A Bayesian Model for the Validation of Magnetic Resonance Imaging (MRI) as a Surrogate Endpoint for a Clinical Endpoint

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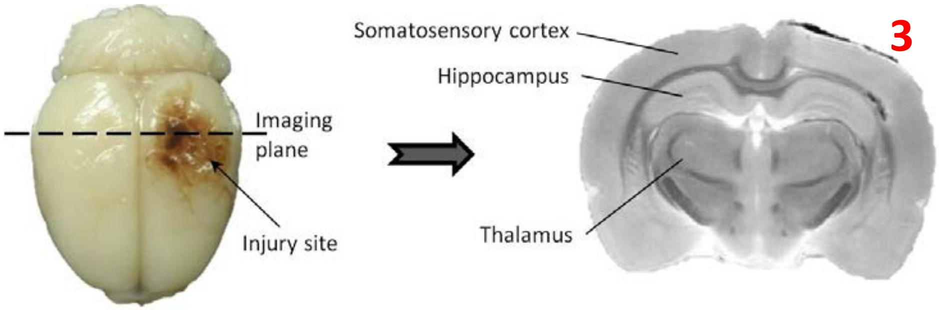
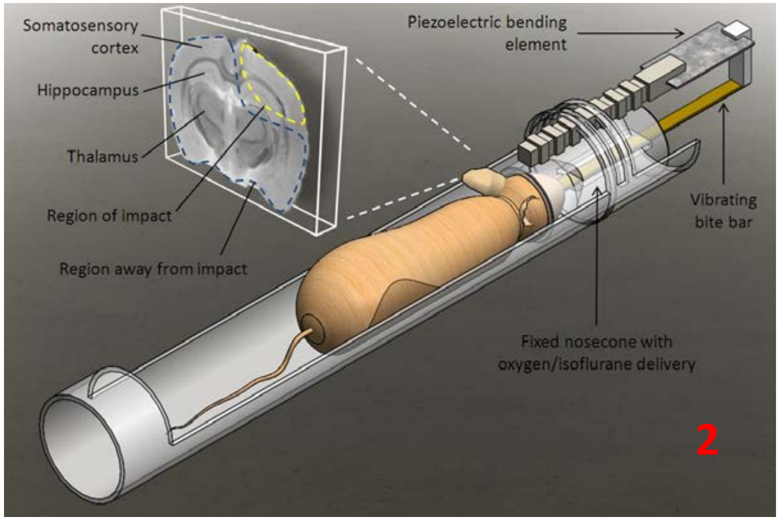
- Histogenix
- Open Analytics
- The MRI Consortium

Introduction

- Alzheimer disease: age-dependent, irreversible.
- Non-invasive screening tools desirable for early detection and management.
- Identification and validation of potential bio-markers crucial- a lot of ongoing research.
- *Evaluate the use of Magnetic Resonance Imaging (MRI) as a surrogate for disease progression*

