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# From Group to Patient-Specific Analysis of Brain Function in Arterial Spin Labelling and BOLD Functional MRI

Camille Maumet

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# From Group to Patient-Specific Analysis of Brain Function in Arterial Spin Labelling and BOLD Functional MRI

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PhD Defense, May 29th, 2013

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CNRS, IRISA, UMR 6074, F-35042 Rennes, France  
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Director: Christian Barillot, Co-director: Pierre Maurel



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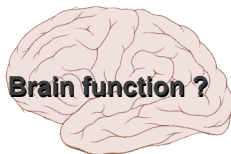
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Two views of brain function:



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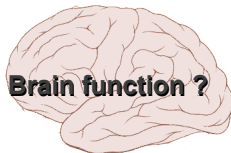
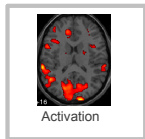
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[Raichle 2010]

# Brain function

Two views of brain function:

Task-evoked activity

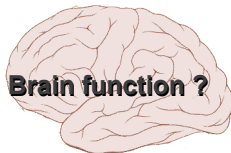
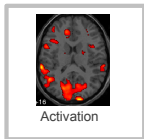


[Raichle 2010]

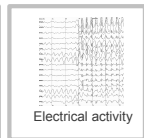
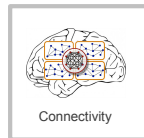
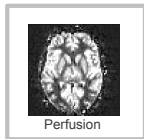
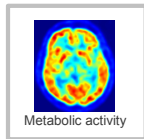
# Brain function

## Two views of brain function:

### Task-evoked activity



### Intrinsic brain function

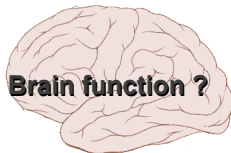


[Raichle 2010]

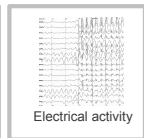
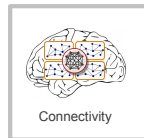
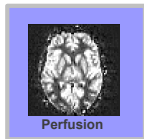
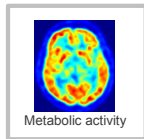
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Two views of brain function:

Task-evoked activity



Intrinsic brain function



[Raichle 2010]

# Brain perfusion

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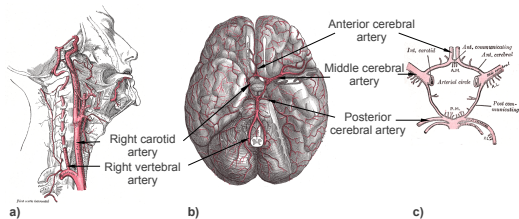
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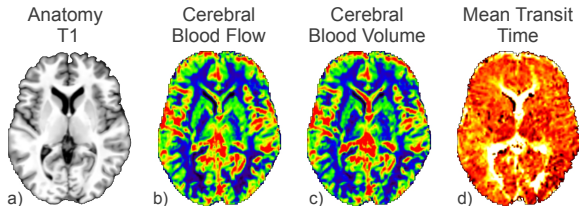
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Blood supply to the brain

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

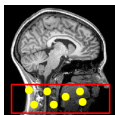


Example of perfusion parameters

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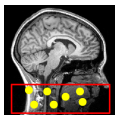
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[Detre et al., MRM 1992]

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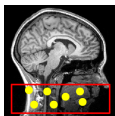
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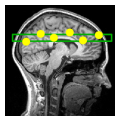
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Readout

[Detre et al., MRM 1992]



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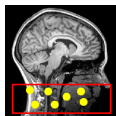
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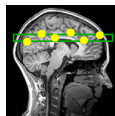
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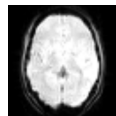
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Label

[Detre et al., MRM 1992]

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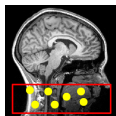
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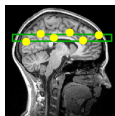
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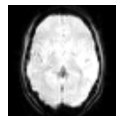
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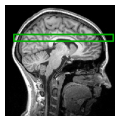
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[Detre et al., MRM 1992]

