Detecting perfusion abnormalities in Arterial Spin Labelling

Random-effects and Mixed-effects GLM

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King's College London - February 14th, 2014

Outline

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Detecting perfusion abnormalities
- Arterial Spin Labelling
- Group analysis
- Single-subject analysis

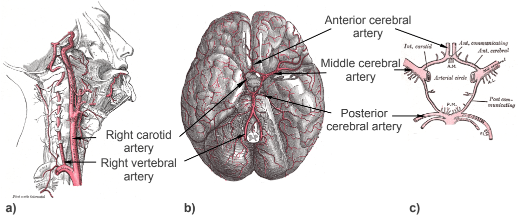
Random-Effects and Mixed-Effects General Linear Model
- Hypothesis testing
- Random-effects and Mixed-effects

Detections in ASL
- Methods
- Experiment
- Results

Conclusions

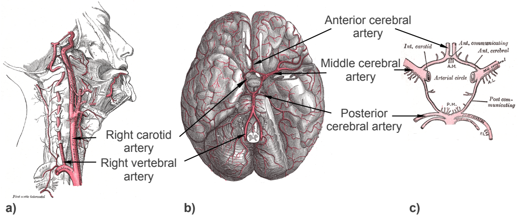
Outline

Brain perfusion



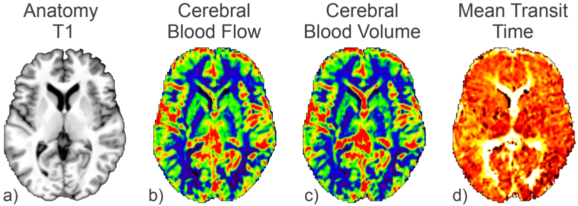
Blood supply to the brain

Brain perfusion



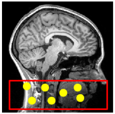
Blood supply to the brain

Brain perfusion is the biological process that ensures the delivery of oxygen and nutrients to the cerebral tissues by means of microcirculation.



Example of perfusion parameters

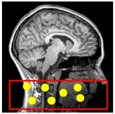
Arterial Spin Labelling (ASL)



Labelling

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)



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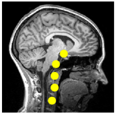

Delay

[Detre et al., MRM 1992]

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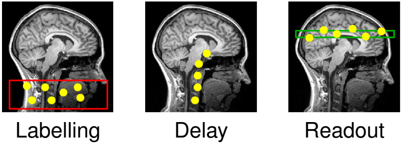

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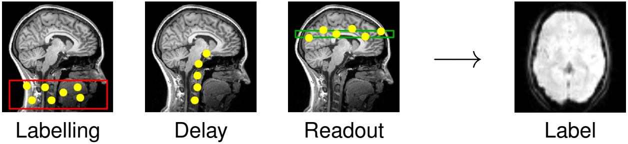

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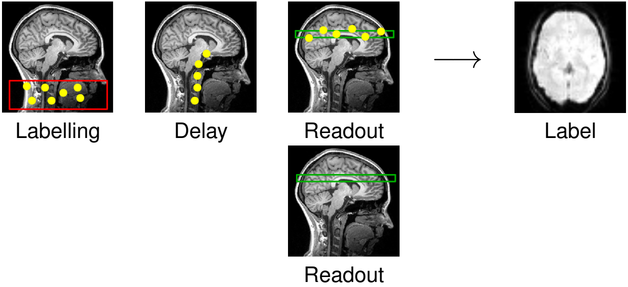

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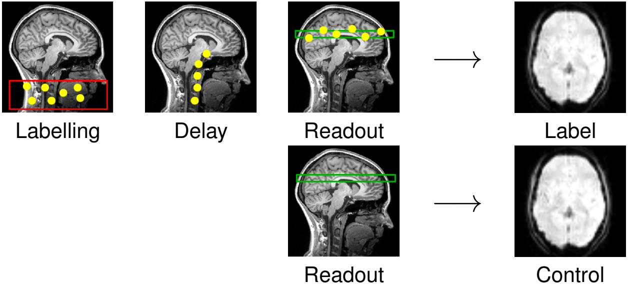

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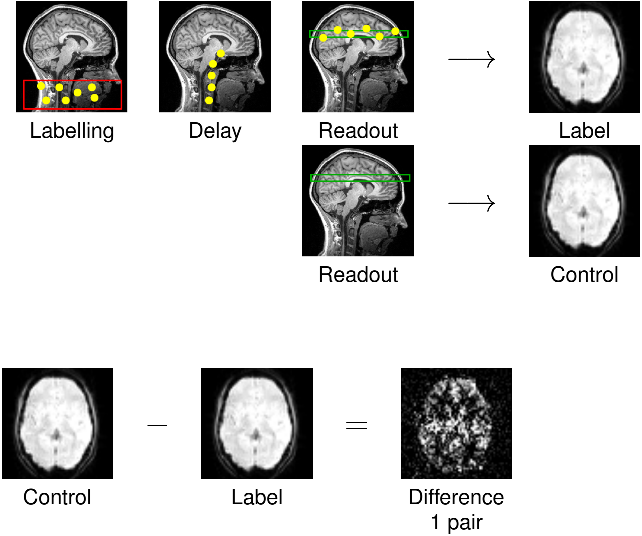

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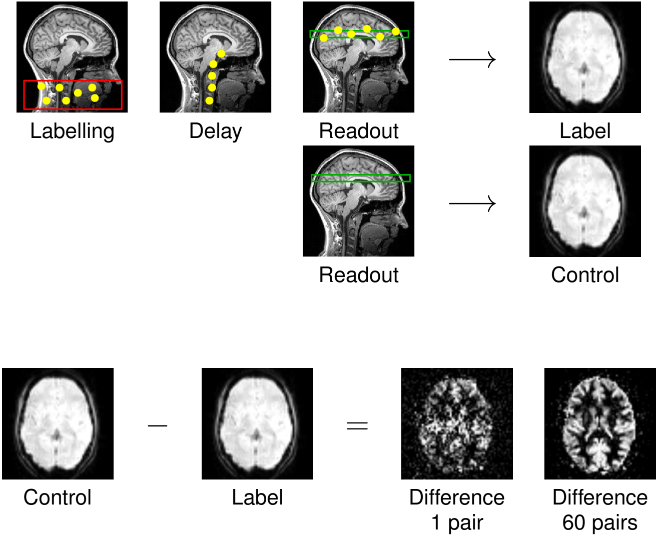
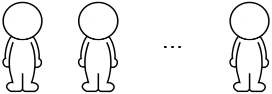


[Detre et al., MRM 1992]

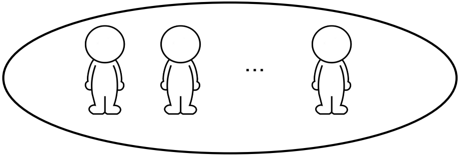
Outline

Within-group analysis



Within-group analysis

Identify common patterns across a group of subjects.



