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Detecting perfusion abnormalities in Arterial Spin Labelling Random-effects and Mixed-effects GLM

Camille Maumet

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Detecting perfusion abnormalities in Arterial Spin Labelling

Random-effects and Mixed-effects GLM

Camille Maumet ^{1,2}

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NeuroImaging seminars, Institute of Psychiatry
King's College London - February 14th, 2014

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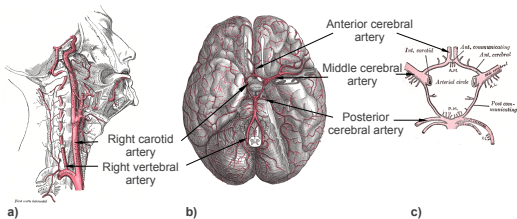
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Brain perfusion

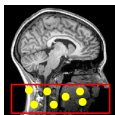


Blood supply to the brain

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[Detre et al., MRM 1992]

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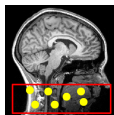
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[Detre et al., MRM 1992]

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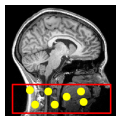
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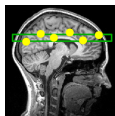
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[Detre et al., MRM 1992]

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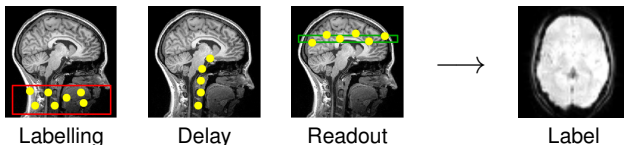
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[Detre et al., MRM 1992]

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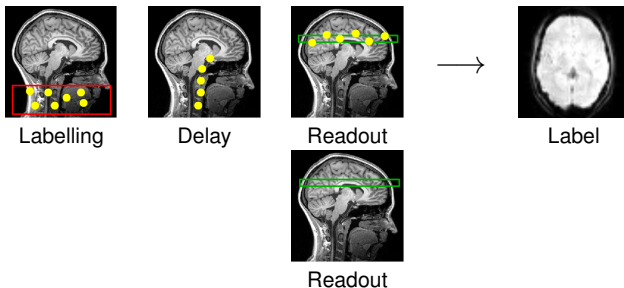
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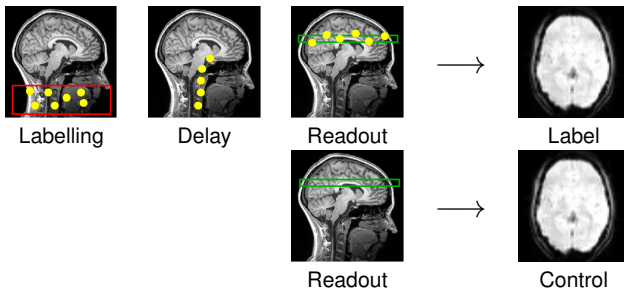
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[Detre et al., MRM 1992]

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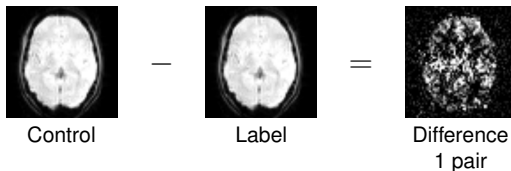
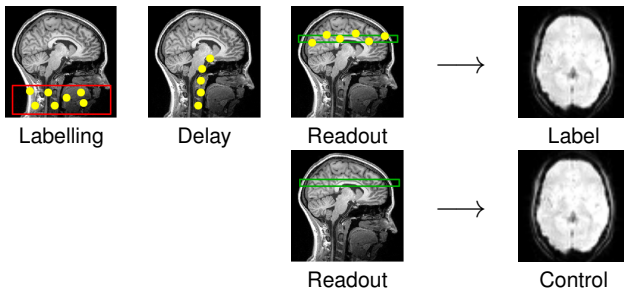
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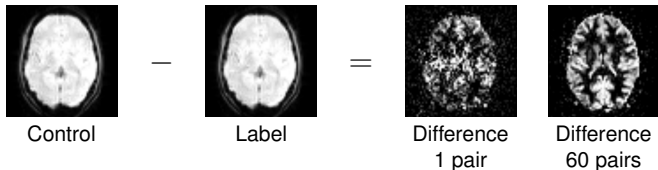
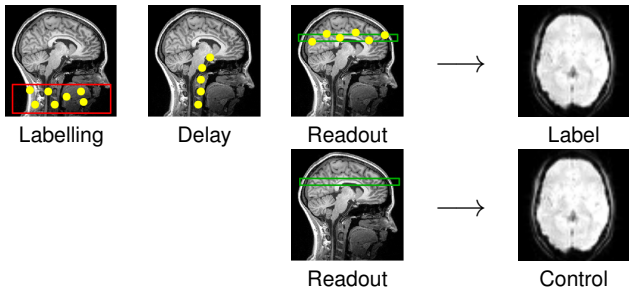
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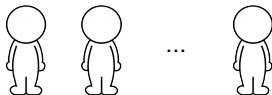
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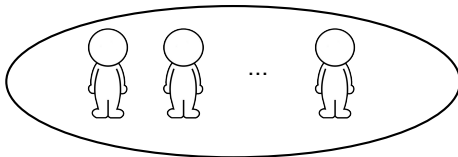
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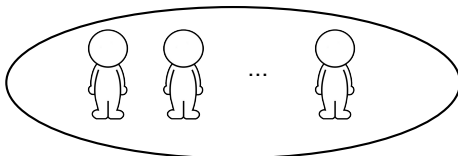
Within-group analysis

Identify common patterns across a group of subjects.

