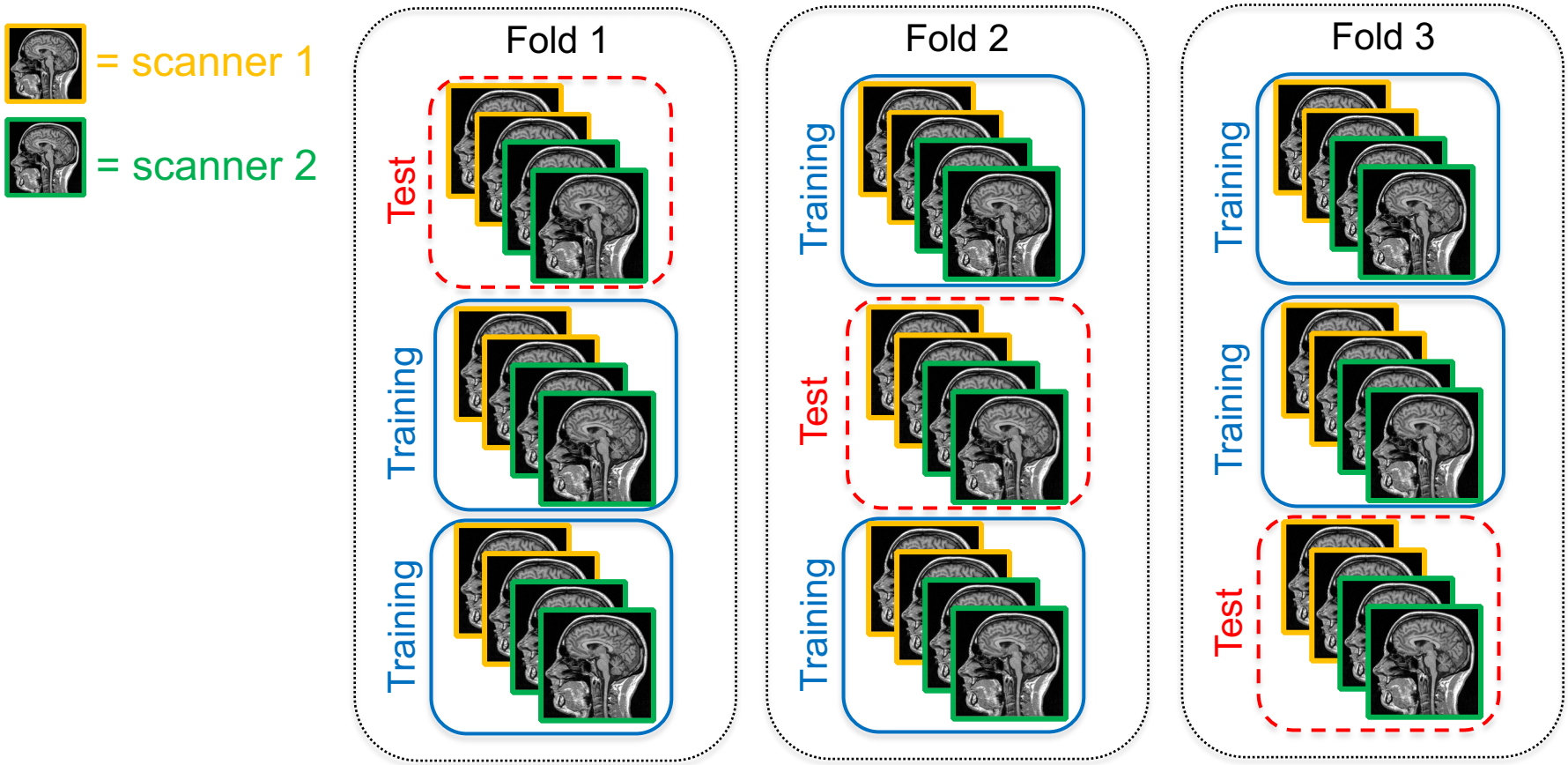
- Matching can be done a priori in the experimental design or post hoc by selecting a subset of a previously acquired sample.

- **Example:** match patients and controls by age and sex in the training and test data.

- **<u>Disadvantages:</u>**
  - **A priori:** the matched sample might not be representative of the population of interest.
  - **Post hoc:** it can reduce the sample size significantly.