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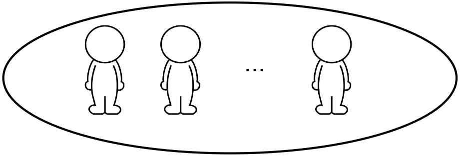
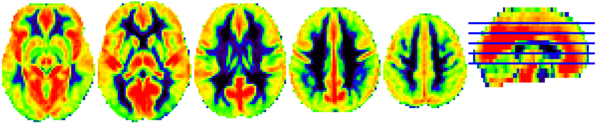
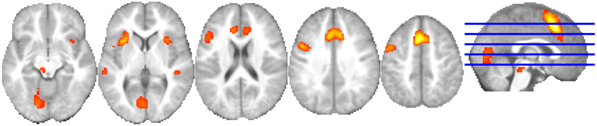


Examples



Group cerebral blood flow.

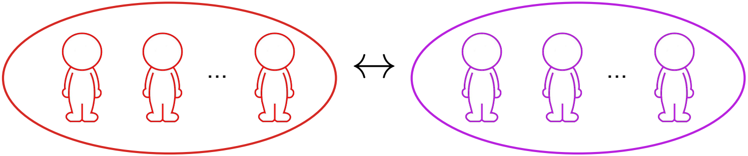


Group activation for a language task.

Between-group analysis

Between-group analysis

Identify differences at the group level.



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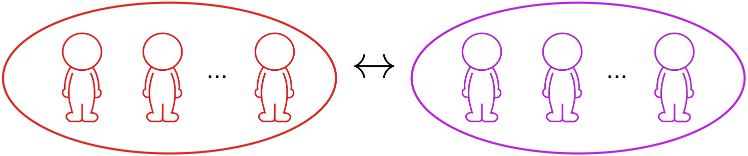
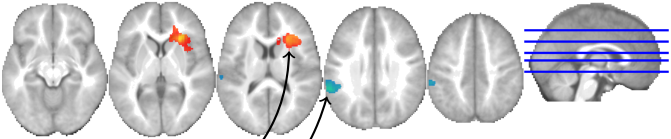


Example



Differences of perfusion between a group of patients and a control group.

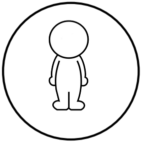
- Hyper-perfusion.
- Hypo-perfusion.

Outline

Within-subject analysis

Within-subject analysis

Identify patterns of perfusion (or activation) in a single subject.



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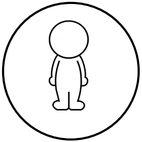
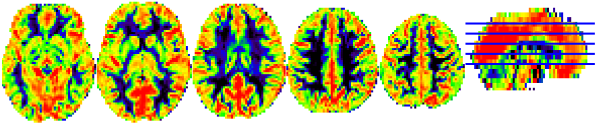
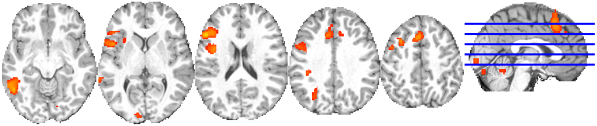


Examples

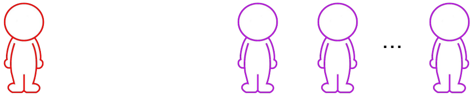


Cerebral blood flow.



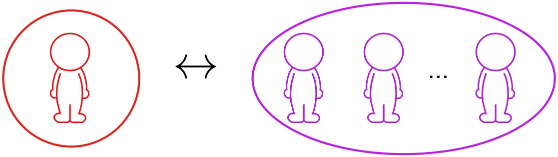
Subject activation for a language task.

Between-group individual analysis



Between-group individual analysis

Identify deviation from normality in a single subject.



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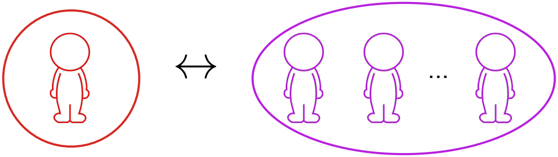

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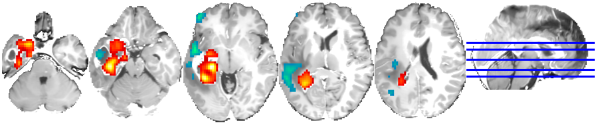
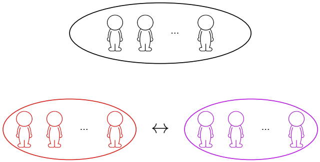


Hyper- and hypo-perfusions in a patient diagnosed with brain tumour.

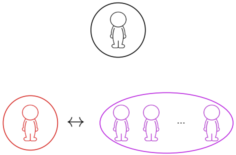
Within-group and between-group analyses

Group analyses



- Study of **typical brain perfusion.**
- Provide a better understanding of **brain dysfunction** associated with a pathology.

Individual analyses

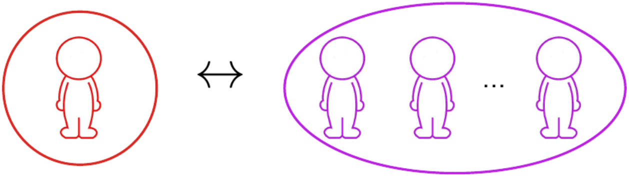


- Study of **brain perfusion in a particular subject.**
- Outline **deviation from normality** (or from a reference group).

