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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

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

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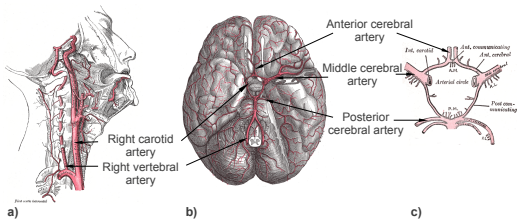
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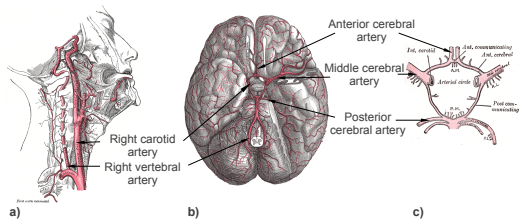
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Brain perfusion



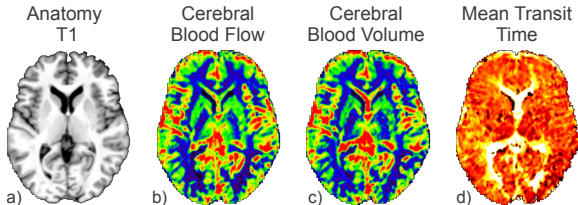
Blood supply to the brain

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.

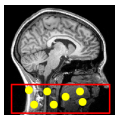


Example of perfusion parameters

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[Detre et al., MRM 1992]

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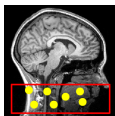
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[Detre et al., MRM 1992]

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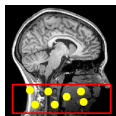
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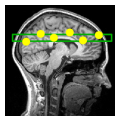
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Readout

[Detre et al., MRM 1992]

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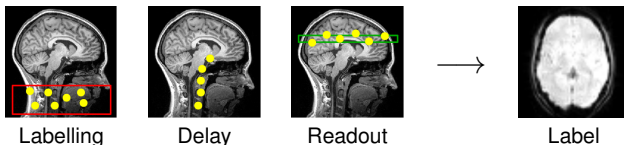
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[Detre et al., MRM 1992]

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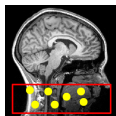
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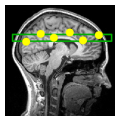
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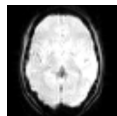
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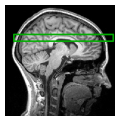
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Readout



Label



Readout

[Detre et al., MRM 1992]

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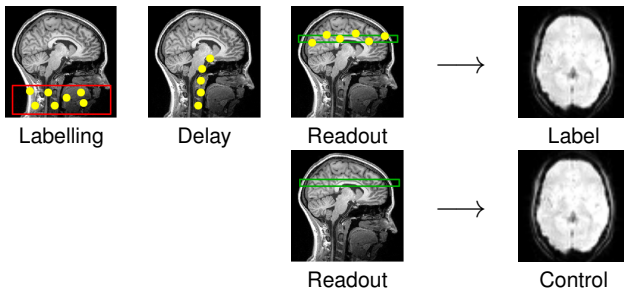
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[Detre et al., MRM 1992]

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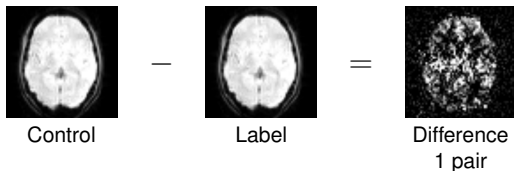
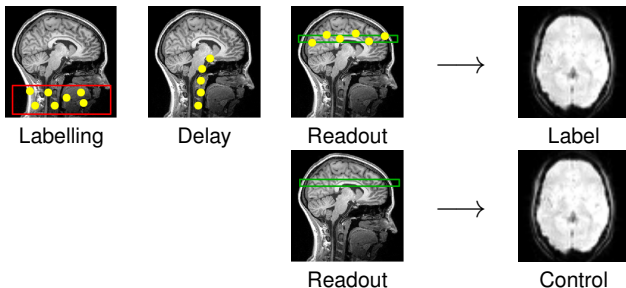
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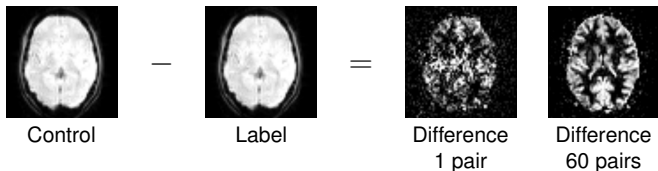
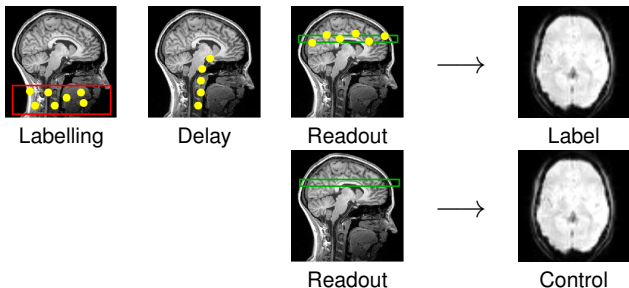
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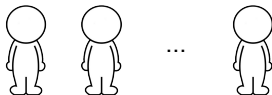
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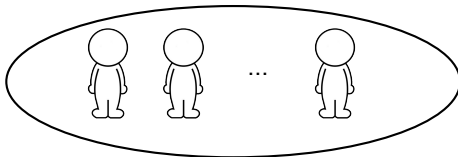
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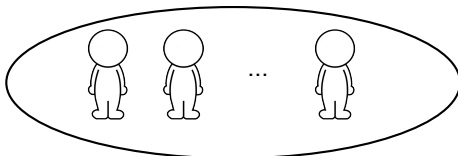
Within-group analysis