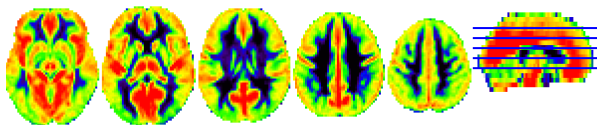


Within-group analysis

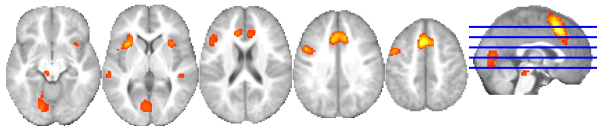
Identify common patterns across a group of subjects.



Examples



Group cerebral blood flow.



Group activation for a language task.

Between-group analysis

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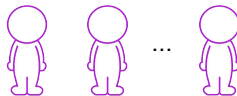
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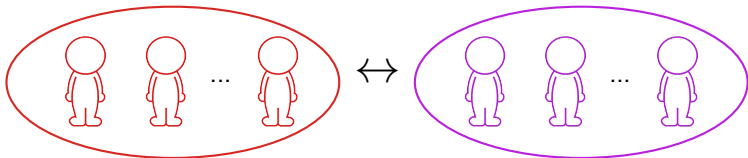
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Between-group analysis

Identify differences at the group level.



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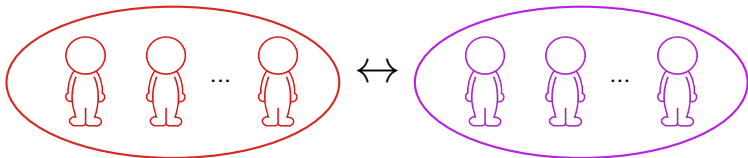
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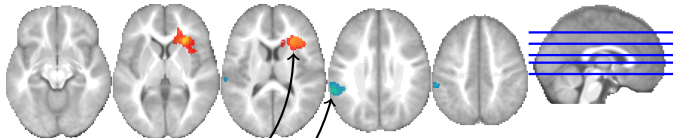
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Between-group analysis

Identify differences at the group level.



Example



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

- ▶ Hyper-perfusion.
- ▶ Hypo-perfusion.

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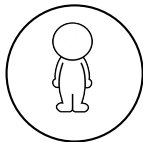
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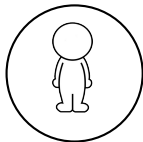
Within-subject analysis

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

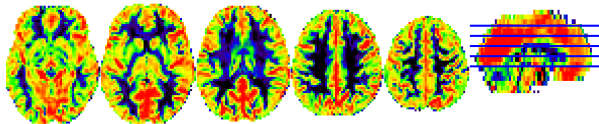


Within-subject analysis

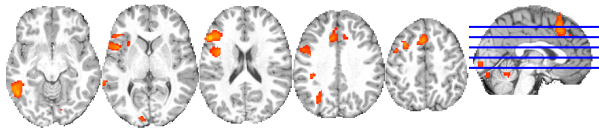
Identify patterns of perfusion (or activation) in a single subject.



Examples



Cerebral blood flow.



Subject activation for a language task.

Between-group individual analysis

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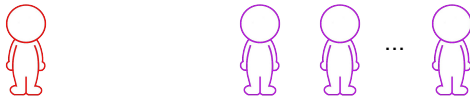
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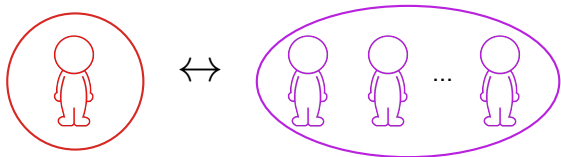
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Between-group individual analysis

Identify deviation from normality in a single subject.



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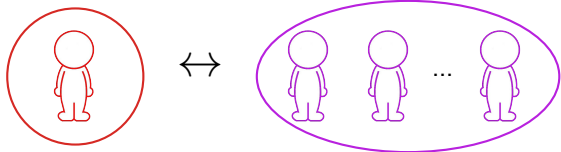
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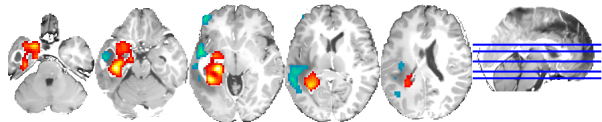
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Identify deviation from normality in a single subject.



Example



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

Within-group and between-group analyses

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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).