Outline

Outline

A massively univariate approach



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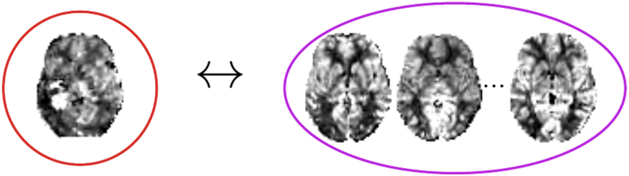

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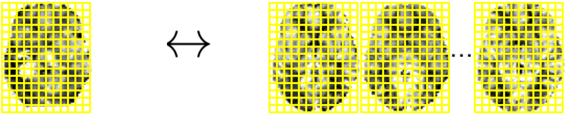

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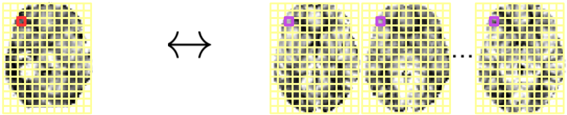

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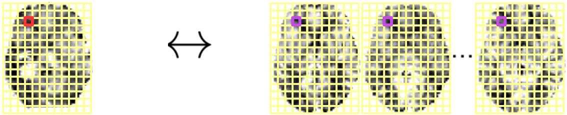

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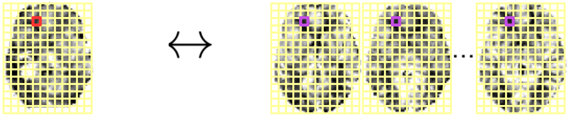
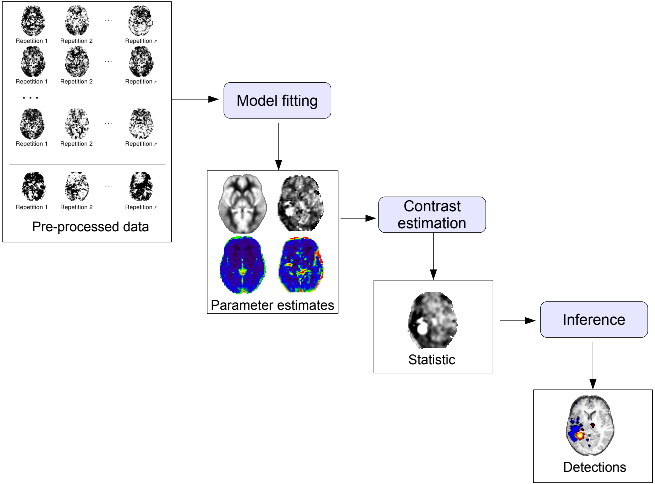


Hypothesis testing: overview



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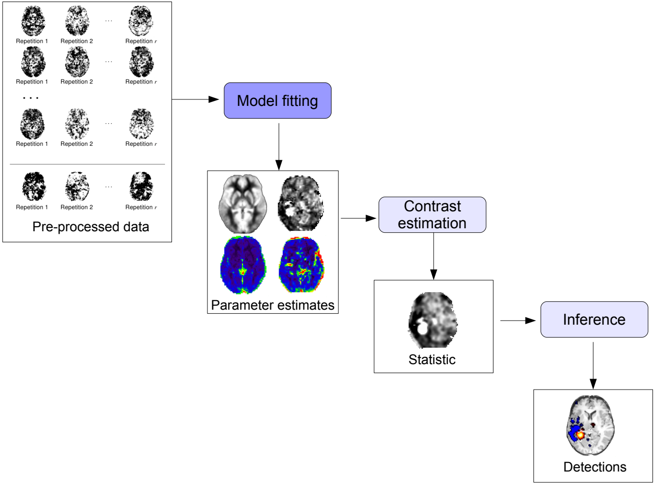
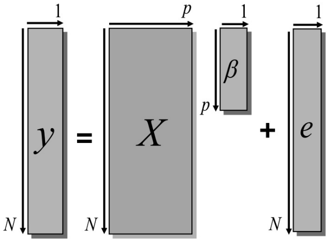


Model fitting

Using the GLM, the dataset of interest is modelled as a linear combination of pre-defined parameters.



Source: “The General Linear Model for fMRI analyses” by FIL Methods Group, SPM Course, 2013.

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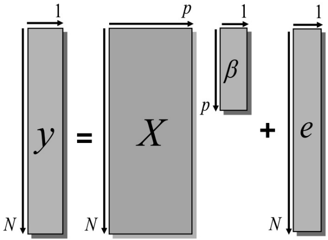

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Independent and identically distributed errors, i.e. given $\boldsymbol{e} \sim \mathcal{N}(0, \sigma^2 \boldsymbol{I})$, we can use Ordinary Least Squares:

$$\hat{\beta}_{OLS} = (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{Y}, \quad \widehat{\mathrm{Var}}(\hat{\beta}_{OLS}) = \hat{\sigma}^2(\boldsymbol{X}^T\boldsymbol{X})^{-1}. \qquad (1)$$

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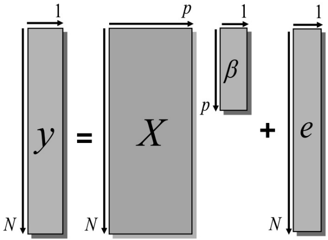

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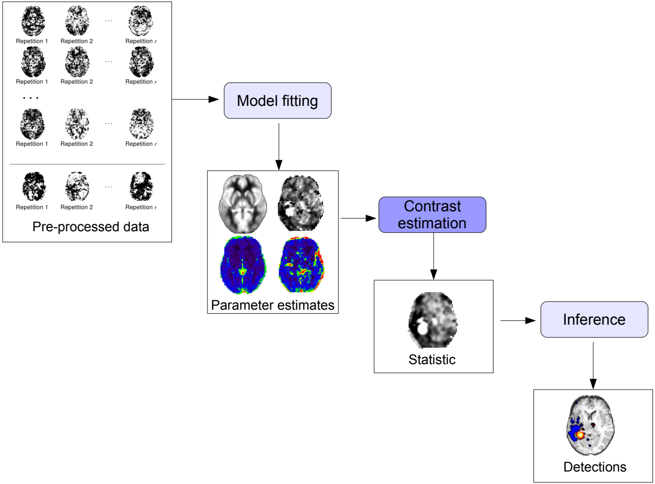
Otherwise, given $\boldsymbol{e} \sim \mathcal{N}(0, \boldsymbol{V})$, Weigthed Least Squares:

$$\hat{\boldsymbol{\beta}}_{\boldsymbol{WLS}} = (\boldsymbol{X}^T \boldsymbol{V}^{-\mathbf{1}} \boldsymbol{X})^{-1} \boldsymbol{X}^T \boldsymbol{V}^{-\mathbf{1}} \boldsymbol{Y}, \ \widehat{\mathrm{Var}}(\hat{\boldsymbol{\beta}}_{\boldsymbol{WLS}}) = (\boldsymbol{X}^T \boldsymbol{V}^{-\mathbf{1}} \boldsymbol{X})^{-1}. \qquad (2)$$