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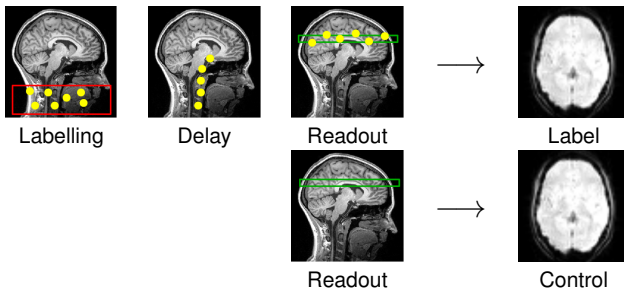
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[Detre et al., MRM 1992]

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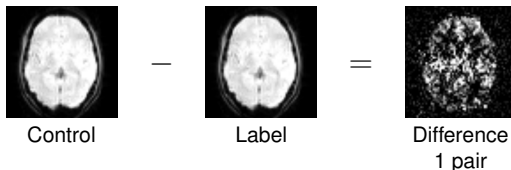
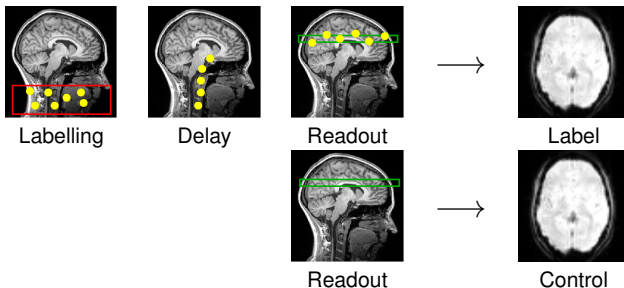
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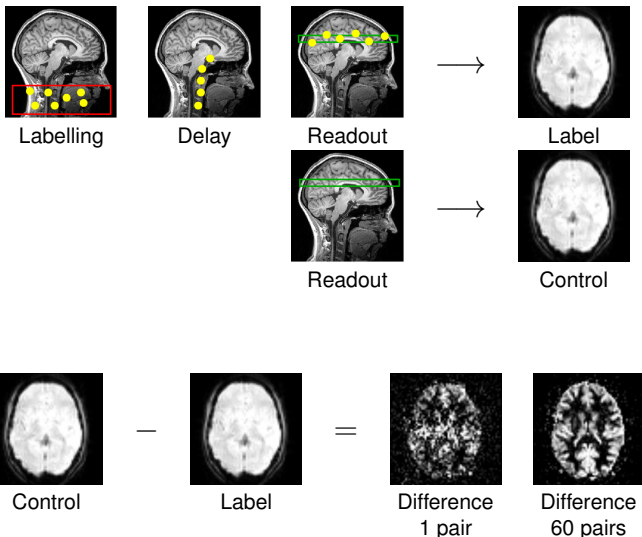
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[Detre et al., MRM 1992]

# Group analyses: definition (1/2)

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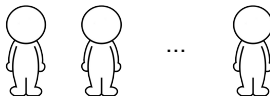
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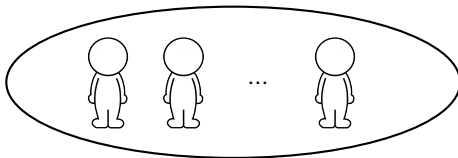
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# Group analyses: definition (1/2)

**Within-group** analyses identify common patterns across a group of subjects.



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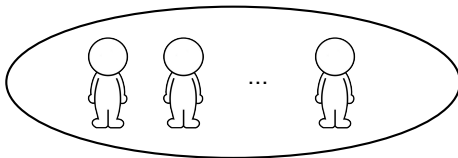
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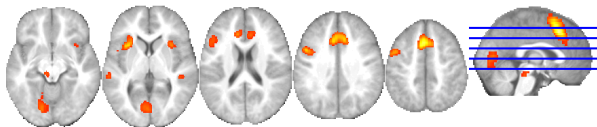
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# Group analyses: definition (1/2)

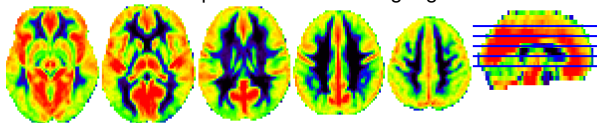
**Within-group** analyses identify common patterns across a group of subjects.



## Examples



Group activation for a language task.



Group cerebral blood flow.