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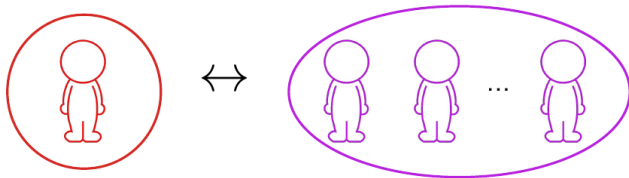
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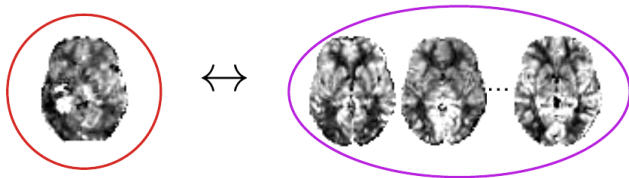
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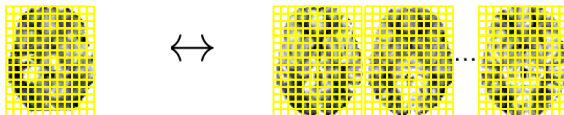
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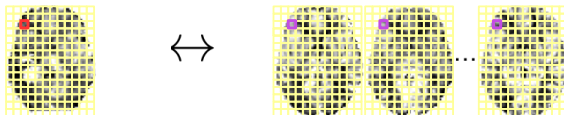
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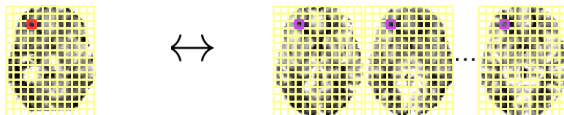
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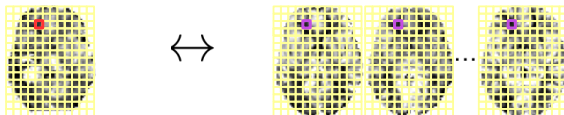
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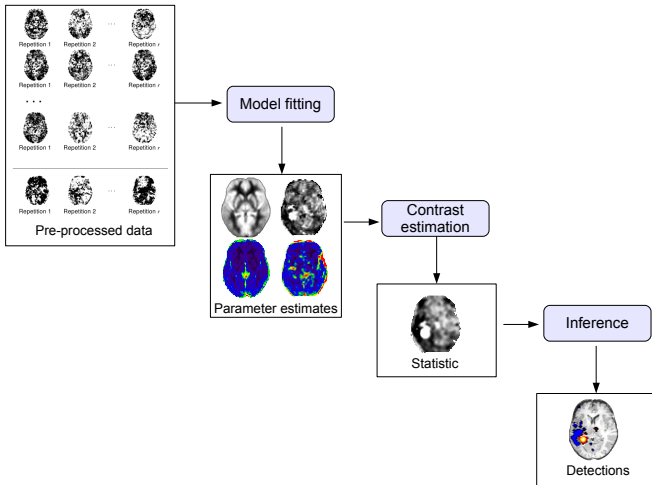
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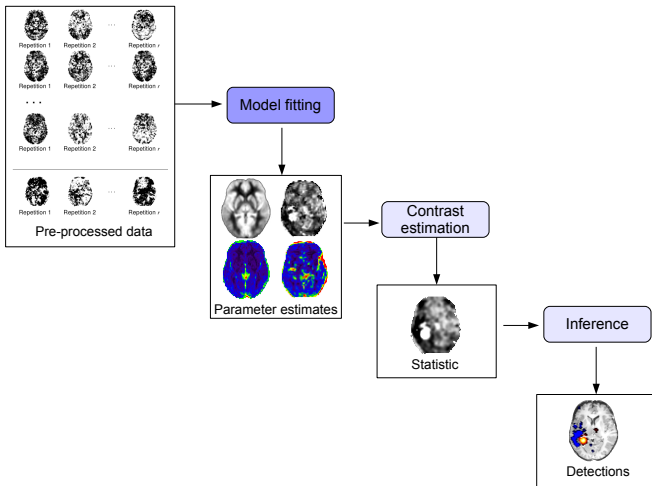
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Model fitting

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

$$\begin{matrix} \begin{matrix} \overbrace{}^1 \\ \downarrow N \end{matrix} \\ y \end{matrix} = \begin{matrix} \begin{matrix} \overbrace{}^p \\ \downarrow N \end{matrix} \\ X \end{matrix} \begin{matrix} \begin{matrix} \overbrace{}^1 \\ \downarrow p \end{matrix} \\ \beta \end{matrix} + \begin{matrix} \begin{matrix} \overbrace{}^1 \\ \downarrow N \end{matrix} \\ e \end{matrix}$$

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

Model fitting

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

$$y = X\beta + e$$

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

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

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

Model fitting

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

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

$$\hat{\beta}_{WLS} = (X^T V^{-1} X)^{-1} X^T V^{-1} Y, \quad \widehat{\text{Var}}(\hat{\beta}_{WLS}) = (X^T V^{-1} X)^{-1}. \quad (2)$$