Hypothesis testing: overview



Hypothesis testing

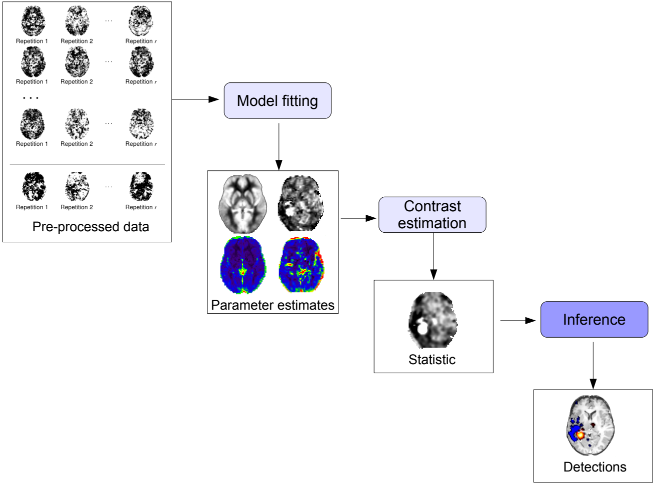
Under the null hypothesis:

$$H_0 : \boldsymbol{c}\boldsymbol{\beta}_{(v)} = 0.$$

Assuming the normality of the error, the t-statistic at voxel v is defined by:

$$\frac{\boldsymbol{c}\hat{\boldsymbol{\beta}}_{(v)}}{\sqrt{\widehat{\mathrm{Var}}(\boldsymbol{c}\hat{\boldsymbol{\beta}}_{(v)})}} \sim \mathcal{T}_{N-p}. \quad (3)$$

Hypothesis testing: overview

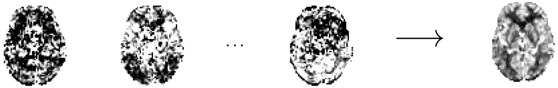


Outline

Modelling: subject level

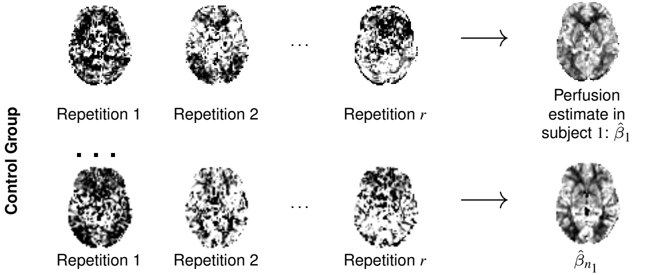
Repetition 1 Repetition 2 Repetition r

Modelling: subject level



Repetition 1 — Repetition 2 — … — Repetition r $\longrightarrow$ Perfusion estimate in subject 1: $\hat{\beta}_1$

Modelling: subject level



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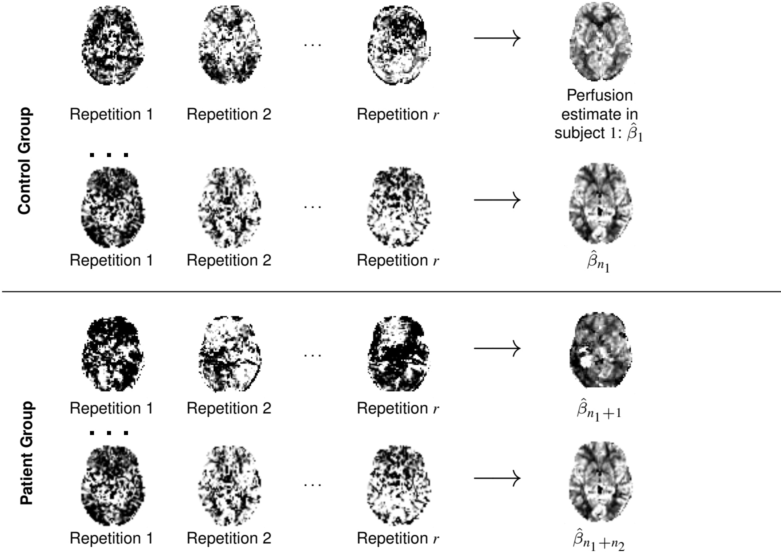
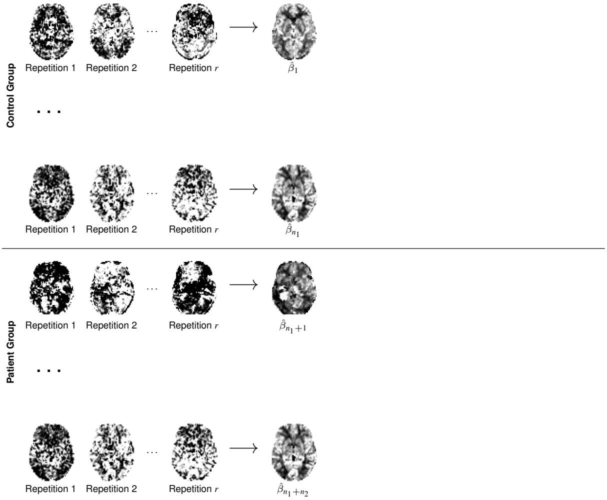


Modelling: group level



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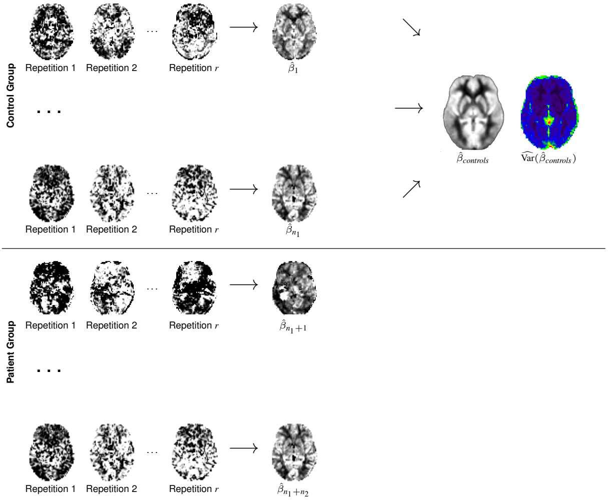