# Group analyses: definition (2/2)

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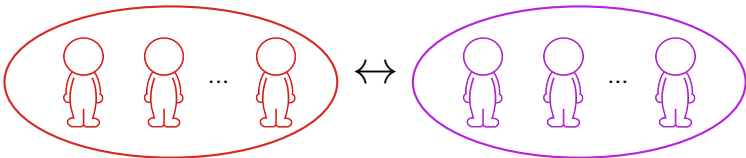
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## Group analyses: definition (2/2)

**Between-group** analyses identify differences at the group level.



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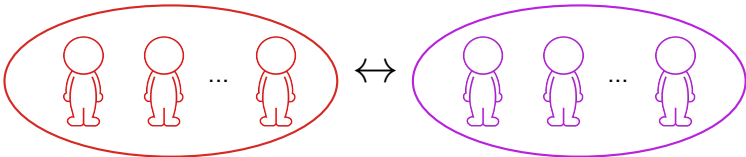
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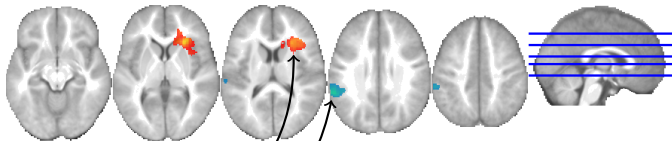
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## Group analyses: definition (2/2)

**Between-group** analyses identify differences at the group level.



### Example



Differences of activation between a group of children diagnosed with specific language impairment and a control group during a language task.

- ▶ Hyperactivation.
- ▶ Hypoactivation.

# Group analyses

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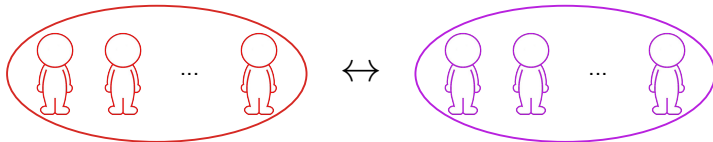
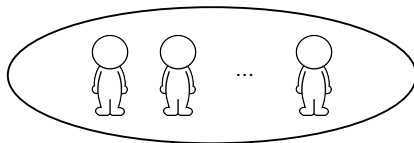
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## Neuroimaging **group analyses**

- ▶ focus on the general patterns of brain function observed in the typical or pathological brain.
- ▶ are the most widespread type of statistical analysis.

# Patient-specific analyses: definition (1/2)

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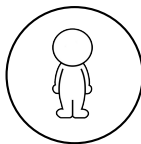
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# Patient-specific analyses: definition (1/2)

**Patient-specific** analyses identify patterns of brain function in a single subject.



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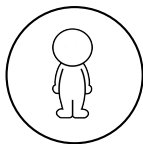
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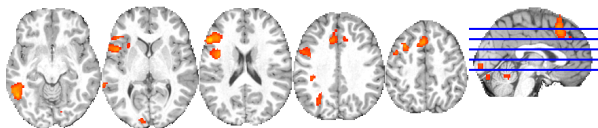
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# Patient-specific analyses: definition (1/2)

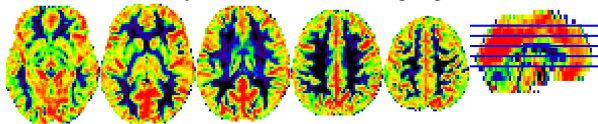
**Patient-specific** analyses identify patterns of brain function in a single subject.



## Examples



Subject activation for a language task.



Cerebral blood flow.

# Patient-specific analyses: definition (2/2)

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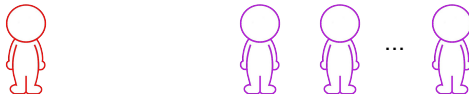
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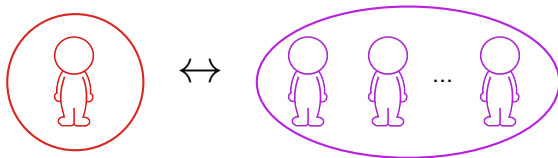


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**Patient-specific** analyses can also identify deviation from normality in a single subject.