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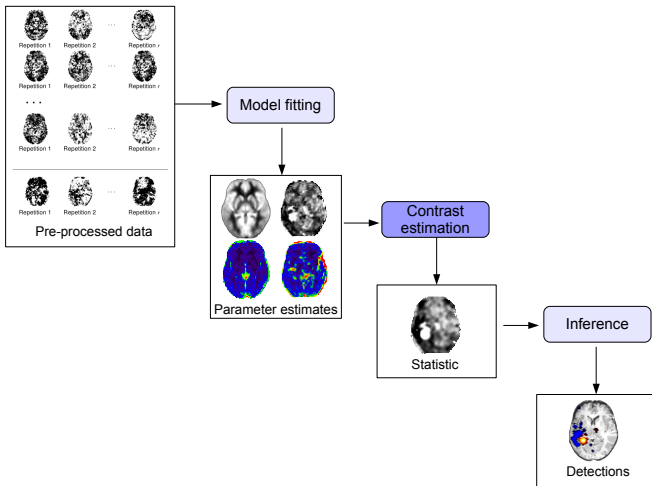
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Under the null hypothesis:

$$H_0 : \mathbf{c}\beta_{(v)} = 0.$$

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

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

Hypothesis testing: overview

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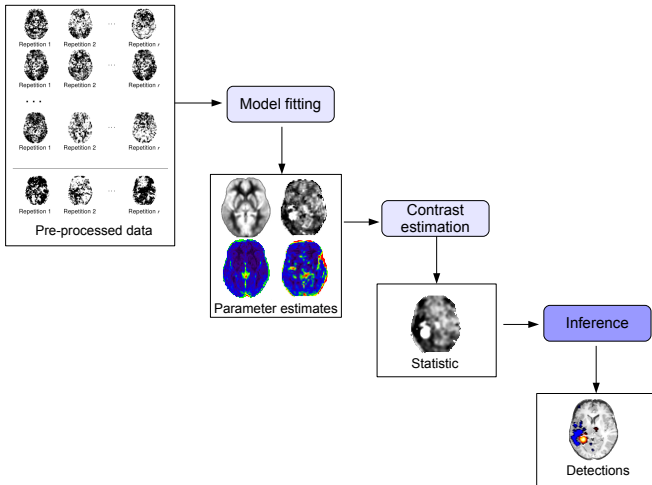
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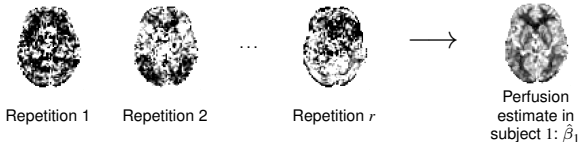
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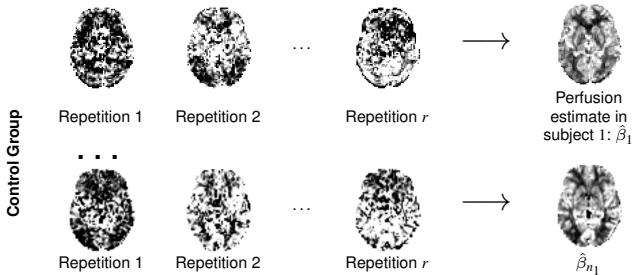
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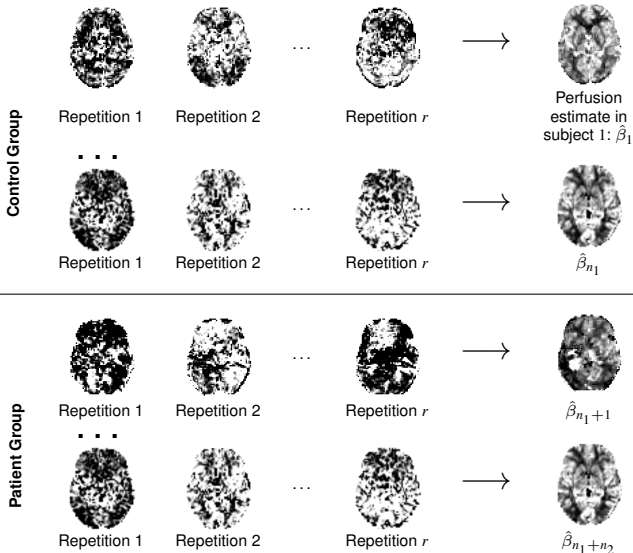
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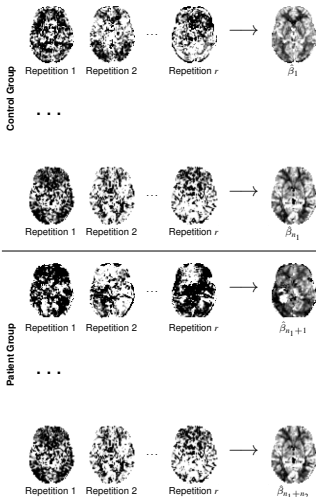