MR Image acquisition





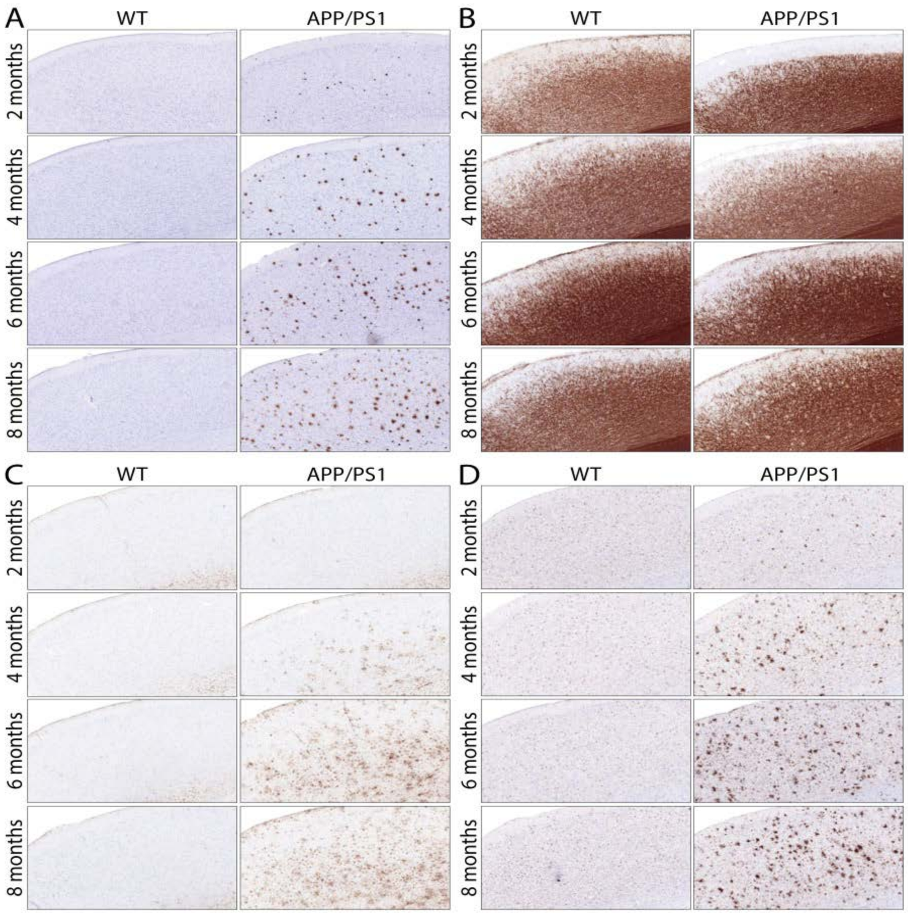
Images downloaded from: TREM, MRSolutions

Numeric values for different parameters

- Diffusion kurtosis imaging
  - Mean Kurtosis (MK)
  - Axial Kurtosis (AK)
  - Radial Kurtosis (RK)
- Diffusion tensor imaging
  - Mean Diffusivity (MD)
  - Axial Diffusivity (AD)
  - Radial Diffusivity (RD)
  - Fractional Anisotropy (FA)

Note: MRI can be acquired longitudinally

Histology Staining: Cortex Motor



A: 4G8
B: MBP
C: GFAP
D: IBA1

- Different histology stains enable detection of different structures
- Plague deposits are quantified
  - % stained area
  - Mean intensity
- Numeric values for statistical analysis
  - MBP staining
  - GFAP staining
  - Iba1 staining
  - 4G8 staining
- Note: Only one set of histology measurements per animal

Data

- Histology can only be acquired once per animal.
- Cross-sectional studies at 2, 4, 6 and 10 months with MRI and histology available.
- Longitudinal MRI study with histology at 8 months
- Resulting into 4 cross-sectional (multivariate) datasets
- 23 brain ROI, 7 MRI parameters, 4 histology parameters
- 23x7x4 =664 models