Identify common patterns across a group of subjects.

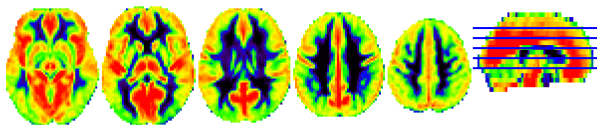


Within-group analysis

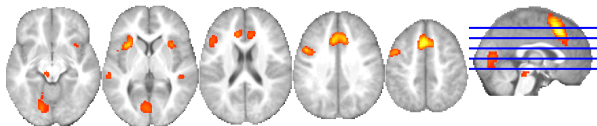
Identify common patterns across a group of subjects.



Examples



Group cerebral blood flow.



Group activation for a language task.

Between-group analysis

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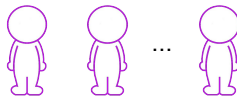
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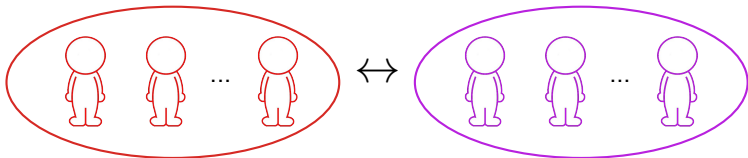
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Between-group analysis

Identify differences at the group level.



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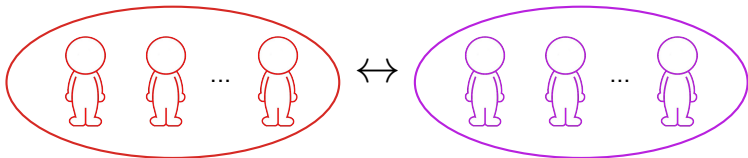
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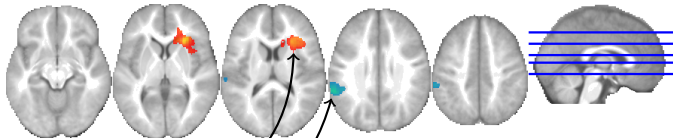
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Between-group analysis

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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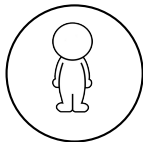
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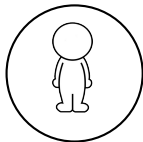
Within-subject analysis

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

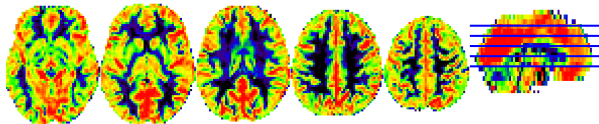


Within-subject analysis

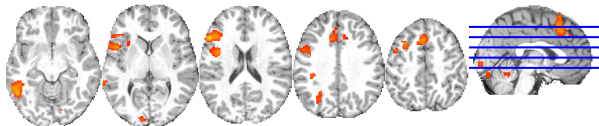
Identify patterns of perfusion (or activation) in a single subject.



Examples



Cerebral blood flow.



Subject activation for a language task.