Modelling: subject level



Modelling: group level

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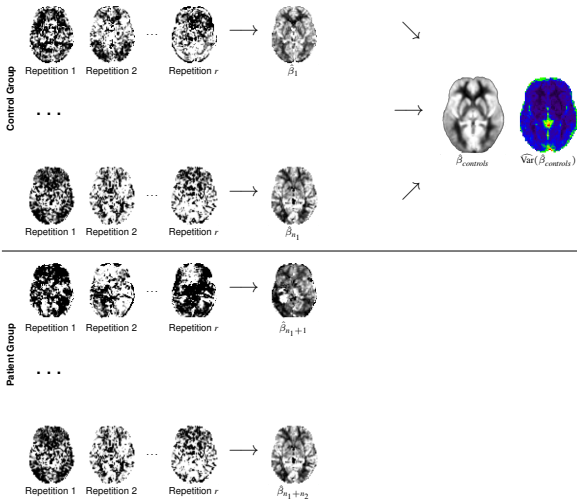
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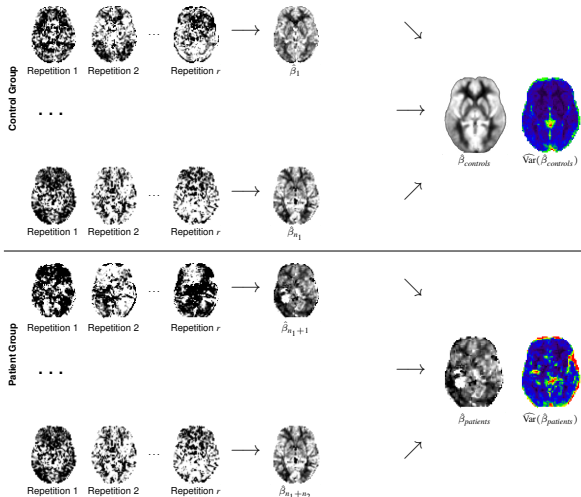
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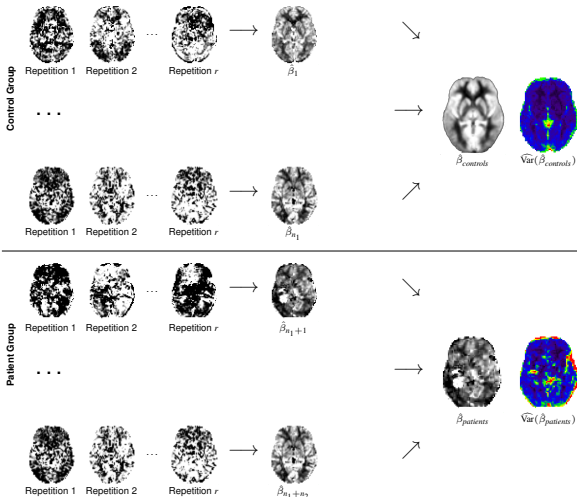
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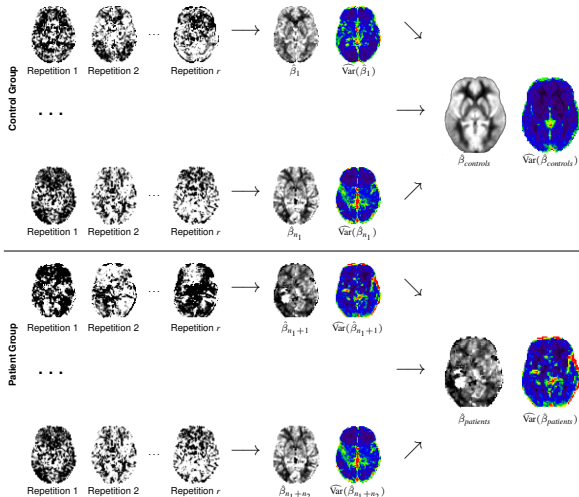
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Random-effects (RFX) analysis.

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Mixed-effects (MFX) analysis.

Random-effects assumptions

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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 (SPM¹)
- ▶ Mixed-effects analyses (FSL², AFNI³).

What about ASL?

¹www.fil.ion.ucl.ac.uk/spm/

²fsl.fmrib.ox.ac.uk/fsl/fslwiki/

³afni.nimh.nih.gov/afni/

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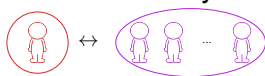
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Between-group analyses



Individual analyses



- ▶ 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.

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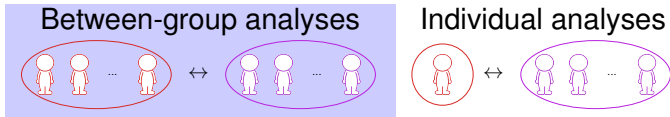
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- ▶ Modelling and estimation using the GLM.
- ▶ Difference between random-effects and mixed-effects analyses.