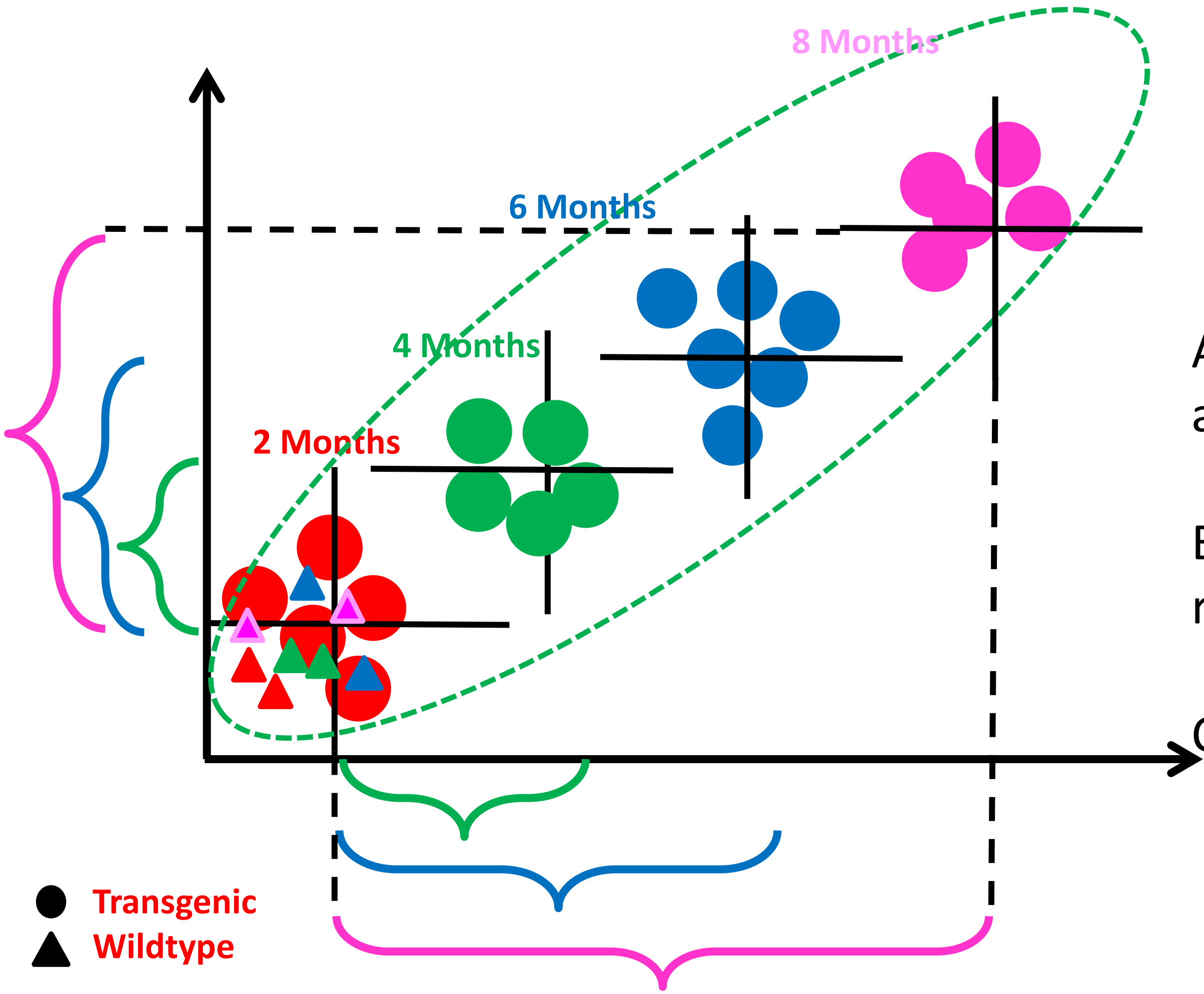
Evaluation of MRI as biomarker for histology

- Methodology: surrogate endpoints in clinical trials.

- Histology: “true” endpoint.
- MRI: “surrogate” endpoint.

- Can we use MRI as a surrogate to histology ?
- Can we replace histology with MRI ?

Illustration: Disease Effects



A covariate with 4 levels = 4 age groups.

Effect of level j compare to the reference group.

Correlation

Two-stage Surrogacy Model

Given a 'True' endpoint T and a surrogate endpoint S,

The two-stage model for surrogacy can generally be denoted as:

$$\begin{pmatrix} T_{ij} \\ S_{ij} \end{pmatrix} \sim N\left(\begin{bmatrix} \mu_{T_j} + \alpha_j Z_i \\ \mu_{s_j} + \beta_j Z_i \end{bmatrix}, \Sigma_k \right)$$

Component for deriving individual-level surrogacy

$$\begin{pmatrix} \alpha_j \\ \beta_j \end{pmatrix} \sim N\left(\begin{bmatrix} \overline{\alpha} \\ \overline{\beta} \end{bmatrix}, D \right)$$