1. Matching / Counterbalancing

- Matching should be done across classes (in classification problems) and across folds (during cross-validation).



2. Image adjustment or regressing-out

- Fit a linear regression model for each image feature ($\mathbf{x}_j$) using the confounds ($\mathbf{C}$) as predictors.

- The residuals of the linear regression model (i.e. adjusted images) are used as the input features in the predictive model.

- **Example:** regress-out age and sex from structural MRI and use the adjusted images as input to a predictive model.

- **<u>Disadvantages:</u>**
  - Assumes a linear relationship between the confound and the image features.
  - If the confound variable is correlated with the targets it removes predictive information from the image features.

2. Image adjustment or regressing-out

- For adjusting all image features simultaneously the following matrix equations can be used to estimate **the model parameters** and the **adjusted features**:

$$\boldsymbol{\beta} = \left(\hat{\mathrm{C}}^{T}\hat{\mathrm{C}}\right)^{-1}\hat{\mathrm{C}}^{T}\mathrm{X}$$

$$\mathrm{X}^{A} = \mathrm{X} - \hat{\mathrm{C}}\boldsymbol{\beta}$$

where $\hat{\mathrm{C}}$ is C augmented with a column of ones.

- However, this approach is often applied before splitting the data into training and test which can lead to bias (Snoek et al, 2019).

2. Image adjustment accounting for training/test separation

- Image adjustment should be done within the cross-validation framework to avoid potential bias.

- In this case the confound-imaging relationship is estimated based on the training data only.

- Considering $\mathbf{X}_{train}$ and $\mathbf{X}_{test}$ two partitions of the data and $\mathbf{C}_{train}$ and $\mathbf{C}_{test}$ being the respective confounds, the following matrix equations be be applied:

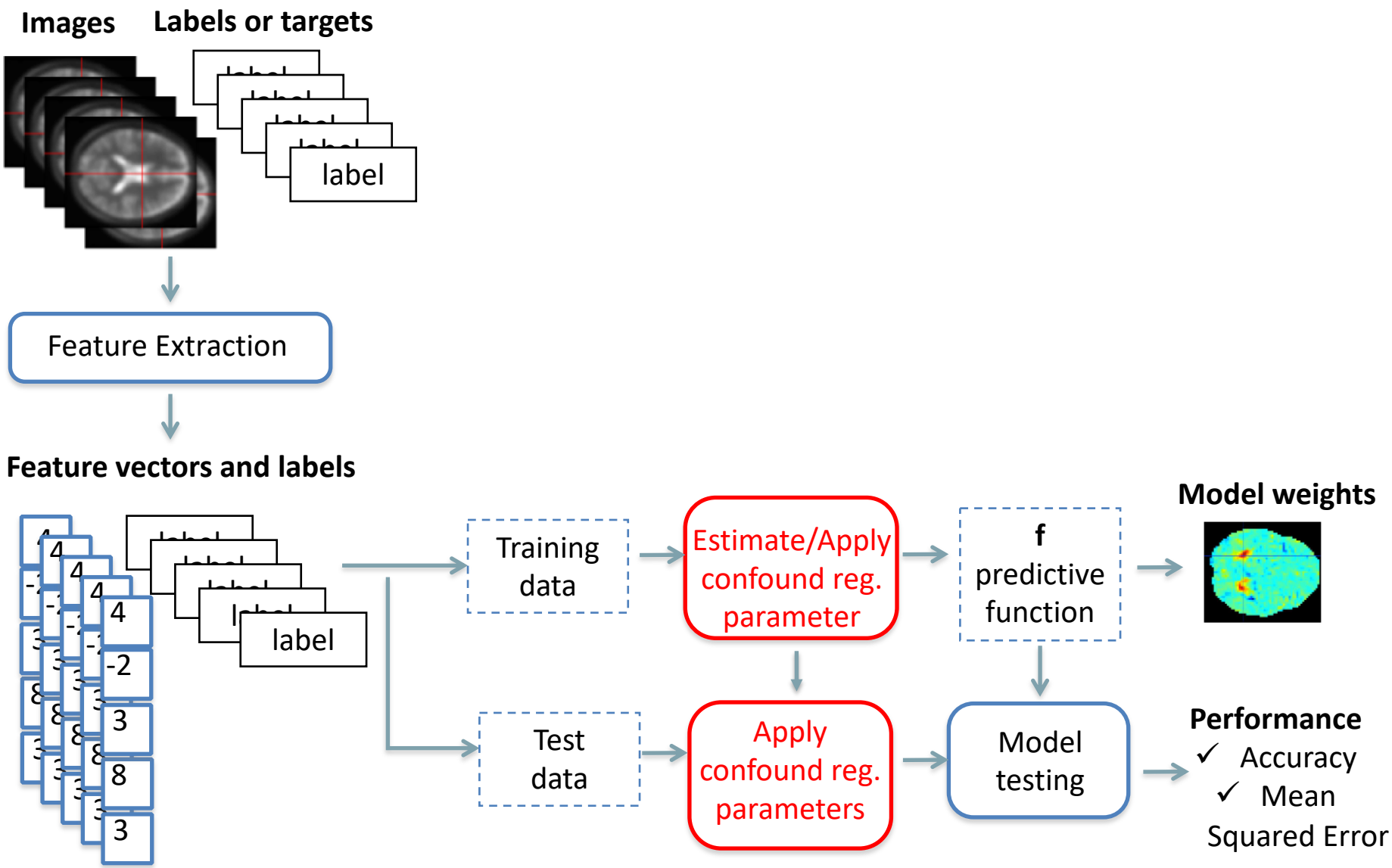
$$\boldsymbol{\beta}_{train} = \left(\hat{\mathbf{C}}_{train}{}^{T}\hat{\mathbf{C}}_{train}\right)^{-1}\hat{\mathbf{C}}_{train}{}^{T}\mathbf{X}_{train}$$