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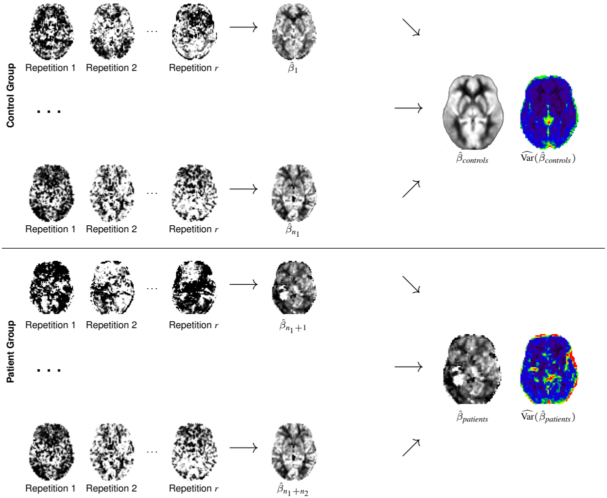
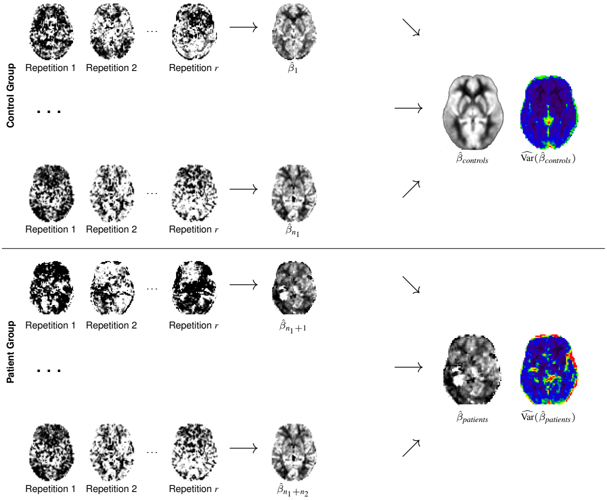
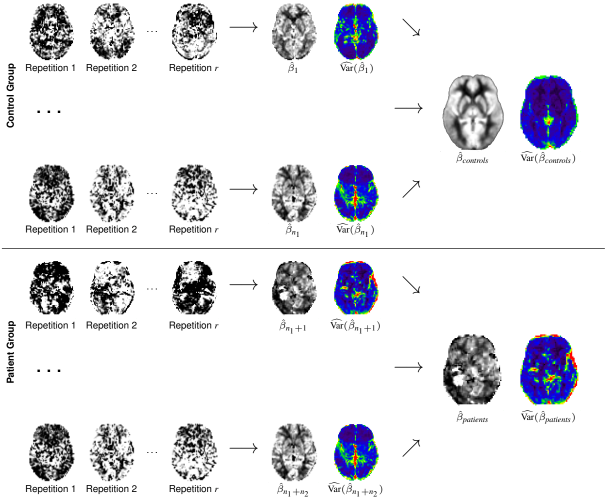


Modelling: group level



Random-effects (RFX) analysis.

Modelling: group level



Mixed-effects (MFX) analysis.

Random-effects assumptions

RFX analyses assume that the **within-subject variance** is:

- **negligible** by comparison to the between-subject variance; or
- **roughly constant** across subjects.

Random-effects or Mixed-effects analyses

In functional MRI there is no consensus:

- Superiority of MFX, [Beckmann 2003, Mumford 2006, Thirion 2007].
- Validity of RFX for one-sample t-tests in BOLD fMRI, [Mumford 2009].
- Invalidity of RFX [Chen 2012].

Both approaches are in use in the neuroimaging community:

- Random-effects analyses (SPM[1])
- Mixed-effects analyses (FSL[2], AFNI[3]).

What about ASL?

[1] www.fil.ion.ucl.ac.uk/spm/
[2] fsl.fmrib.ox.ac.uk/fsl/fslwiki/
[3] afni.nimh.nih.gov/afni/

Outline

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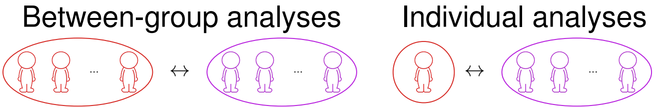
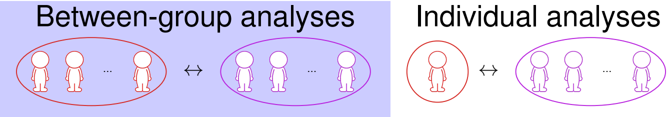
Detecting perfusion abnormalities using the GLM



- Modelling and estimation using the GLM.
- Difference between random-effects and mixed-effects analyses.

Note: For ease of calculation, the models will be presented in the following without covariates.

Detecting perfusion abnormalities using the GLM



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GLM: subject level

Repetition 1 Repetition 2 . . . Repetition r

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Given a voxel, for each subject s we have:

$$Y_s = X_s \, \beta_s + \epsilon_s, \tag{4}$$

where

- Y_s vector of observations;
- X_s subject-level design matrix;
- β_s parameters to be estimated;
- ϵ_s residual error

GLM: subject level

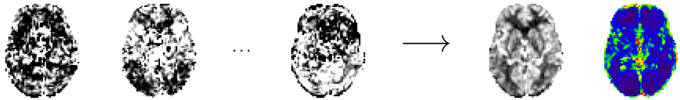
Given a voxel, for each subject s we have:

$$Y_s = \begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix} \beta_s + \epsilon_s. \tag{5}$$

where

- Y_s vector of observations;
- X_s subject-level design matrix;
- β_s parameters to be estimated;
- ϵ_s residual error, $\epsilon_s \sim \mathcal{N}(0, \sigma_s^2)$. [Aguirre 2002]

GLM: subject level



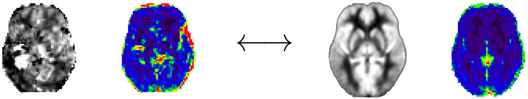
Assuming $\epsilon_s \sim \mathcal{N}(0, \sigma_s^2)$, by ordinary least squares we have:

$$\hat{\beta}_s = \frac{1}{r}\sum_{i=1}^{r} y_{s,i}, \text{ and } \widehat{\mathrm{Var}}(\hat{\beta}_s) = \frac{\hat{\sigma}_s^2}{r}$$

where

- $y_{s,i}$ is the i[th] element of vector Y_s
- $\hat{\sigma}_s^2$ the estimated within-subjet variance.

GLM: between-group



$\hat{\beta}_{patients}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{patients})$ $\longleftrightarrow$ $\hat{\beta}_{controls}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{controls})$

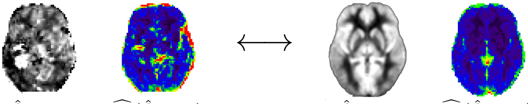
The subject parameters $(\beta_s)_{1 \leq s \leq \mathrm{n}_1+1}$ can be combined using:

$$\begin{bmatrix} \beta_1 \\ \vdots \\ \beta_{n_1+n_2} \end{bmatrix} = X_G \, \beta_G + \gamma_G, \tag{6}$$

where

- X_G is the group-level design matrix;
- β_G the group parameters;
- γ_G^s the residual error term.