Component for deriving trial-level surrogacy

Joint Model for MRI and Histology at ROI

For a given region in the brain, MRI parameter and histology stain

$$T_{ij} = \mu_{T_j} + \alpha_j Z_i + \varepsilon_{T_{ij}}$$

$$S_{ij} = \mu_{S_j} + \beta_j Z_i + \varepsilon_{S_{ij}}$$

$$\begin{pmatrix} \varepsilon_{T_{ij}} \\ \varepsilon_{S_{ij}} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \Sigma_k\right), k = 1, 2$$

$$Transgenic : \Sigma_1 = \begin{pmatrix} \sigma^2_{App,hist} & \sigma_{App,hist:mri} \\ \sigma_{App,hist:mri} & \sigma^2_{App,mri} \end{pmatrix}$$

$$Wildtype : \Sigma_2 = \begin{pmatrix} \sigma^2_{Wt,hist} & \sigma_{Wt,hist:mri} \\ \sigma_{Wt,hist:mri} & \sigma^2_{Wt,mri} \end{pmatrix}$$

Two Measures of Surrogacy

1: Individual-level surrogacy

$$\Sigma_k \Rightarrow \rho(MRI, Hist.)$$

$$Transgenic: \rho_1 = \frac{\sigma_{App,hist:mri}}{\sqrt{\sigma^2_{App,mri}.\sigma^2_{App,hist}}}$$

$$Wildtype: \rho_2 = \frac{\sigma_{Wt,hist:mri}}{\sqrt{\sigma^2_{Wt,mri}.\sigma^2_{Wt,hist}}}$$

2: Disease- level surrogacy

- Correlation between the disease effects

$$D \Rightarrow \rho\left(\alpha_j, \beta_j\right)$$

$$\rho_D = \frac{\sigma_{\alpha,\beta}}{\sqrt{\sigma^2_{\alpha}.\sigma^2_{\beta}}}$$

- Predicting effects in histology by the effects in MRI

Bayesian Prior Specification

$$\mu_{S_j} \sim N(0.0, \tau_{SS}),$$

$$\mu_{T_j} \sim N(0.0, \tau_{TT}),$$

$$\tau_{SS} \sim \text{Gamma}(0.001, 0.001),$$

$$\tau_{TT} \sim \text{Gamma}(0.001, 0.001),$$

$$\Sigma_1^{-1} \sim Wishart(R_W, \phi),$$

$$\Sigma_2^{-1} \sim Wishart(R_A, \phi),$$

$$\begin{pmatrix} \alpha_j \\ \beta_j \end{pmatrix} \sim N\left(\begin{pmatrix} \overline{\mu}_S \\ \overline{\mu}_T \end{pmatrix}, D_{22}\right),$$