$$\mathbf{X}_{train}{}^{A} = \mathbf{X}_{train} - \hat{\mathbf{C}}_{train}\,\boldsymbol{\beta}_{train}$$

$$\mathbf{X}_{test}{}^{A} = \mathbf{X}_{test} - \hat{\mathbf{C}}_{test}\boldsymbol{\beta}_{train}$$

where $\hat{\mathbf{C}}_{train}$ and $\hat{\mathbf{C}}_{test}$ are $\mathbf{C}_{train}$ and $\mathbf{C}_{test}$ augmented with a column of ones

2. Image adjustment accounting for train/test



3. Incorporating confounds as predictors

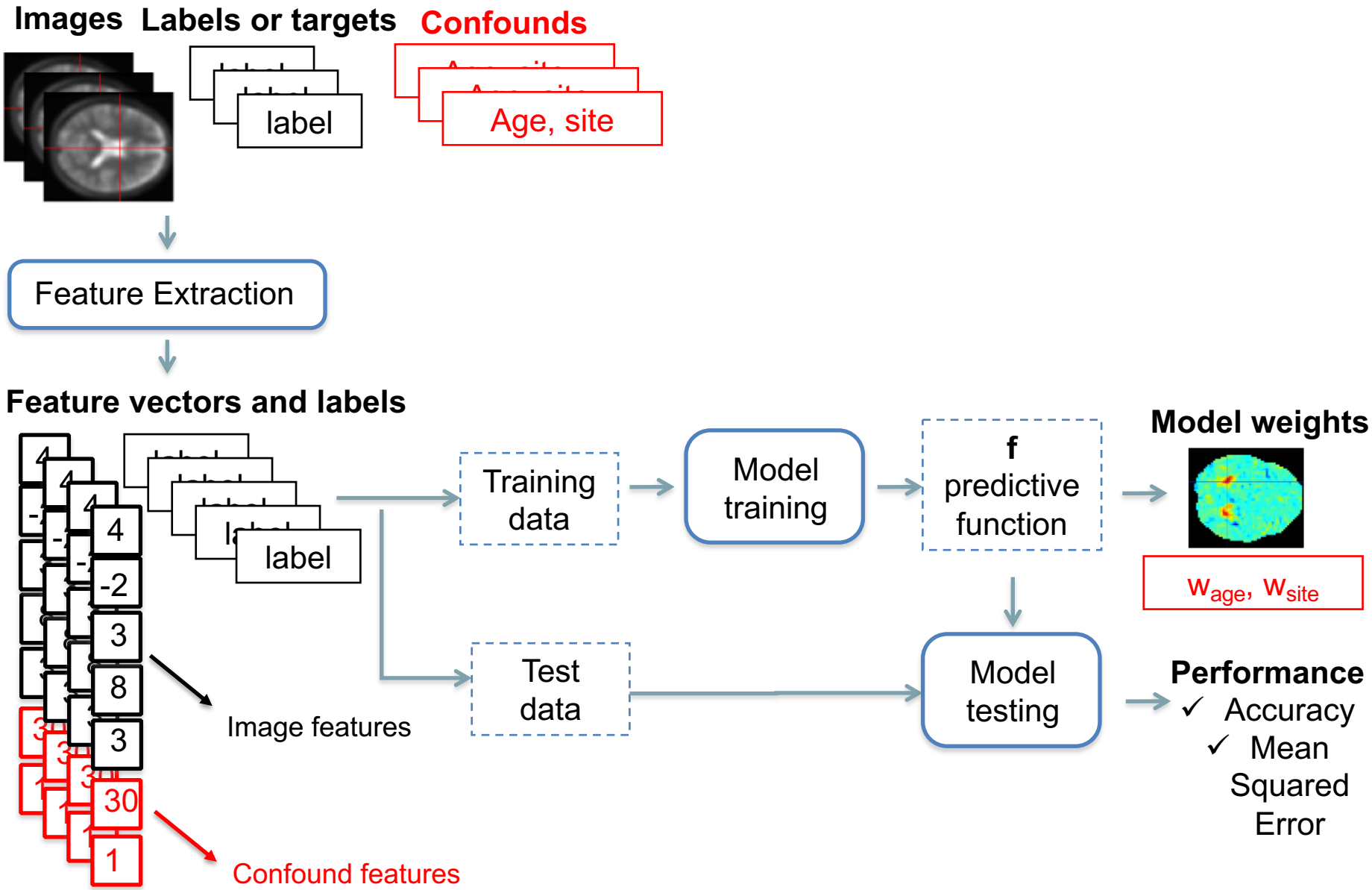
- The confounds are included as predictors (additional features) in the model.