GLM: between-group



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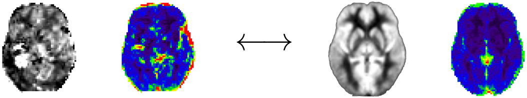
$$\begin{bmatrix} \beta_1 \\ \vdots \\ \beta_{n_1} \\ \beta_{n_1+1} \\ \vdots \\ \beta_{n_1+n_2} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \beta_{controls} \\ \beta_{patients} \end{bmatrix} + \gamma_G. \tag{7}$$

where

- γ_G the residual error term, $\gamma_G^s \sim \mathcal{N}(0, \sigma^2_{G,i})$.

GLM: between-group



$\hat{\beta}_{patients}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{patients})$ $\longleftrightarrow$ $\hat{\beta}_{controls}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{controls})$

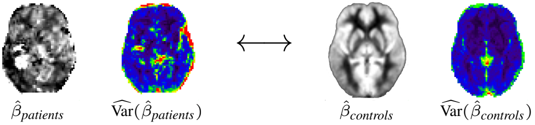
The subject parameters $(\beta_s)_{1\leq s\leq n_1+1}$ can be combined using:

$$\begin{bmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_{n_1} \\ \hat{\beta}_{n_1+1} \\ \vdots \\ \hat{\beta}_{n_1+n_2} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \beta_{controls} \\ \beta_{patients} \end{bmatrix} + \gamma_{G_C}. \tag{8}$$

where

- γ_{G_C} the residual error term, $\gamma_{G_C}^s \sim \mathcal{N}\left(0, \sigma_{G,i}^2 + \frac{\sigma_s^2}{r}\right)$.

Contrast of interest



We are interested in the null hypothesis:

$$H0 : \beta_{controls} = \beta_{patients}. \tag{9}$$

$$H0 : c\,\beta_G = 0. \tag{10}$$

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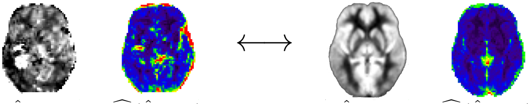

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We are interested in the null hypothesis:

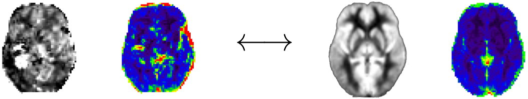
$$H0 : \beta_{controls} = \beta_{patients}. \quad (9)$$

$$H0 : c\,\beta_G = 0. \quad (10)$$

Corresponding to the patient versus control group contrast:

$$c \quad = \quad [1 - 1] \quad (11)$$

Random-effects (RFX) between-group analysis



$\hat{\beta}_{patients}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{patients})$ $\longleftrightarrow$ $\hat{\beta}_{controls}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{controls})$

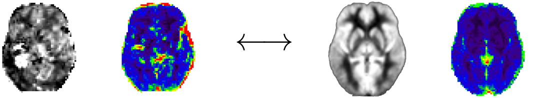
Assuming $\gamma^{s}_{G_C,i} \sim \mathcal{N}(0, \sigma^2_{G_C,i})$, by weighted least squares we have:

$$\hat{\beta}^{RFX}_{controls} = \frac{1}{n_1}\sum_{s=1}^{n_1}\hat{\beta}_s, \quad \hat{\beta}^{RFX}_{patients} = \frac{1}{n_2}\sum_{s=n_1+1}^{n_1+n_2}\hat{\beta}_s, \tag{12}$$

The associated sampling variances are:

$$\widehat{\mathrm{Var}}(\hat{\beta}^{RFX}_{controls}) = \frac{\hat{\sigma}^2_{G_C,1}}{n_1}, \quad \widehat{\mathrm{Var}}(\hat{\beta}^{RFX}_{patients}) = \frac{\hat{\sigma}^2_{G_C,2}}{n_2} \tag{13}$$

Mixed-effects (MFX) between-group analysis



$\hat{\beta}_{patients}$ $\widehat{\text{Var}}(\hat{\beta}_{patients})$ $\longleftrightarrow$ $\hat{\beta}_{controls}$ $\widehat{\text{Var}}(\hat{\beta}_{controls})$

Assuming $\gamma^{s}_{G_C,i} \sim \mathcal{N}(0, \sigma^2_{G,i} + \frac{\sigma^2_s}{r})$, by weighted least squares we have:

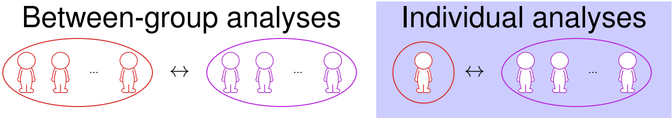
$$\hat{\beta}^{MFX}_{controls} = \frac{1}{\sum_{j=1}^{n_1} w_{j,1}} \sum_{s=1}^{n_1} w_{s,1}\,\hat{\beta}_s, \quad \text{where } w_{s,i} = \frac{1}{\hat{\sigma}^2_{G,i} + \frac{\hat{\sigma}^2_s}{r}}$$

$$\hat{\beta}^{MFX}_{patients} = \frac{1}{\sum_{j=n_1+1}^{n_1+n_2} w_{j,2}} \sum_{s=n_1+1}^{n_1+n_2} w_{s,2}\,\hat{\beta}_s. \tag{14}$$

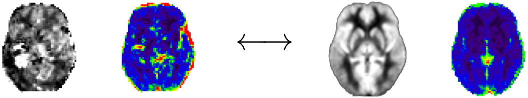
The associated sampling variances are:

$$\widehat{\text{Var}}(\hat{\beta}^{MFX}_{controls}) = \frac{1}{\sum_{s=1}^{n_1} w_{s,1}}, \quad \widehat{\text{Var}}(\hat{\beta}^{MFX}_{patients}) = \frac{1}{\sum_{s=n_1+1}^{n_1+n_2} w_{s,2}} \tag{15}$$

Detecting perfusion abnormalities using the GLM



Random-effects (RFX) analysis



$\hat{\beta}_{patients}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{patients})$ $\longleftrightarrow$ $\hat{\beta}_{controls}$ $\widehat{\mathrm{Var}}(\hat{\beta}_{controls})$