$$D_{22}^{-1} \sim \text{Wishart}(R_{D_{22}}, \phi),$$

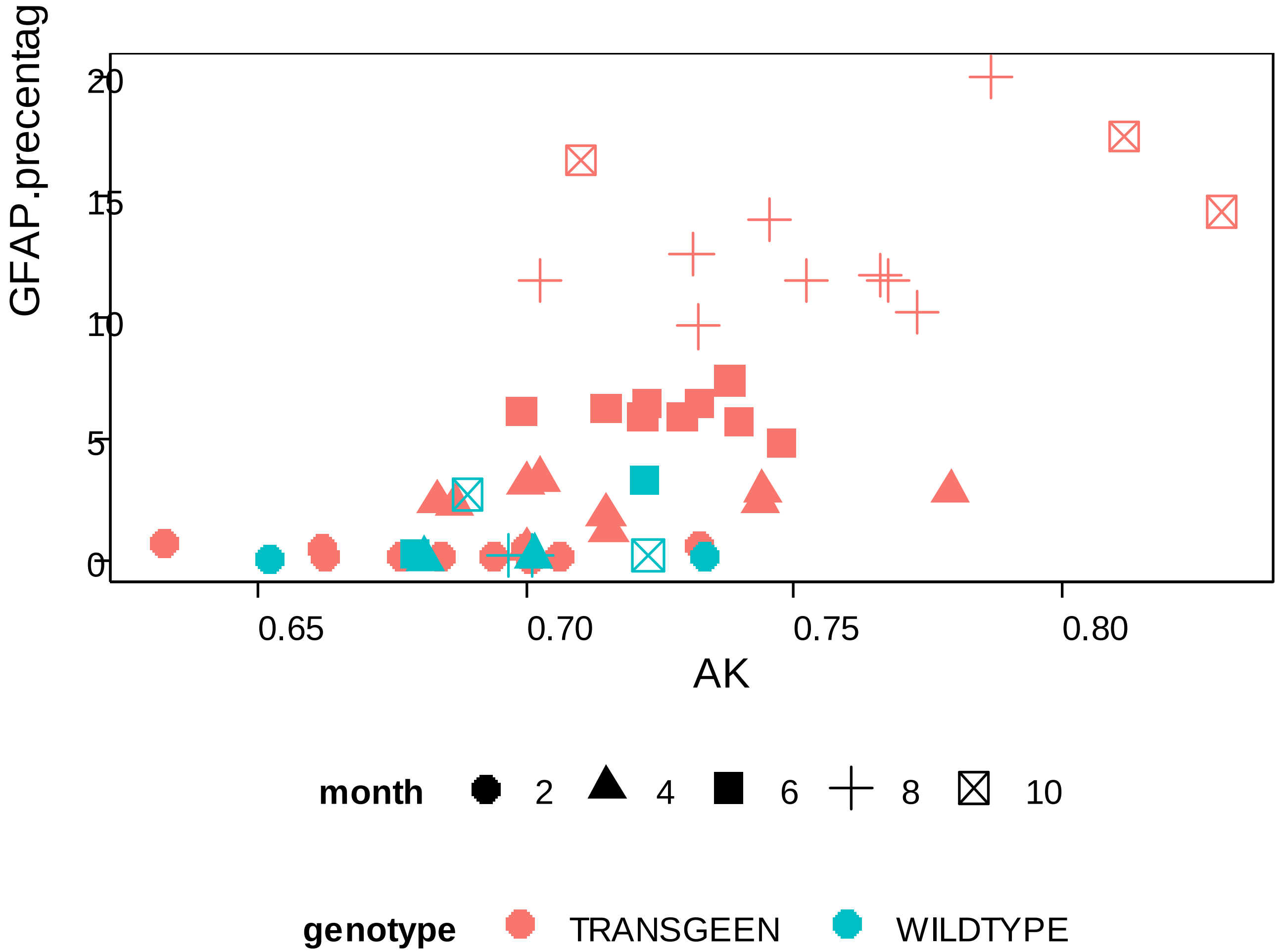
$$\overline{\mu}_S \sim N(0.0, 1.0E-6),$$

$$\overline{\mu}_T \sim N(0.0, 1.0E-6).$$

Example 1

Cortex Motor: MRI-AK with GFAP Staining

Cortex Motor: Observed Data (MRI-AK with GFAP)



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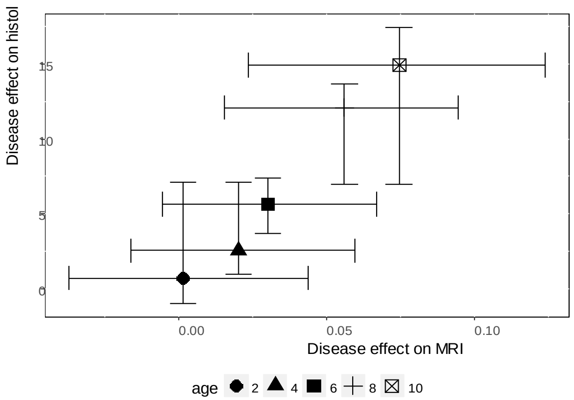
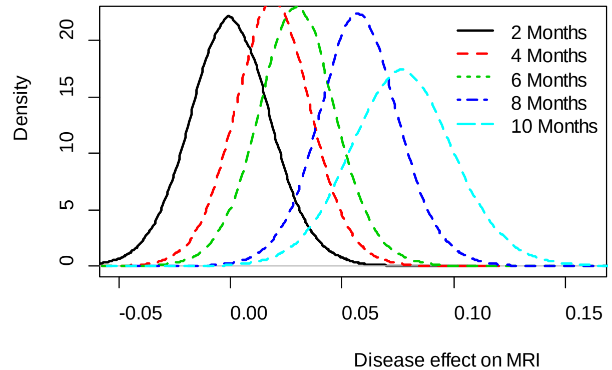
Results: Cortex Motor (MRI-AK with GFAP)