Between-group individual analysis

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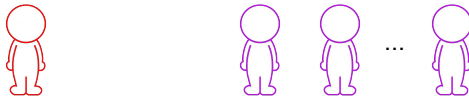
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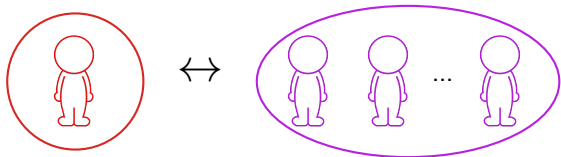
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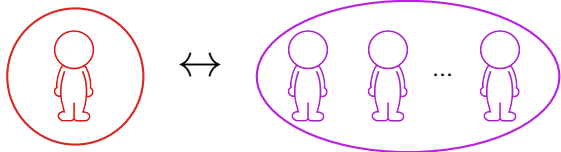
Between-group individual analysis

Identify deviation from normality in a single subject.

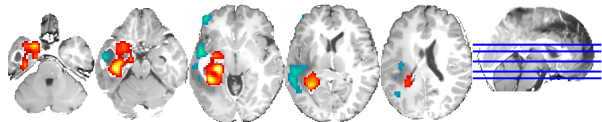


Between-group individual analysis

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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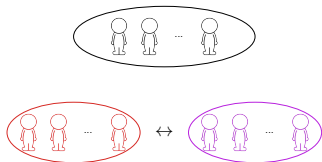
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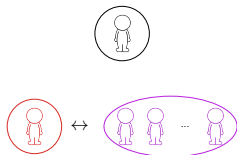
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Group analyses



- ▶ 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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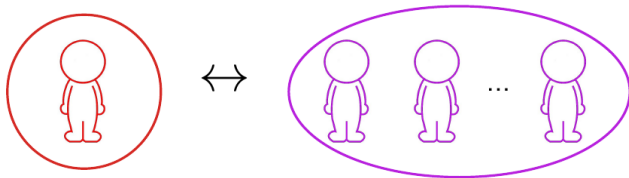
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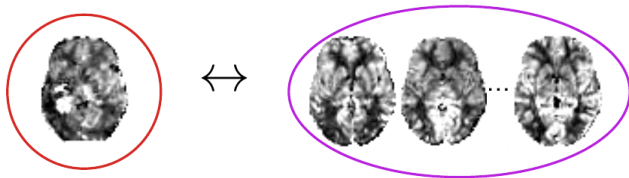
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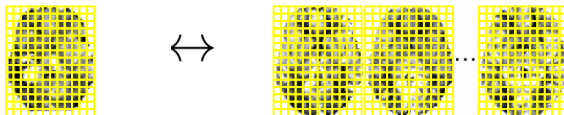
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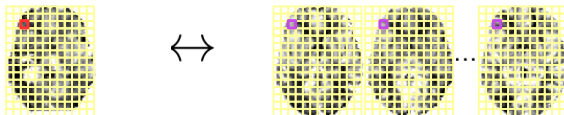
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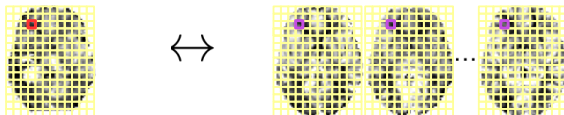
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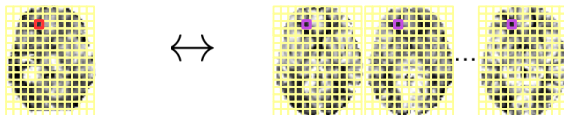
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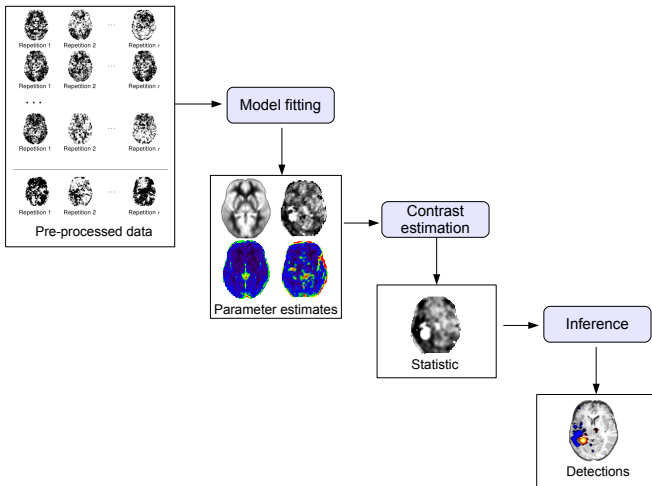
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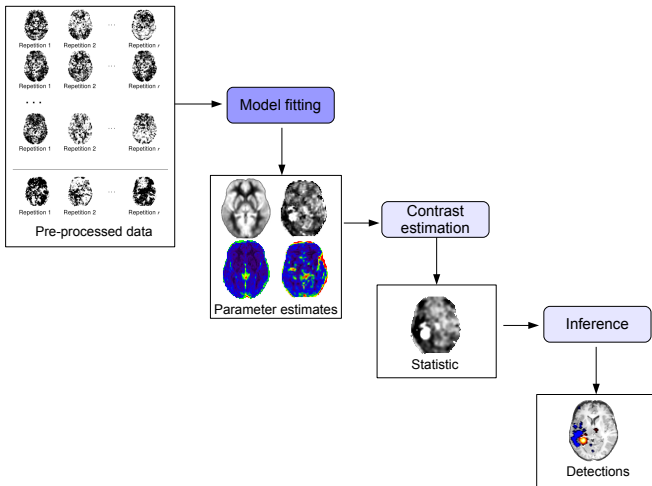
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Model fitting