- The goal is to learn the relative contribution of the confounds for the predictive model.

- **Example:** adding age and sex as an additional features to the feature vector containing the image features.

- **<u>Disadvantages:</u>**
  - It is not easy to separate the contribution of individual features in predictive models (model's weights are usually difficult to interpret).

3. Incorporating confounds as predictors



4. Instance-based weighting

- Weights the samples to produce a pseudo-sample in which the association between the target ($\mathbf{y}$) and the confounds ($\mathbf{C}$) has been removed (Linn et al., 2016 and Rao et al., 2017).

- Instance-based weighting proceeds in two stages:
  - In the first stage it models the relationship between the confound and the target.
  - In the second stage this relationship is used to weight the training examples in the predictive modelling.

- **<u>Disadvantages:</u>**
  - In case of high dimensional data it does not demonstrate a clear advantage over the other methods in terms of overall performance (Rao et al, 2017).

4. Instance-based weighting

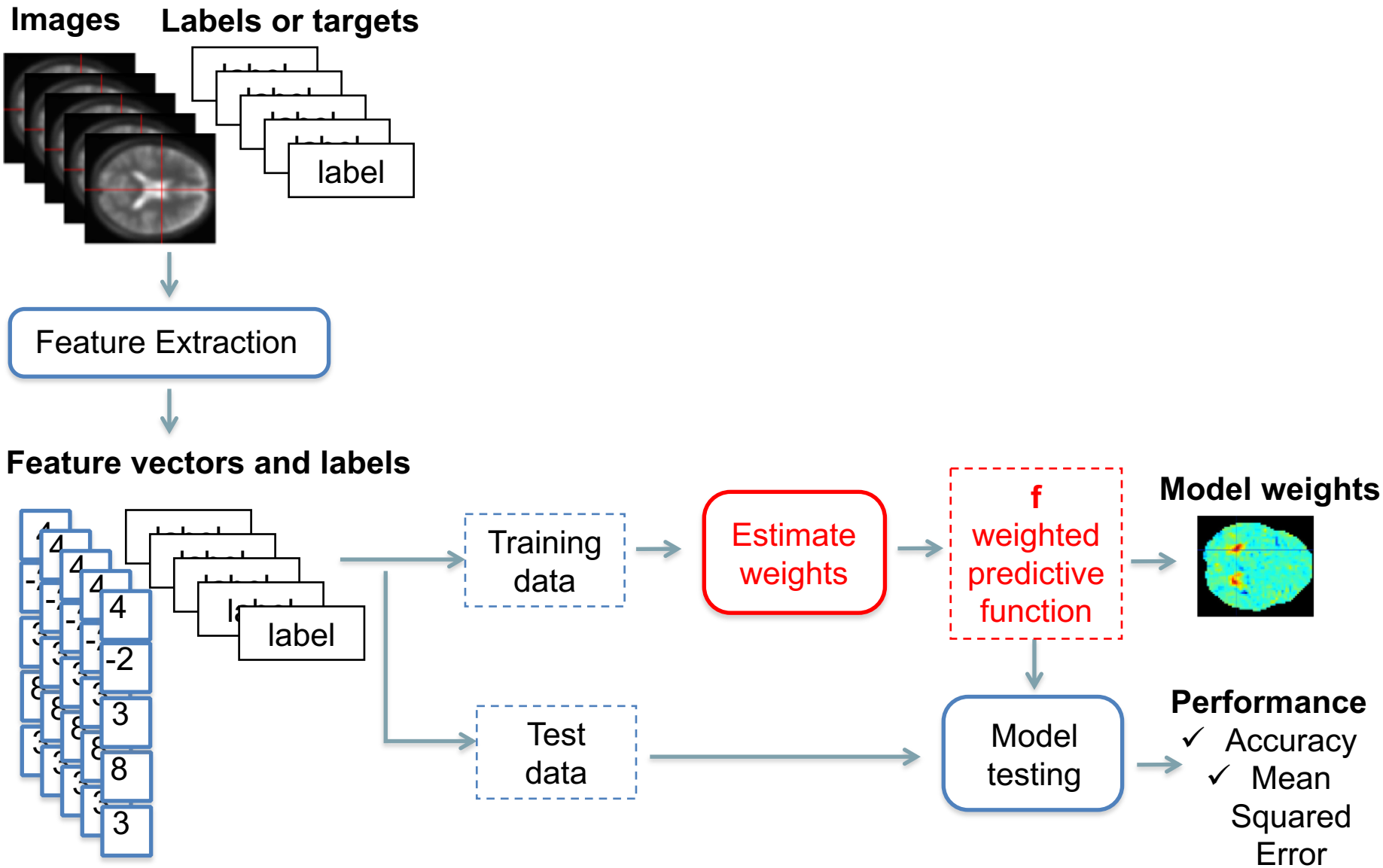
- In order to perform instance weighting, we first need to **estimate the weights** w_i for each training example:

$$w_i = \frac{P(y_i)}{P(y_i/\mathbf{c}_i)}$$

- This involves estimating the ratio between the marginal and conditional distributions $P(y)$ and $P(y/\mathbf{c})$ from the training data and evaluating w_i at each training point i.

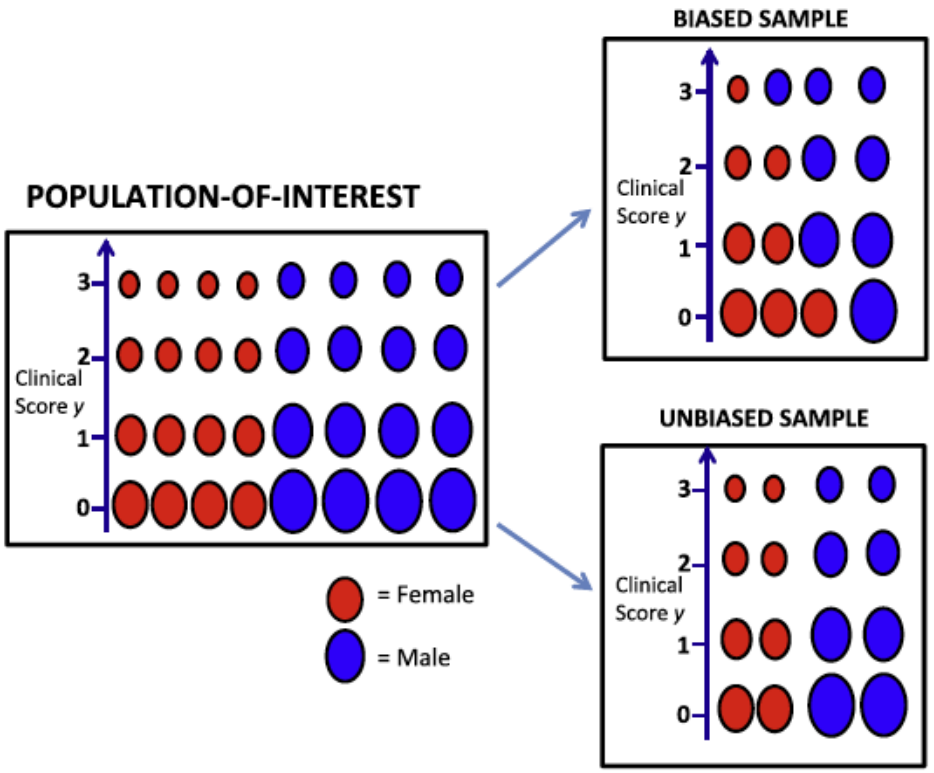
- The next step is to learn a **weighted predictive function**: e.g. a ***weighted* Kernel Ridge Regression** in which the loss associated with the training point i is weighted by w_i.