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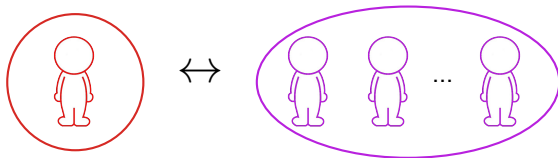
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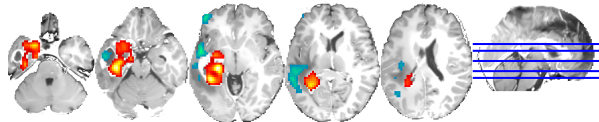
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# Patient-specific analyses: definition (2/2)

**Patient-specific** analyses can also identify deviation from normality in a single subject.



## Examples



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

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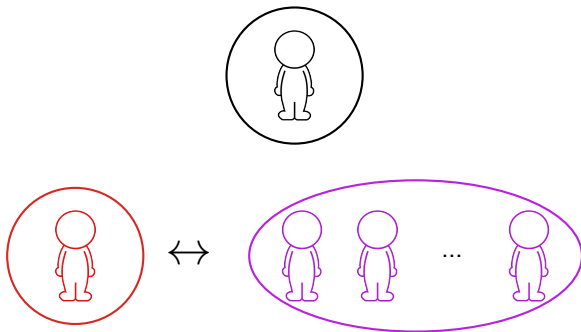
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## Neuroimaging **patient-specific analyses**

- ▶ focus on the specific patterns of brain function observed in a single brain.
- ▶ perform based either on a single subject dataset or on a subject and a group of controls.

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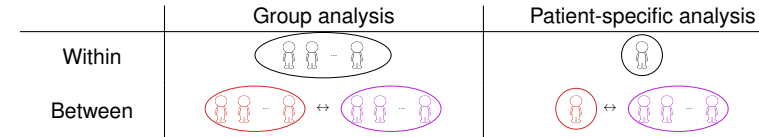
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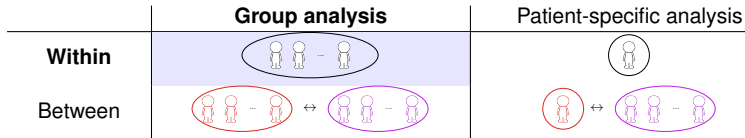
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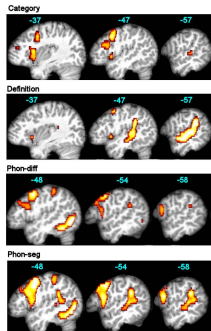
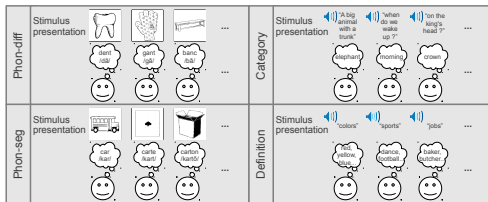
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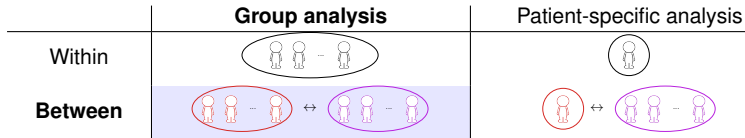
# Contributions: overview



A panel of 4 fMRI tasks for language mapping in children.

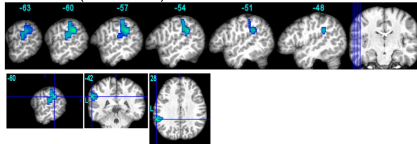


# Contributions: overview

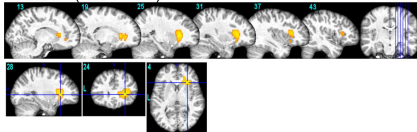


Atypical activity and lateralisation of brain function in children diagnosed with typical specific language impairment.

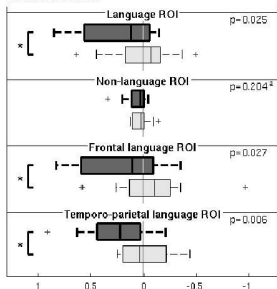
Definition task (Control > T-SLI)



PhonDiff task (T-SLI > Control)



Combined Tasks



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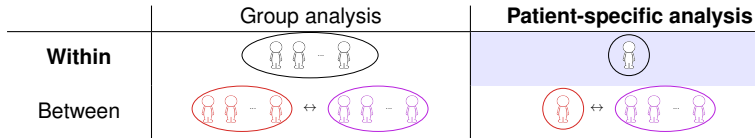
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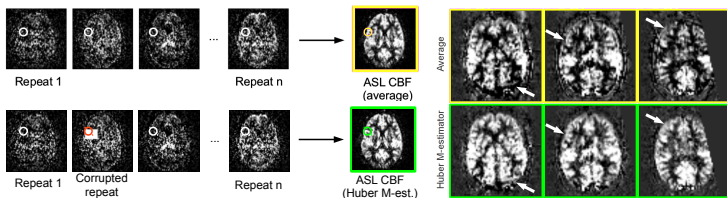
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# Contributions: overview