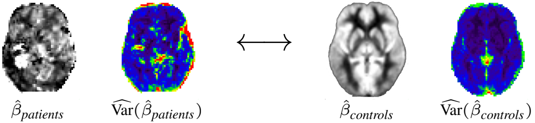
Assuming $\gamma^s_{G_C} \sim \mathcal{N}(0, \sigma^2_{G_C})$, by ordinary least squares we have:

$$\hat{\beta}^{RFX}_{controls} = \frac{1}{n_1} \sum_{s=1}^{n_1} \hat{\beta}_s, \quad \hat{\beta}^{RFX}_{patient} = \hat{\beta}_{n_1+1}, \tag{16}$$

The associated sampling variances are:

$$\widehat{\mathrm{Var}}(\hat{\beta}^{RFX}_{controls}) = \frac{\hat{\sigma}^2_{G_C}}{n_1}, \quad \widehat{\mathrm{Var}}(\hat{\beta}^{RFX}_{patient}) = \hat{\sigma}^2_{G_C} \tag{17}$$

Mixed-effects (MFX) analysis



Assuming $\gamma^s_{G_C} \sim \mathcal{N}(0, \sigma^2_G + \frac{\sigma^2_s}{r})$, by weighted least squares we get:

$$\hat{\beta}^{MFX}_{controls} = \frac{1}{\sum_{j=1}^{n_1} w_{j,1}} \sum_{s=1}^{n_1} w_{s,1}\, \hat{\beta}_s, \quad \hat{\beta}^{MFX}_{patient} = \hat{\beta}_{n_1+1}$$
$$\text{where } w_s = \frac{1}{\hat{\sigma}^2_G + \frac{\hat{\sigma}^2_s}{r}}. \tag{18}$$

The associated sampling variances are:

$$\widehat{\mathrm{Var}}(\hat{\beta}^{MFX}_{controls}) = \frac{1}{\sum_{s=1}^{n_1} w_s}, \quad \widehat{\mathrm{Var}}(\hat{\beta}^{MFX}_{patients}) = \hat{\sigma}^2_G + \frac{\hat{\sigma}^2_{n_1+1}}{r} \tag{19}$$

Random-effects and Mixed-effects analyses

Control group and patient estimates and sampling variances with RFX and MFX.

	$\hat{\beta}_{controls}$	$\hat{\beta}_{patient}$	$\widehat{Var}(\hat{\beta}_{controls})$	$\widehat{Var}(\hat{\beta}_{patient})$
RFX	$\frac{1}{n_1}\sum_{s=1}^{n_1}\hat{\beta}_s$	$\hat{\beta}_{\mathrm{n}_1+1}$	$\frac{\hat{\sigma}^2_{G_C}}{n_1}$	$\hat{\sigma}^2_{G_C}$
MFX	$\frac{1}{\sum_{j=1}^{n_1}\frac{1}{\hat{\sigma}^2_G+\frac{\hat{\sigma}^2_j}{r}}}\sum_{s=1}^{n_1}\frac{1}{\hat{\sigma}^2_G+\frac{\hat{\sigma}^2_s}{r}}\hat{\beta}_s$	$\hat{\beta}_{\mathrm{n}_1+1}$	$\frac{1}{\sum_{s=1}^{n_1}\frac{1}{\hat{\sigma}^2_G+\frac{\hat{\sigma}^2_s}{r}}}$	$\hat{\sigma}^2_G+\frac{\hat{\sigma}^2_{\mathrm{n}_1+1}}{r}$

Outline

Subjects and imaging protocol

25 patients diagnosed with brain tumours and 61 control subjects participated in this study.

Imaging protocol:

- PICORE Q2TIPS Pulsed ASL, 60 repetitions
- MPRAGE T1 3D
- T2 FLAIR

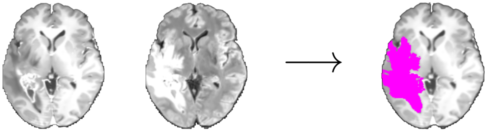
For the patients only:

- T1 3D Gadolinium
- Dynamic Susceptibility Contrast imaging (DSC)

Validation: Ground Truth

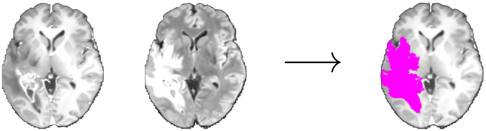
Validation: Ground Truth

1. Segmentation of the tumour:



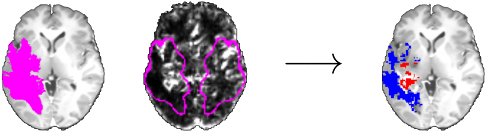
Validation: Ground Truth

1. Segmentation of the tumour:



T1 Gadolinium | T2 FLAIR | Tumour and oedema segmentation

2. Combination with T2 perfusion information:



Tumour segmentation | DSC CBF | "Ground truth"

Validation: Ground Truth

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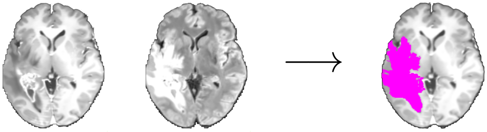

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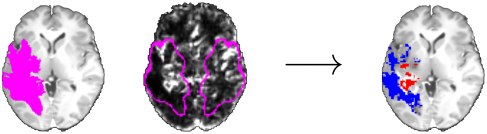

Tumour segmentation — DSC CBF — "Ground truth"

3. Visual assessment and manual corrections by a clinician.

Outline

Assumptions of RFX analyses

- Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.

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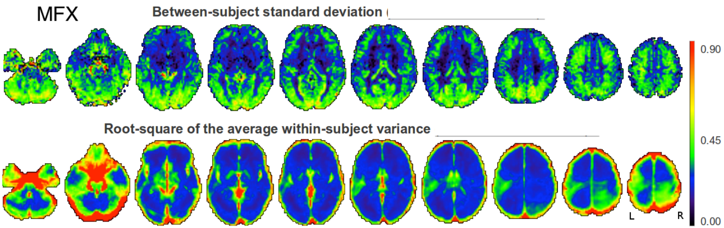

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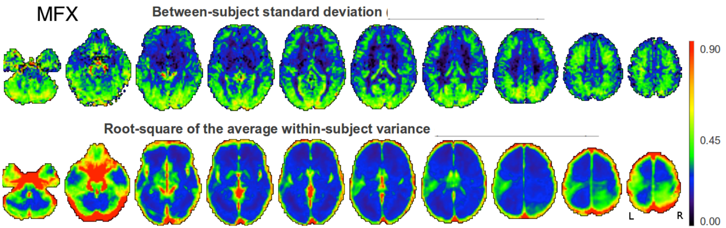