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

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

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

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

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

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

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

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

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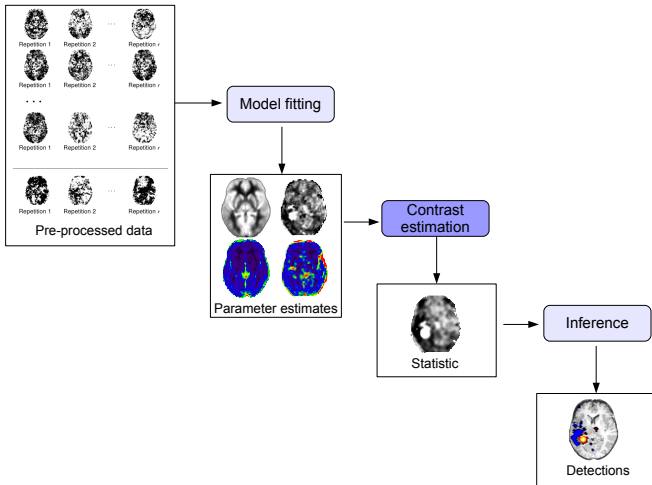
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Under the null hypothesis:

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

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

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

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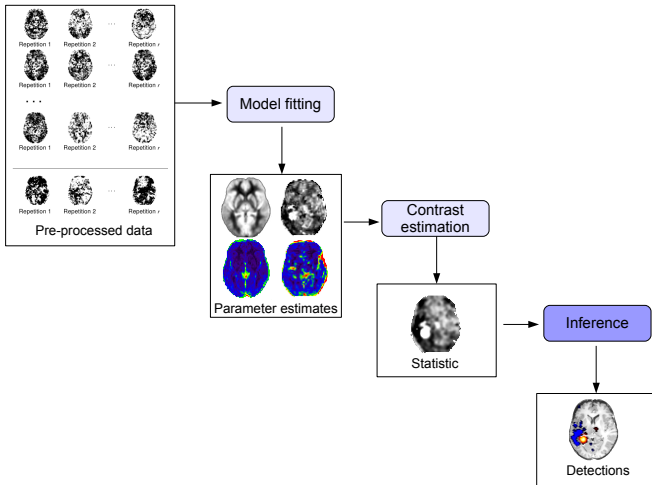
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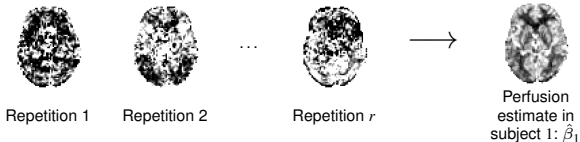
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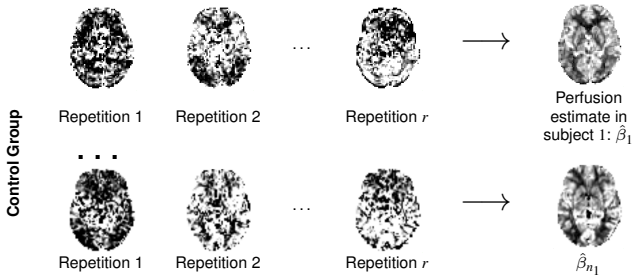
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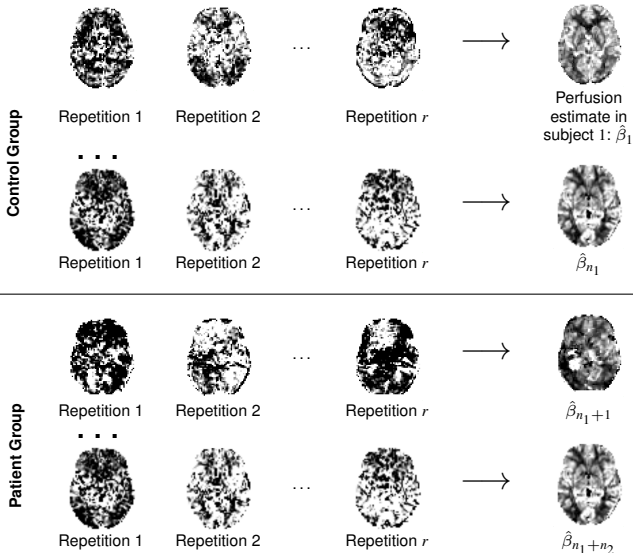
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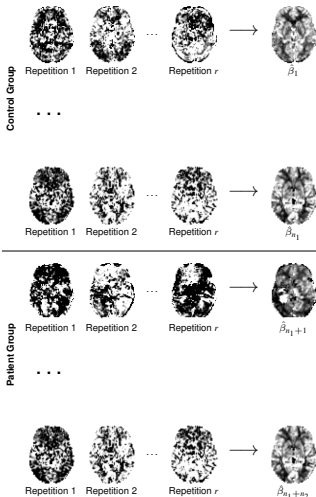