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

GLM: subject level

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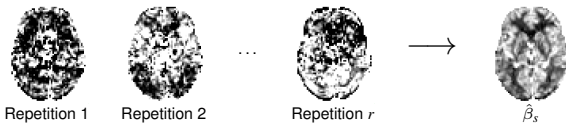
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GLM: subject level

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GLM: subject level



Given a voxel, for each subject s we have:

$$Y_s = X_s \beta_s + \epsilon_s, \quad (4)$$

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:

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

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



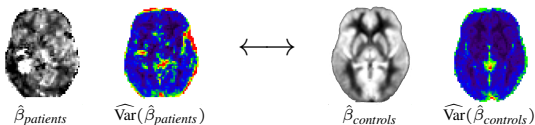
Assuming $\epsilon_s \sim \mathcal{N}(0, \sigma_s^2)$, by ordinary least squares we have:

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

where

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

GLM: between-group



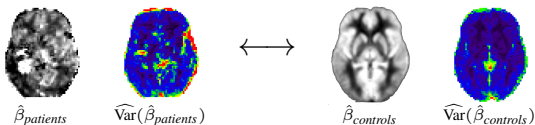
The subject parameters $(\beta_s)_{1 \leq s \leq n_1+1}$ can be combined using:

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

where

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

GLM: between-group



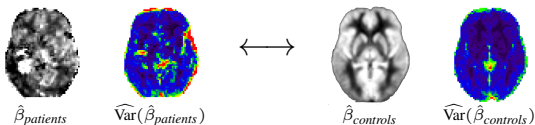
The subject parameters $(\beta_s)_{1 \leq s \leq n_1+1}$ can be combined using:

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

where

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

GLM: between-group



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

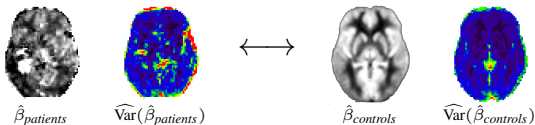
$$\begin{bmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_{n_1} \\ \hat{\beta}_{n_1+1} \\ \vdots \\ \hat{\beta}_{n_1+n_2} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \beta_{controls} \\ \beta_{patients} \end{bmatrix}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

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

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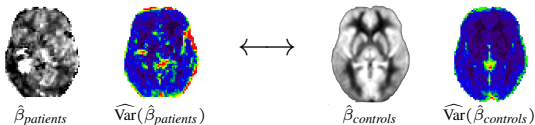


We are interested in the null hypothesis:

$$H_0 : \beta_{controls} = \beta_{patients}. \quad (9)$$

$$H_0 : c \beta_G = 0. \quad (10)$$

Contrast of interest



We are interested in the null hypothesis:

$$H_0 : \beta_{controls} = \beta_{patients}. \quad (9)$$

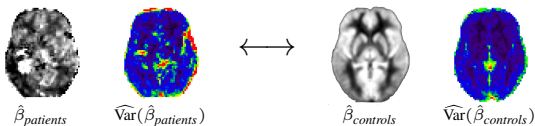
$$H_0 : c \beta_G = 0. \quad (10)$$

Corresponding to the patient versus control group contrast:

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

Random-effects (RFX) between-group analysis

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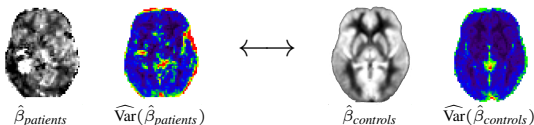
Assuming $\gamma_{GC,i}^s \sim \mathcal{N}(0, \sigma_{GC,i}^2)$, by weighted least squares we have:

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

The associated sampling variances are:

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

Mixed-effects (MFX) between-group analysis



Assuming $\gamma_{GC,i}^s \sim \mathcal{N}(0, \sigma_{G,i}^2 + \frac{\sigma_s^2}{r})$, by weighted least squares we have:

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

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

The associated sampling variances are:

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

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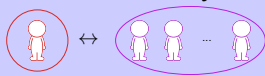
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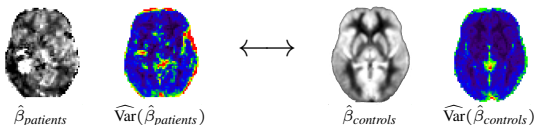
Between-group analyses



Individual analyses



Random-effects (RFX) analysis



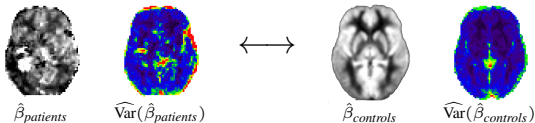
Assuming $\gamma_{GC}^s \sim \mathcal{N}(0, \sigma_{GC}^2)$, by ordinary least squares we have:

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

The associated sampling variances are:

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

Mixed-effects (MFX) analysis



Assuming $\gamma_{GC}^s \sim \mathcal{N}(0, \sigma_G^2 + \frac{\sigma_s^2}{r})$, by weighted least squares we get:

$$\hat{\beta}_{controls}^{MFX} = \frac{1}{\sum_{j=1}^{n_1} w_{j,1}} \sum_{s=1}^{n_1} w_{s,1} \hat{\beta}_s, \quad \hat{\beta}_{patient}^{MFX} = \hat{\beta}_{n_1+1} \quad (18)$$

$$\text{where } w_s = \frac{1}{\hat{\sigma}_G^2 + \frac{\hat{\sigma}_s^2}{r}}.$$

The associated sampling variances are:

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

Random-effects and Mixed-effects analyses

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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	$\frac{1}{n_1} \sum_{s=1}^{n_1} \hat{\beta}_s$	$\hat{\beta}_{n_1+1}$	$\frac{\hat{\sigma}_{GC}^2}{n_1}$	$\hat{\sigma}_{GC}^2$
MFX	$\frac{1}{\sum_{j=1}^{n_1} \frac{1}{\hat{\sigma}_G^2 + \frac{\hat{\sigma}_j^2}{r}}} \sum_{s=1}^{n_1} \frac{1}{\hat{\sigma}_G^2 + \frac{\hat{\sigma}_s^2}{r}} \hat{\beta}_s$	$\hat{\beta}_{n_1+1}$	$\frac{1}{\sum_{s=1}^{n_1} \frac{1}{\hat{\sigma}_G^2 + \frac{\hat{\sigma}_s^2}{r}}}$	$\hat{\sigma}_G^2 + \frac{\hat{\sigma}_{n_1+1}^2}{r}$

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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

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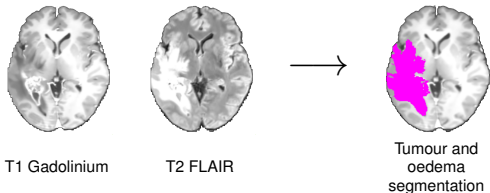
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Validation: Ground Truth

1. Segmentation of the tumour:



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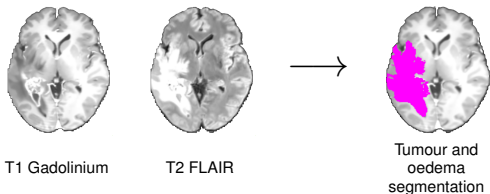
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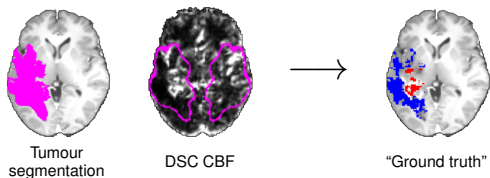
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1. Segmentation of the tumour:

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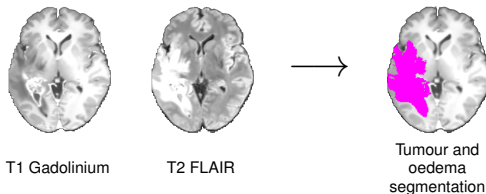


2. Combination with T2 perfusion information:

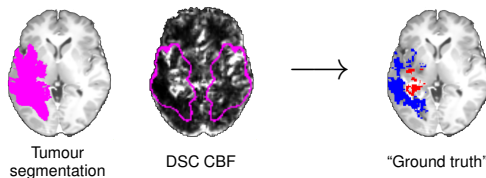


Validation: Ground Truth

1. Segmentation of the tumour:



2. Combination with T2 perfusion information:



3. Visual assessment and manual corrections by a clinician.

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Assumptions of RFX analyses

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

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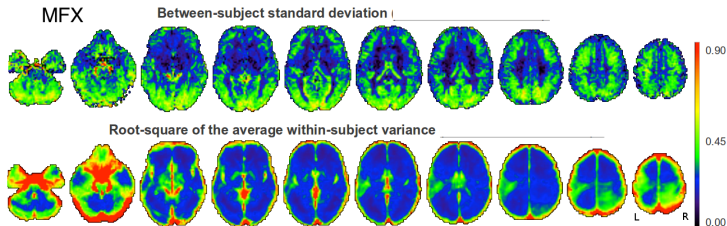
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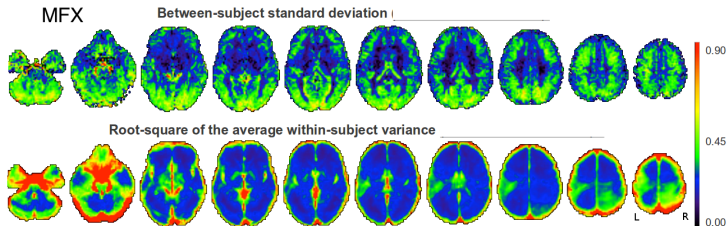
- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



Assumptions of RFX analyses

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



× not verified

Assumptions of RFX analyses

- ▶ Assumption 2: Within-subject variance roughly constant across subjects.

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Detecting
perfusion
abnormalities

ASL

Group

Single-subject

General Linear
Model: MFX and
RFX

Hypothesis
testing

RFX and MFX

Detections in ASL

Methods

Experiment

Results

Conclusions

Assumptions of RFX analyses

Camille Maumet

- ▶ Assumption 2: Within-subject variance roughly constant across subjects.