× not verified

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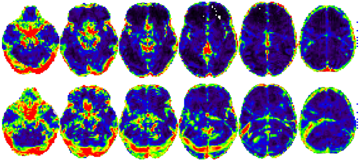
Within-subject standard deviation in two control subjects:



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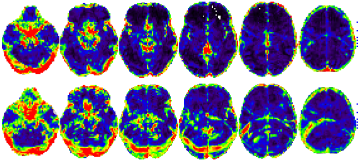

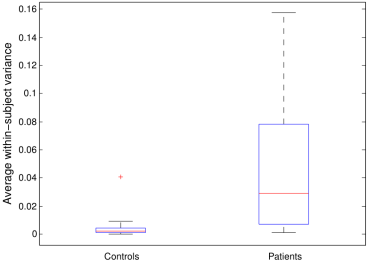

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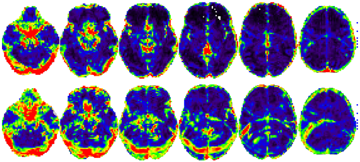
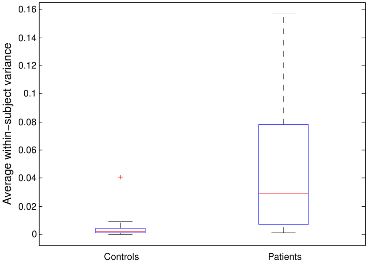
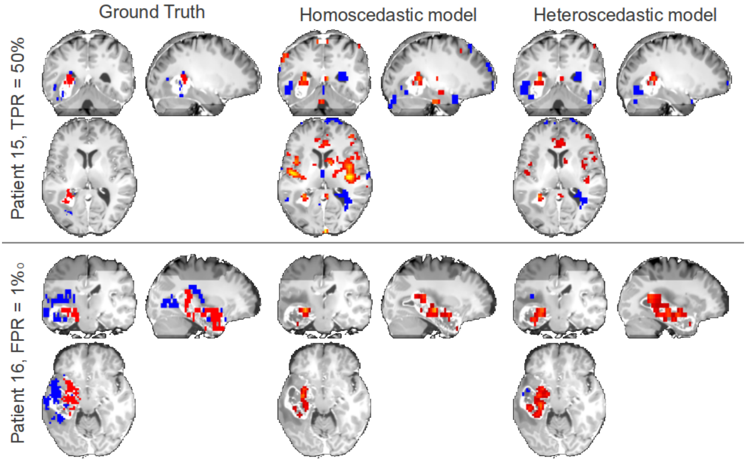




× not verified

Results: RFX versus MFX



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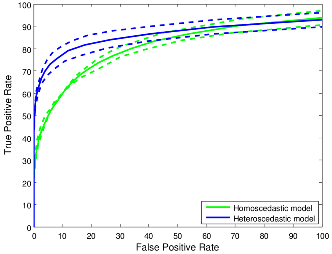

ROC curves for perfusion abnormality detections.
[Maumet et al., NeuroImage 2013]

	Random-effects analysis				
FWHM (mm^3)	0	4	6	8	10
ROC Area	0.46	**0.49**	**0.49**	**0.49**	0.48

	Mixed-effects analysis				
FWHM (mm^3)	0	4	6	8	10
ROC Area	0.63	0.70	**0.72**	**0.72**	0.69

Area under the ROC curve.

Outline

Conclusion

We demonstrated on a dataset of PICORE Q2TIPS ASL images that:

- the assumptions of RFX analyses were violated.
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- Software packages: **RFX (SPM), MFX (FSL, AFNI)**.
- More details on RFX and MFX [Beckmann 2003, Mumford 2006, Mumford 2009].

Thank you

VisAGeS team:

- Christian Barillot.
- Pierre Maurel.
- Jean-Christophe Ferré.
- Béatrice Carsin.

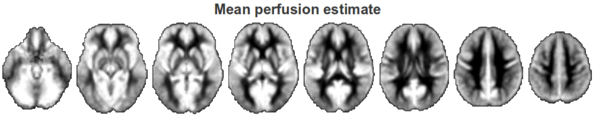
C. Maumet, P. Maurel, J-C. Ferré, B. Carsin, C. Barillot. *Patient-specific detection of perfusion abnormalities combining within-subject and between-subject variances in Arterial Spin Labeling.* NeuroImage, 2013, 81C, pp. 121-130. Freely available online.

Q & A

Outline

A model of normal perfusion

Perfusion estimate $\hat{\beta}_{controls}$



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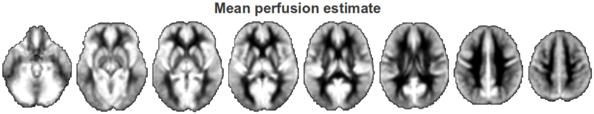
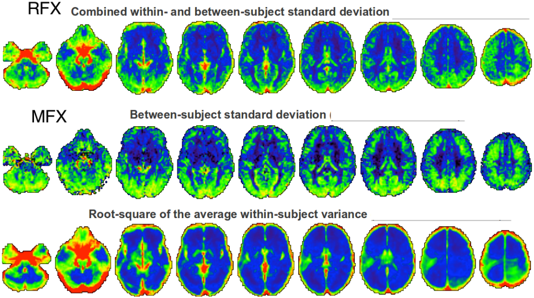


Standard deviation estimates

RFX

MFX



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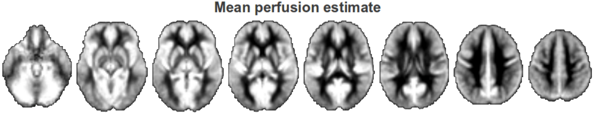

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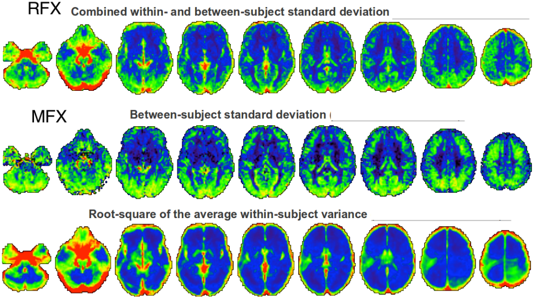
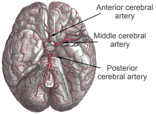
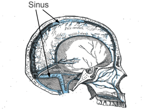




Brain arteries



Brain veins