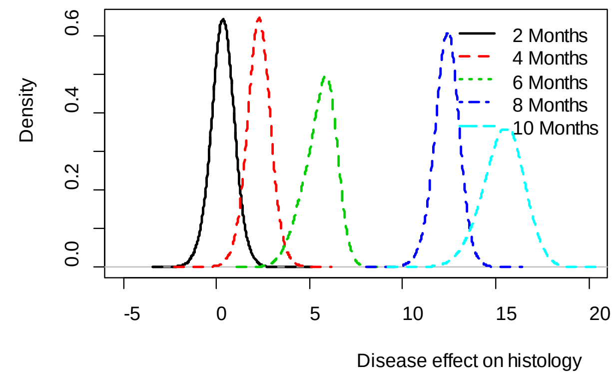
Posterior means with error bars

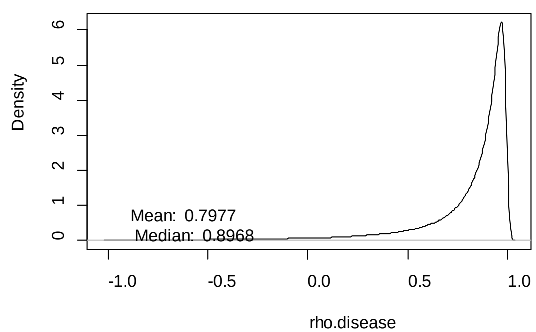


Disease effects on MRI

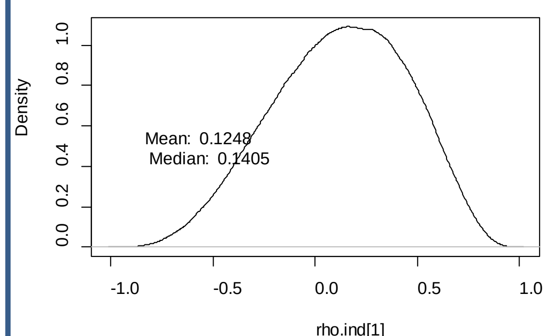


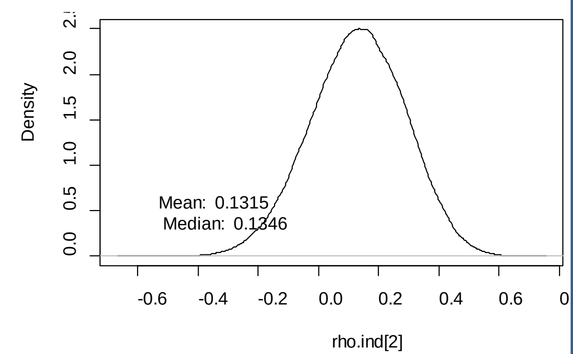
Disease effect on histology





- MRI (AK) is a **good biomarker** for histology at **disease-level**
- We **can** predict the effect in histology using the effect in MRI





- **Poor individual-level surrogacy**
- We **cannot** predict histology values from MRI values for an individual