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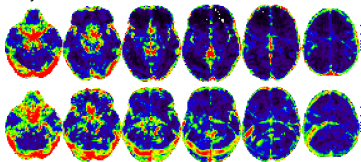
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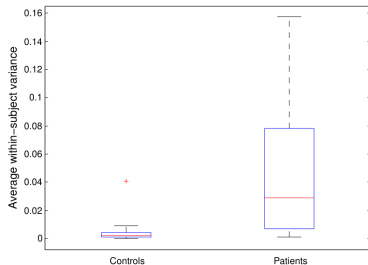
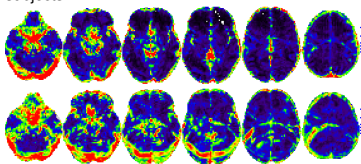
Within-subject standard deviation in two control subjects:



Assumptions of RFX analyses

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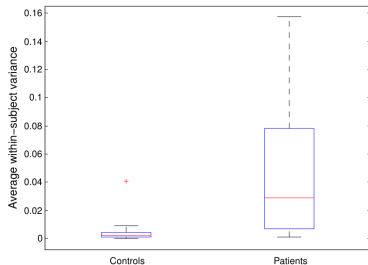
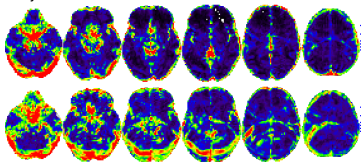
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Within-subject standard deviation in two control subjects:



× not verified

Results: RFX versus MFX

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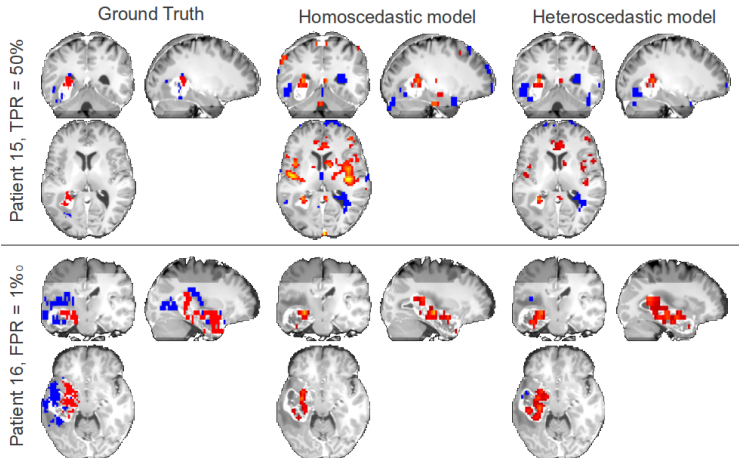
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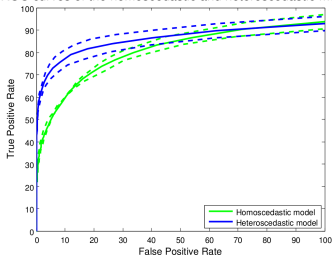
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Results: RFX versus MFX

ROC curves of the homoscedastic and heteroscedastic models



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

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

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

- ▶ the assumptions of RFX analyses were violated.
- ▶ using an **MFX analysis** was essential in the detection of perfusion abnormalities at the patient level.

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- ▶ 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.

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Q & A

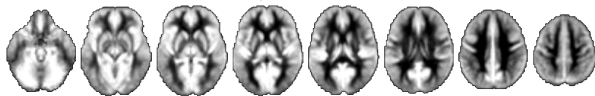
Outline

Appendix

A model of normal perfusion

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

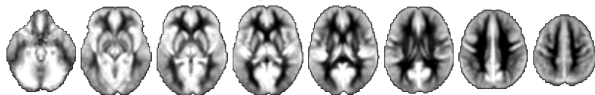
Mean perfusion estimate



A model of normal perfusion

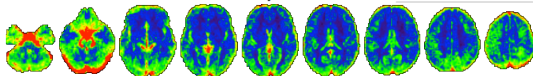
Perfusion estimate $\hat{\beta}_{controls}$

Mean perfusion estimate

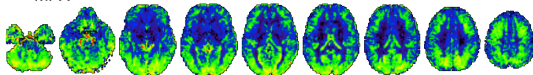


Standard deviation estimates

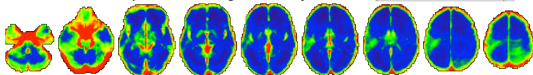
RFX Combined within- and between-subject standard deviation



MFX Between-subject standard deviation



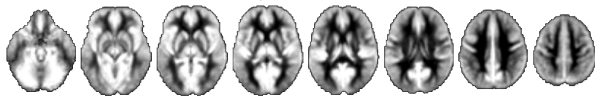
Root-square of the average within-subject variance



A model of normal perfusion

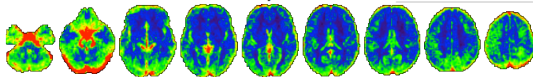
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Mean perfusion estimate

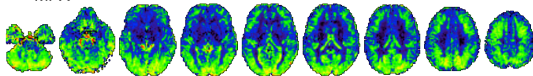


Standard deviation estimates

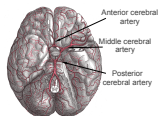
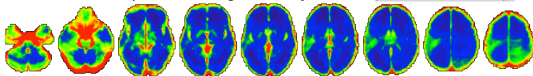
RFX Combined within- and between-subject standard deviation



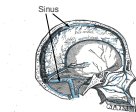
MFX Between-subject standard deviation



Root-square of the average within-subject variance



Brain arteries



Brain veins