4. Instance-based weighting



Comparative Results

Example illustrating biased and unbiased samples from a population of interest



- The **population of interest** contain no association between the **clinical score** and **sex**.
- The **biased sample** contains a correlation between **sex** and the **clinical score**.
- The **unbiased sample** does not contain a correlation between **sex** and the **clinical score**.
- **Sex** is a **confound** in the biased sample.

Source: Rao et al. 2017

Example 1: Predicting Mini-Mental State Examination (MMSE) from sMRI

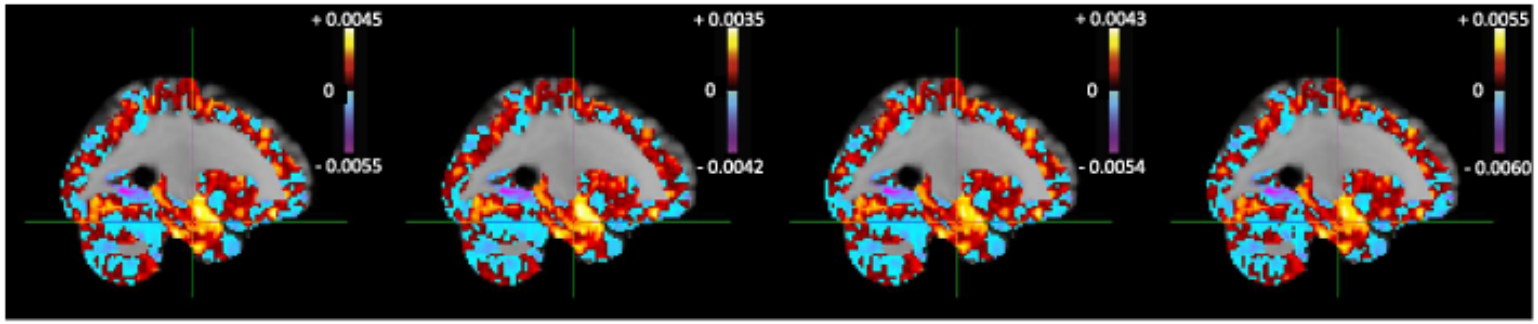
- ✓ A **biased** and an **unbiased** samples were selected from the **Alzheimer's Disease Neuroimaging Initiative** (**ADNI**) dataset.
- ✓ The **biased sampled** contained a correlation between **sex** and **MMSE scores**.
- ✓ The **unbiased sample** did not contain a correlation between **sex** and **MMSE scores**.

	Biased training sample	Unbiased training sample
Model	**MSE (unbiased test sample)**	**MSE (unbiased test sample)**
Images only (baseline)	8.02*	7.58*
Adjusted Images	7.94*	7.64*
Images & Confounds	8.43*	7.57*
Instance Weighting	8.02*	7.61*

* Indicates better performance than chance, p-value <0.05
All models used a Gaussian Process Regression as predictive model