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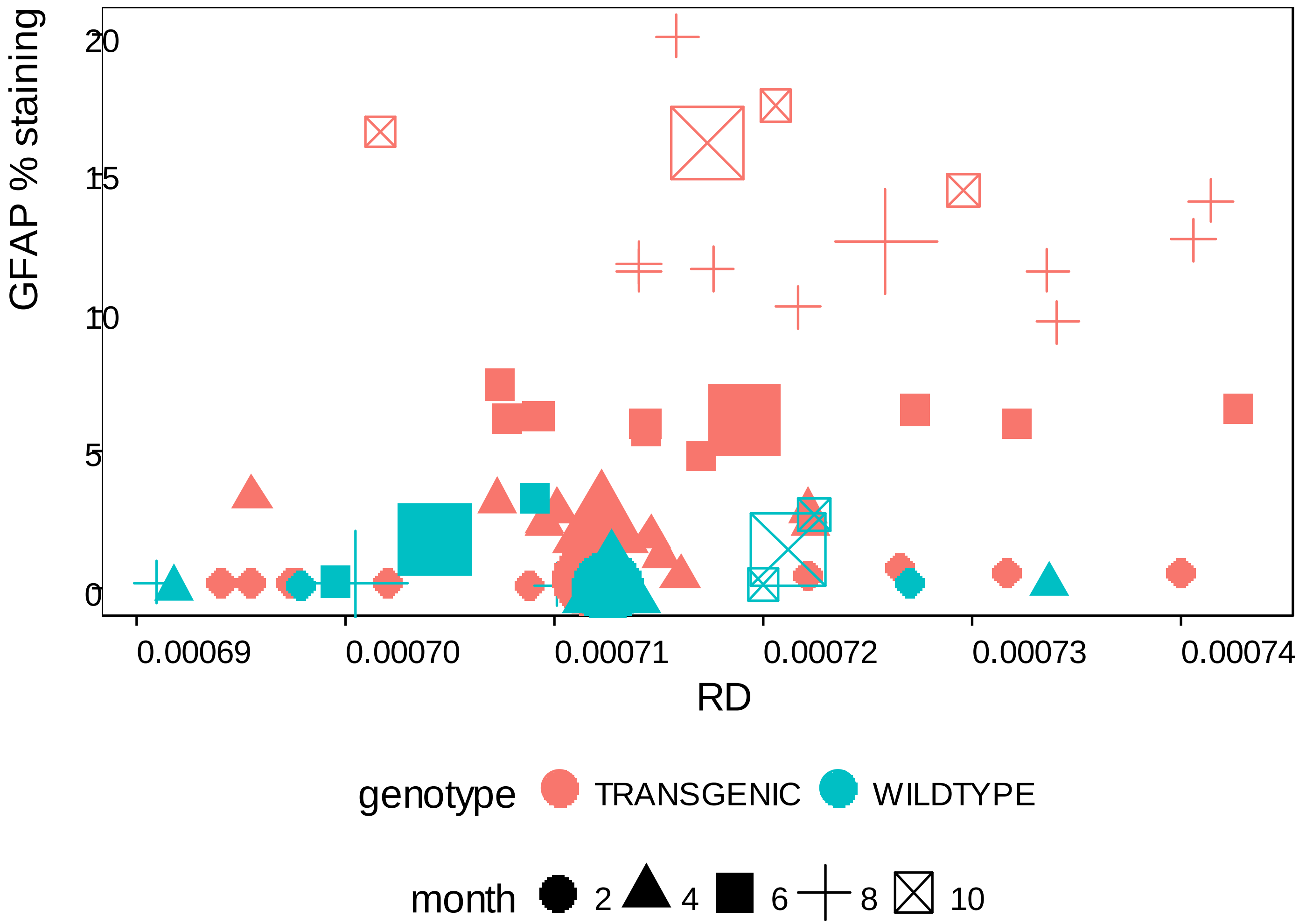
Example 2

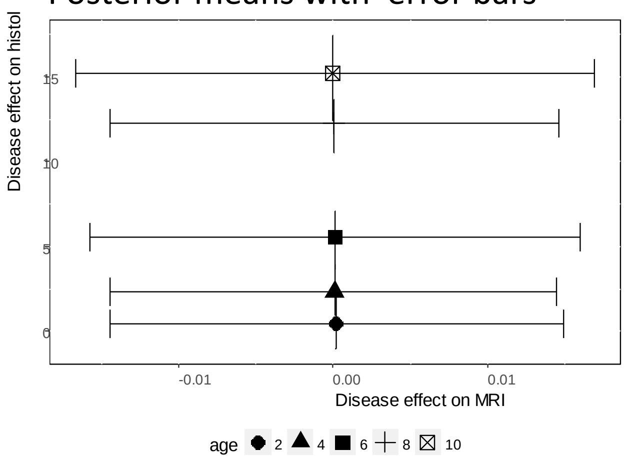
Cortex Motor: MRI-RD with GFAP Staining

Cortex Motor: Observed Data (MRI-RD with GFAP)