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Modelling: group level

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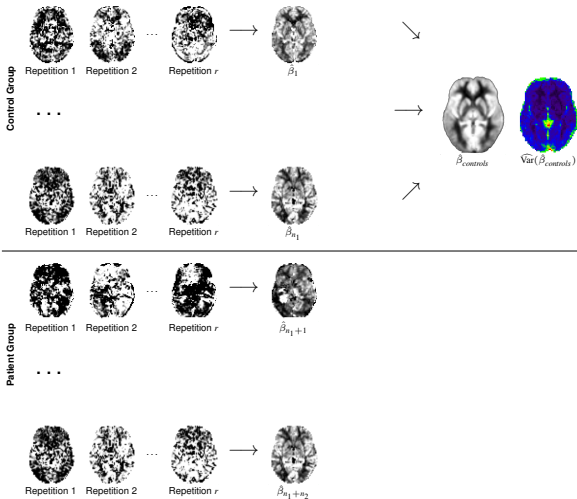
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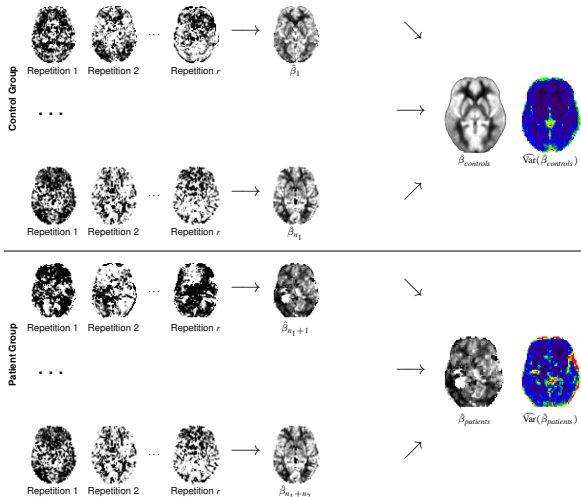
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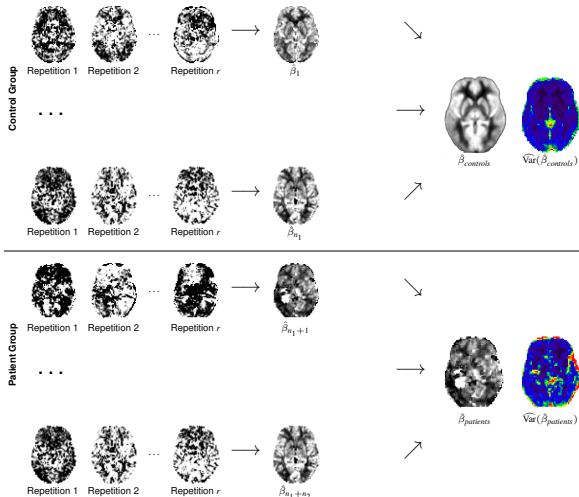
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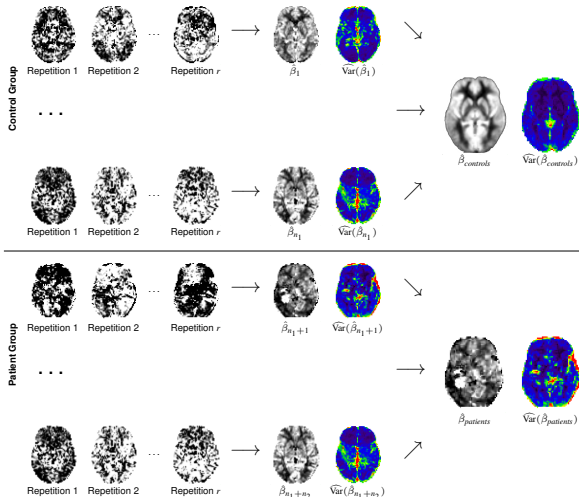
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Random-effects (RFX) analysis.