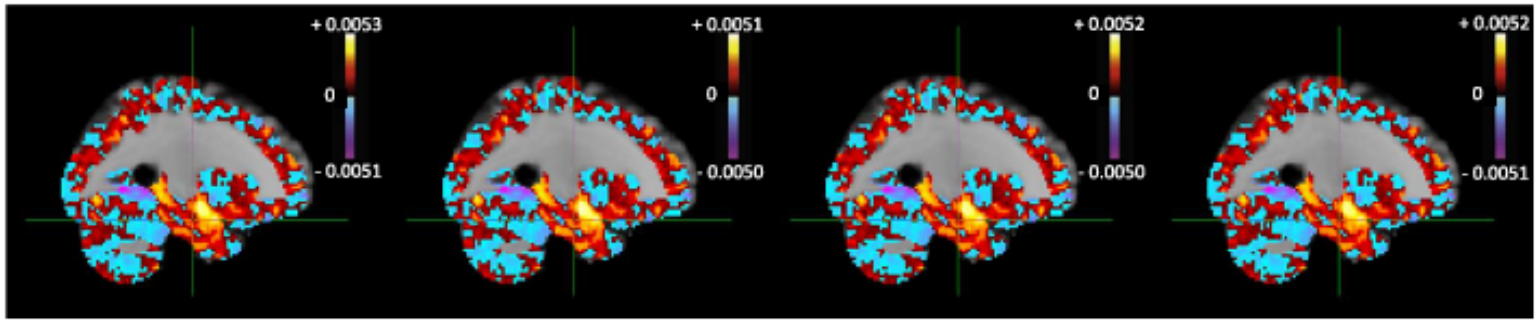
Source: Rao et al. 2017

Average weight map for each model trained to predict MMSE scores from structural MRI



Images Only | Adjusted Images | Images & Confounds | Instance Weighted

(a) Biased Training Samples



Images Only | Adjusted Images | Images & Confounds | Instance Weighted

(b) Unbiased Training Samples

Example 2: Predicting age from sMRI

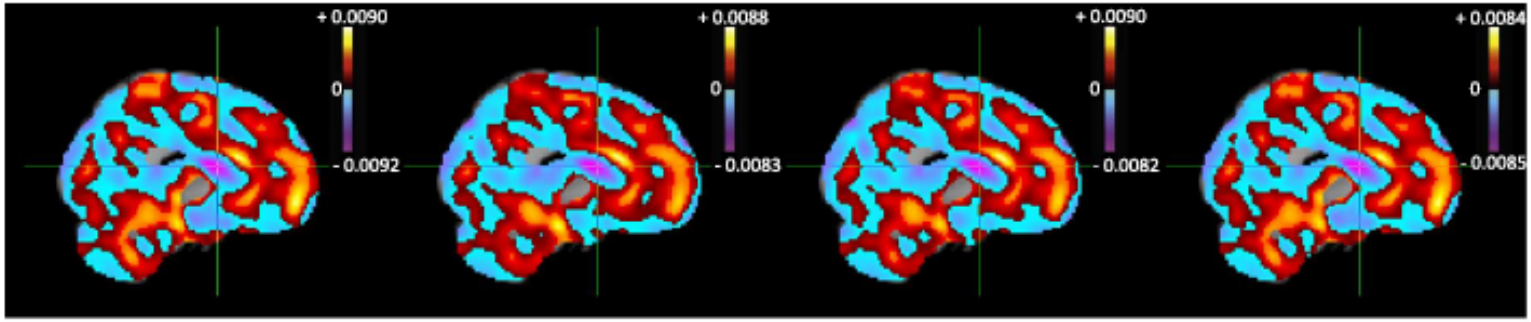
- ✓ A **biased** and an **unbiased** samples were selected from the IXI (http://brain-development.org/ixidataset/) dataset.
- ✓ The **biased sampled** contained a correlation between **age** and **site**.
- ✓ The **unbiased sample** did not contain a correlation between **age** and **site**.

	Biased training sample	Unbiased training sample
Model	**MSE (unbiased test sample)**	**MSE (unbiased test sample)**
Images only (baseline)	30.08*	25.21*
Adjusted Images	31.66*	25.34*
Images & Confounds	31.54*	25.84*
Instance Weighting	29.91*	25.21*

* Indicates better performance than chance, p-value <0.05
All models used a Gaussian Process Regression as predictive model