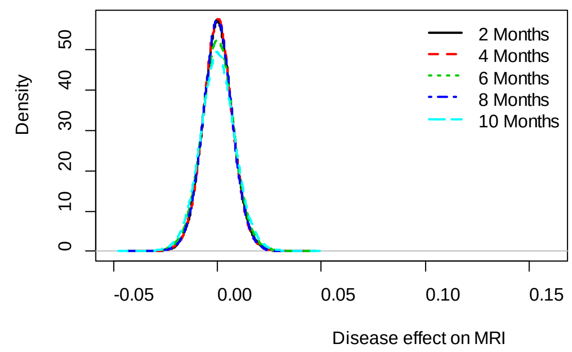


Results: Cortex Motor (MRI-RD with GFAP)

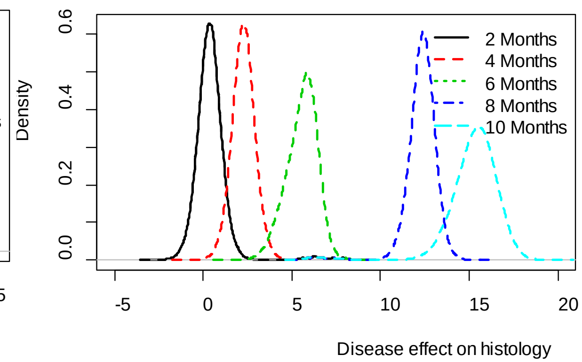
Posterior means with error bars

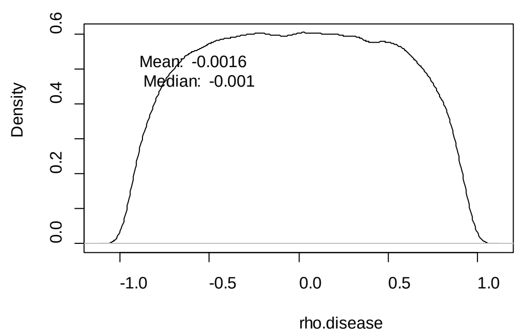


Disease effects on MRI

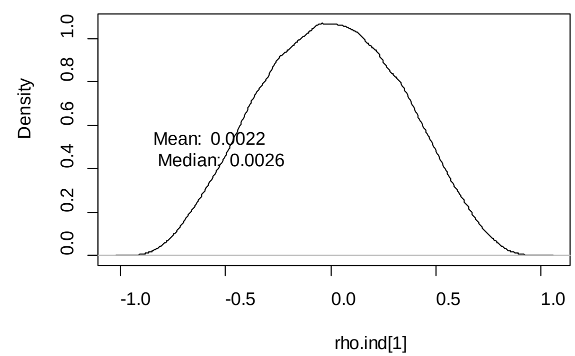


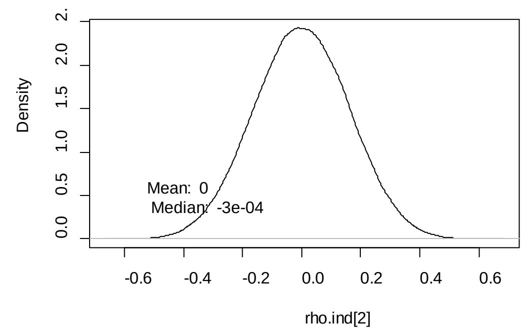
Disease effect on histology





- MRI (AK) is a **poor biomarker** for histology at **disease-level**
- We can **NOT** predict the effect in histology using the effect in MRI





- **Poor individual-level surrogacy**
- We **cannot** predict histology values from MRI values for an individual

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Conclusion

- MRI has potential to be a biomarker at disease level
- Surrogacy depends on MRI parameters, histology stain and brain region
- Assess model improvement at resolution higher than the ROI (unit level analysis)
- Evaluation of multivariate markers jointly?