Modelling: group level



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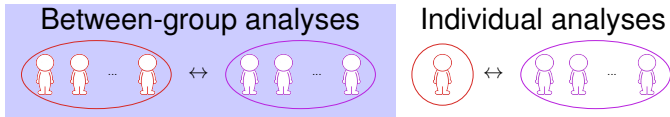
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- ▶ Modelling and estimation using the GLM.
- ▶ Difference between random-effects and mixed-effects analyses.

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

GLM: subject level

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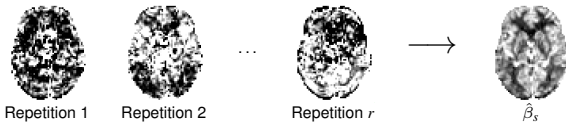
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GLM: subject level



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



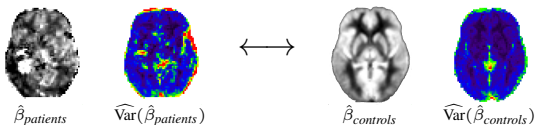
Assuming $\epsilon_s \sim \mathcal{N}(0, \sigma_s^2)$, by ordinary least squares we have:

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

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



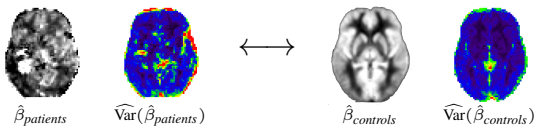
The subject parameters $(\beta_s)_{1 \leq s \leq n_1+1}$ can be combined using:

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

where

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

GLM: between-group



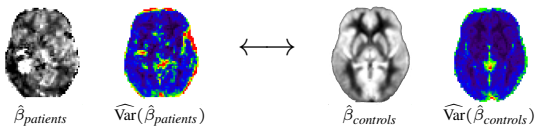
The subject parameters $(\beta_s)_{1 \leq s \leq n_1+1}$ can be combined using:

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

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:

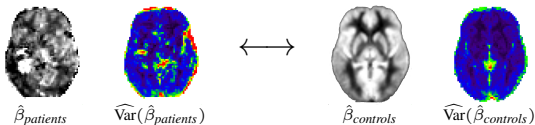
$$\begin{bmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_{n_1} \\ \hat{\beta}_{n_1+1} \\ \vdots \\ \hat{\beta}_{n_1+n_2} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \beta_{controls} \\ \beta_{patients} \end{bmatrix}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

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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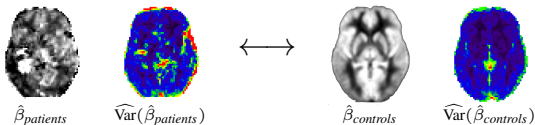
We are interested in the null hypothesis:

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

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

Contrast of interest

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We are interested in the null hypothesis:

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

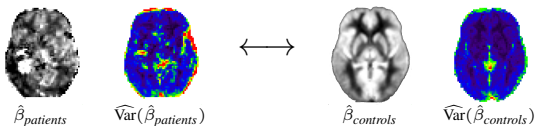
$$H_0 : c \beta_G = 0. \quad (10)$$

Corresponding to the patient versus control group contrast:

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

Random-effects (RFX) between-group analysis

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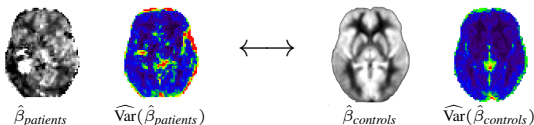
Assuming $\gamma_{GC,i}^s \sim \mathcal{N}(0, \sigma_{GC,i}^2)$, by weighted least squares we have:

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

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:

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

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

The associated sampling variances are:

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

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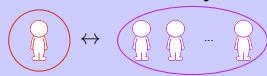
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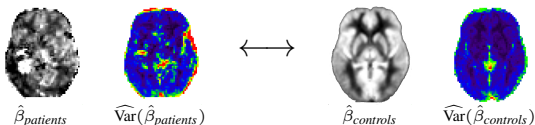


Individual analyses



Random-effects (RFX) analysis

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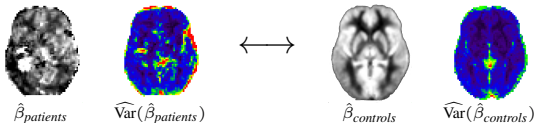
Assuming $\gamma_{GC}^s \sim \mathcal{N}(0, \sigma_{GC}^2)$, by ordinary least squares we have:

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

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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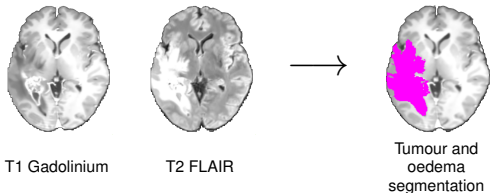
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1. Segmentation of the tumour:



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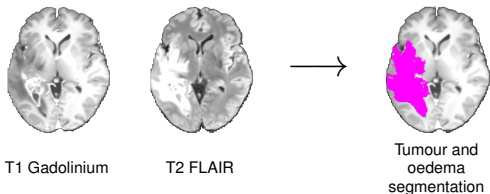
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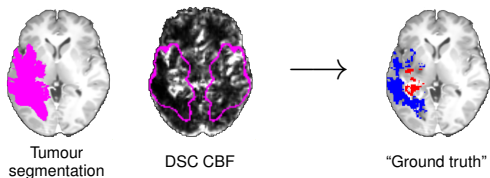
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1. Segmentation of the tumour:



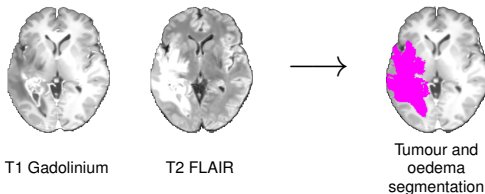
2. Combination with T2 perfusion information:



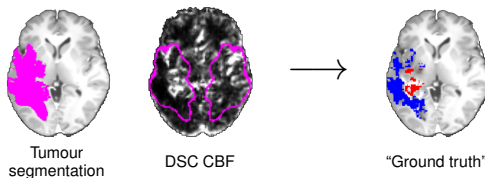
Validation: Ground Truth

Camille Maumet

1. Segmentation of the tumour:



2. Combination with T2 perfusion information:



3. Visual assessment and manual corrections by a clinician.

Outline

Detecting perfusion abnormalities

Arterial Spin Labelling

Group analysis

Single-subject analysis

Random-Effects and Mixed-Effects General Linear Model

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Random-effects and Mixed-effects

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Assumptions of RFX analyses

Detecting
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Camille Maumet

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

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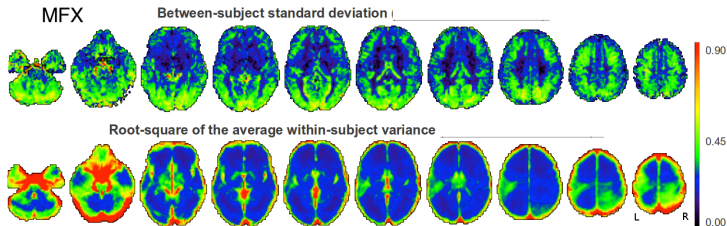
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Assumptions of RFX analyses

Camille Maumet

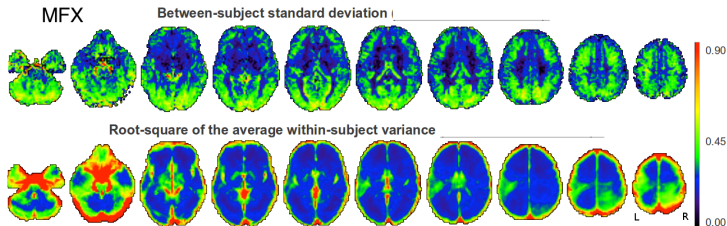
- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



Assumptions of RFX analyses

Camille Maumet

- ▶ 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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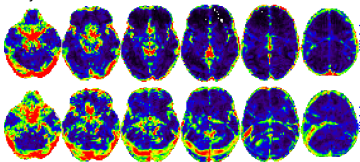
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Within-subject standard deviation in two control subjects:

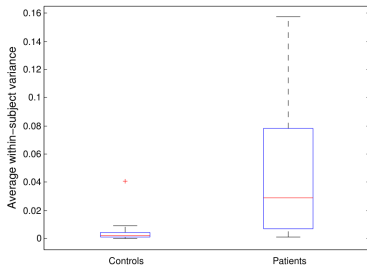
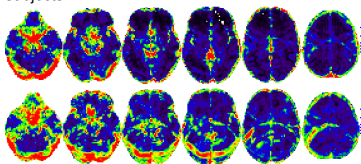


Assumptions of RFX analyses

Camille Maumet

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

Within-subject standard deviation in two control subjects:

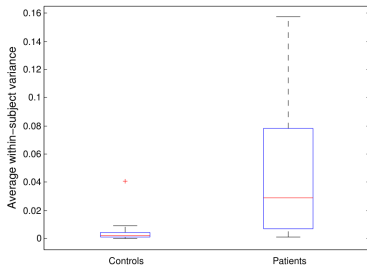
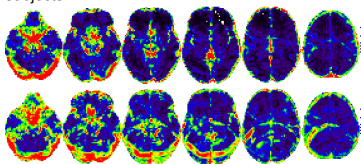


Assumptions of RFX analyses

Camille Maumet

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Within-subject standard deviation in two control subjects:



✗ not verified

Results: RFX versus MFX

Camille Maumet

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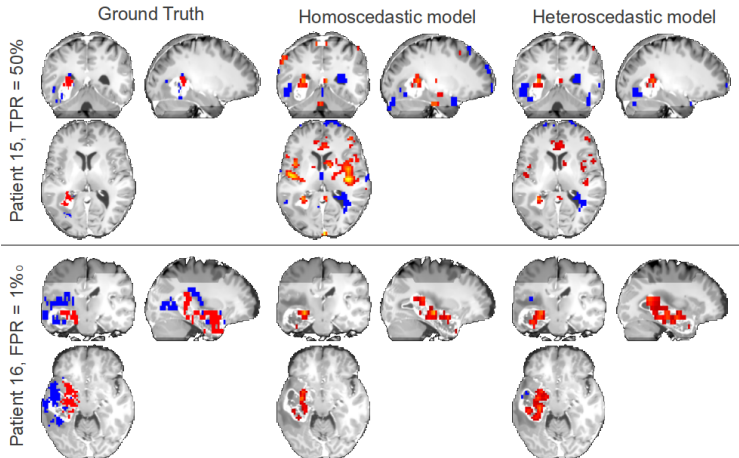
Detections in ASL

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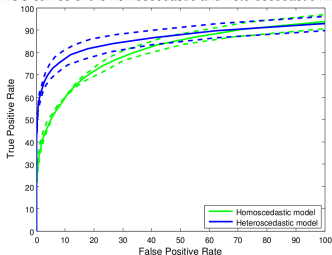
Results

Conclusions



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.

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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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- ▶ According to the literature, the difference between RFX and MFX is less pronounced when comparing 2 groups.

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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.

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Q & A

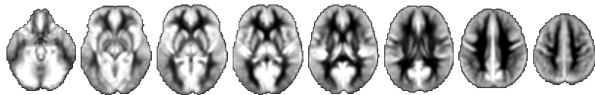
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Appendix

A model of normal perfusion

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

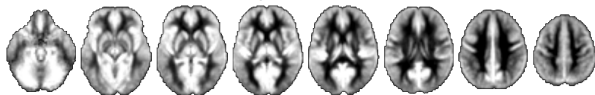
Mean perfusion estimate



A model of normal perfusion

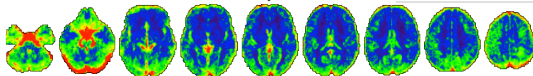
Perfusion estimate $\hat{\beta}_{controls}$

Mean perfusion estimate

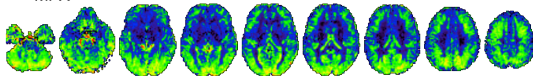


Standard deviation estimates

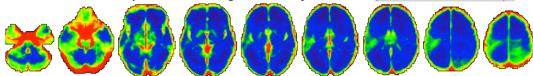
RFX Combined within- and between-subject standard deviation



MFX Between-subject standard deviation



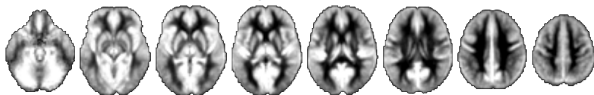
Root-square of the average within-subject variance



A model of normal perfusion

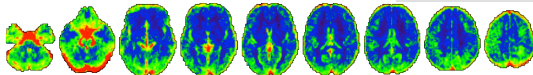
Perfusion estimate $\hat{\beta}_{controls}$

Mean perfusion estimate

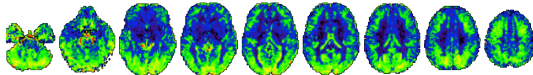


Standard deviation estimates

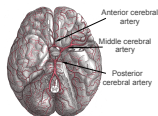
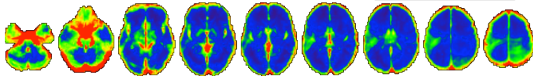
RFX Combined within- and between-subject standard deviation



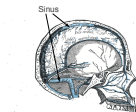
MFX Between-subject standard deviation



Root-square of the average within-subject variance



Brain arteries



Brain veins