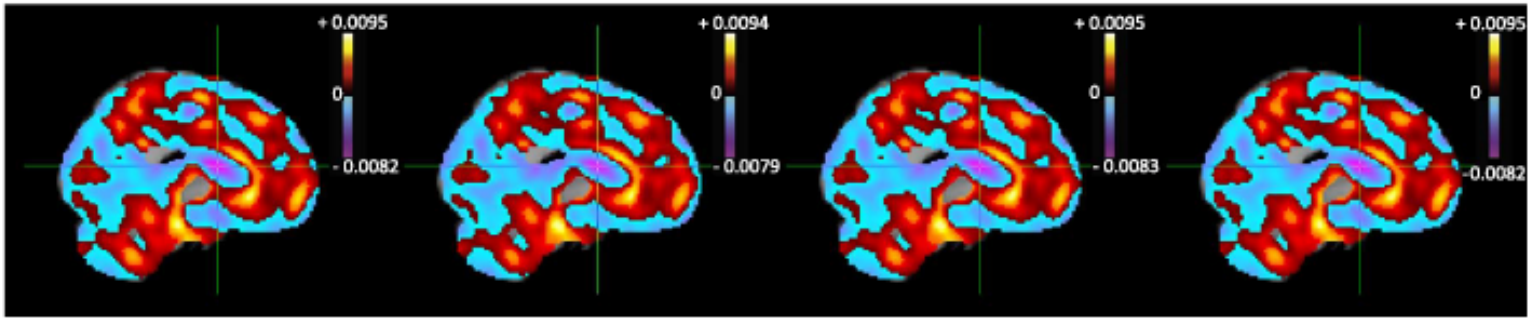
Source: Rao et al. 2017

Average weight map for each model trained to predict age from structural MRI



Images Only | Adjusted Images | Images & Confounds | Instance Weighted

(a) Biased Training Samples



Images Only | Adjusted Images | Images & Confounds | Instance Weighted

(b) Unbiased Training Samples

Results Summary

- **All models performed better than chance**, i.e. they were able to learn information that is useful for prediction of unbiased data despite the presence of confounding.

- **All models perform better when training with the unbiased samples** compared to when using the biased.

- The **performance of the different methods** for dealing with confounding **varied for the different datasets**.

- None of the methods gave more accurate predictions than the baseline ‘Images Only’ model for both datasets.

- Including the confound as a predictor gave less accurate predictions than the baseline model for both datasets.

Accounting for confounds during significance testing

- When permutation test is used one should use a **constrained permutation** (e.g. permuting the targets within site when considering site as confound).

- This procedure preserves the association between the targets and the confound, while breaking the relationship between the imaging data and the targets.

A machine learning perspective

- The problem of **confounds** is related to the **dataset shift** problem in machine learning.

- **Dataset shift** occurs when the distributions on the training and test set do not match.

- Examples of **dataset shift**:
  - **Covariate Shift:** the distribution of the features in the training and test sets are different.
  - **Prior Probability Shift:** the distribution of the targets in the training and test sets are different.
  - **Sample Selection Bias:** the distributions differ as a result of an unknown sample rejection process.

- Different approaches have been proposed in the machine learning field for dealing with **dataset shift** (e.g. Quionero-Candela et al. 2009).

Domain Adaptation and Transfer Learning

- **Domain Adaptation:** aims to learn a model from a **source data** distribution that performs well on a different (but related) **target data** distribution (e.g. Long et al. 2015, Bousmalis et al. 2016).

- **Example of domain adaptation:** adapting a predictive model trained on data collected from a specific scanner to make it compatible for testing data obtained from another scanner.

- **Transfer learning:** aims to transfer knowledge gained while solving one problem to a different but related problem (e.g. Shin et al. 2016).

- **Example of transfer learning:** training a classifier to discriminate Alzheimer patients from healthy controls and then fine-tune it to classify frontotemporal dementia patients from healthy controls.

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Useful references

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Shin H-C., Roth, H. R., Gao M., Lu, L., Xu, Z., Nogues, I., Yao, J., Mollura, D., Summers, R. M. Deep Convolutional Neural Networks for Computer-Aided Detection: CNN Architectures, Dataset Characteristics and Transfer Learning. In IEEE Transactions on Medical Imaging, vol. 35, no. 5, 1285–1298, 2016.

Useful tools

PRoNTo (http://www.mlnl.cs.ucl.ac.uk/pronto/) includes operations for image adjustment accounting for training and test separation.

Confounds library
https://crossinvalidation.com/2020/03/04/conquering-confounds-and-covariates-in-machine-learning/

PALM toolbox **(https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM)** for generating restricted permutations.