## Robust Estimation of the Cerebral Blood Flow in Arterial Spin Labelling.



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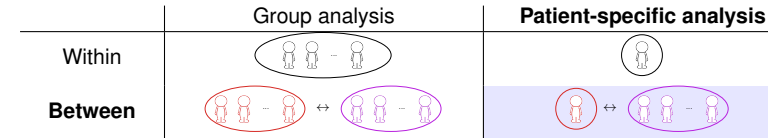
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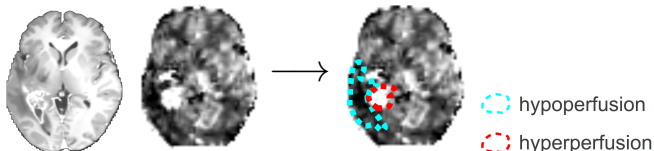
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# Contributions: overview



Objective: Quantitative identification of voxelwise patient-specific perfusion abnormalities.



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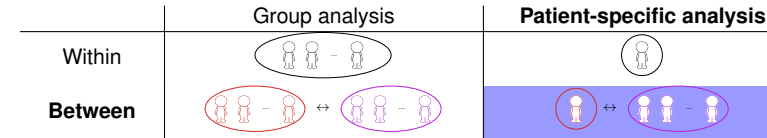
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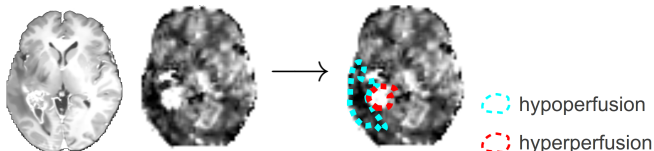
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Objective: Quantitative identification of voxelwise patient-specific perfusion abnormalities.



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

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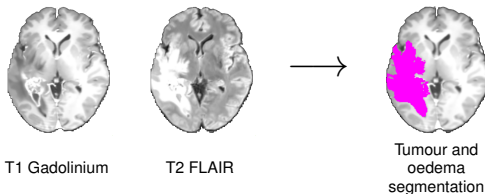
- ▶ PICORE Q2TIPS Pulsed ASL, 60 repetitions
- ▶ MPRAGE T1 3D
- ▶ T2 FLAIR

For the patients only:

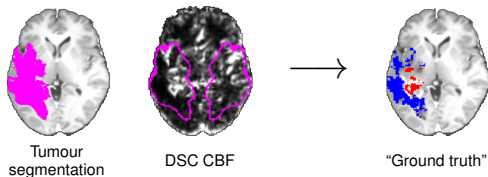
- ▶ T1 3D Gadolinium
- ▶ Dynamic Susceptibility Contrast imaging (DSC)

# Validation: Ground Truth

## 1. Segmentation of the tumour:



## 2. Combination with T2 perfusion information:



## 3. Visual assessment and manual corrections by a clinician.

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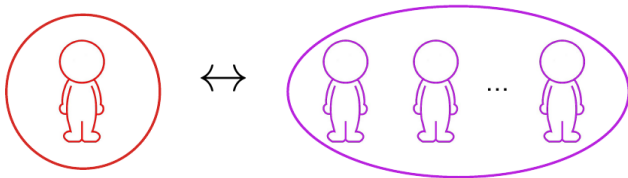
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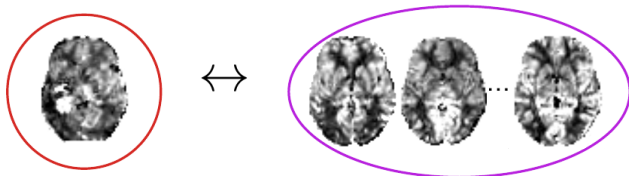
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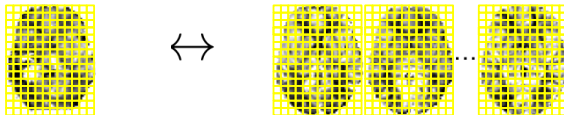
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## Massively univariate approaches:



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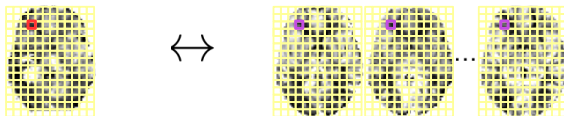
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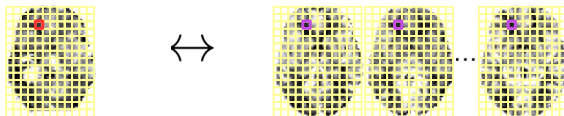
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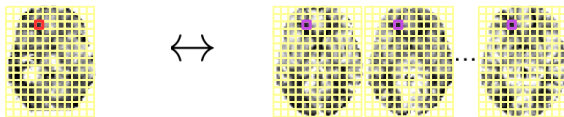
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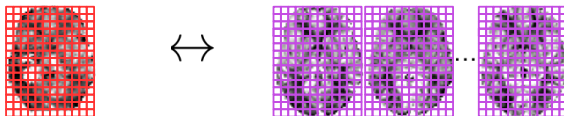
## Massively univariate approaches:



- ✓ The standard approach, e.g. [Holmes 1998, Beckmann 2003].
- ✓ Computationally efficient.
- ✗ No integration of information cross-voxels (pre-smoothing).

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## Multivariate approaches:



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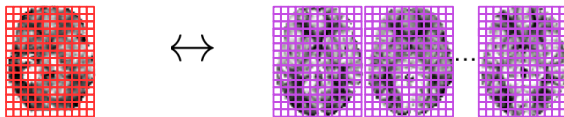
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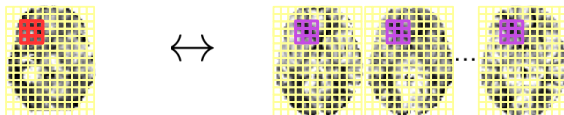
## Multivariate approaches:



- ✓ Combination of voxel information (no smoothing).
- ✗ Require specific methods: machine learning, e.g. [Mourão Miranda 2011].
- ✗ Can be time consuming and computationally intensive.

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## Locally multivariate approaches:



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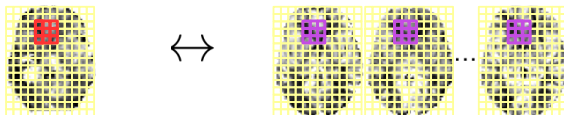
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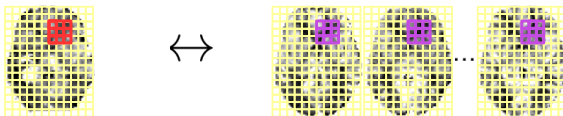
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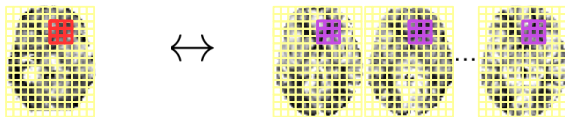
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## Locally multivariate approaches:



- ✓ Combination of local voxel information (no smoothing), e.g. [Kriegeskorte 2006].
- ✓ Standard statistics or machine learning.
- ✓ Less time consuming than full brain.
- ✗ Can still be time consuming (machine learning).
- ✗ Only local information is combined.

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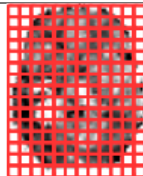
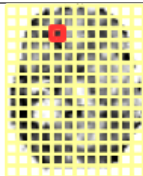
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Massively univariate    Locally multivariate    Multivariate



Comput. efficiency

++

+ / -

-

Cross-voxels info.

-

+

++

# Univariate / Multivariate - overview

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	Massively univariate	Locally multivariate	Multivariate
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

1. The massively univariate GLM: **homoscedastic and heteroscedastic models.**

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	Massively univariate	Locally multivariate	Multivariate
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

1. The massively univariate GLM: **homoscedastic and heteroscedastic models.**
2. The ***a contrario*** approach as a new locally multivariate procedure.

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	Massively univariate	Locally multivariate	Multivariate
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

1. The massively univariate GLM: **homoscedastic and heteroscedastic models.**
2. The *a contrario* approach as a new locally multivariate procedure.

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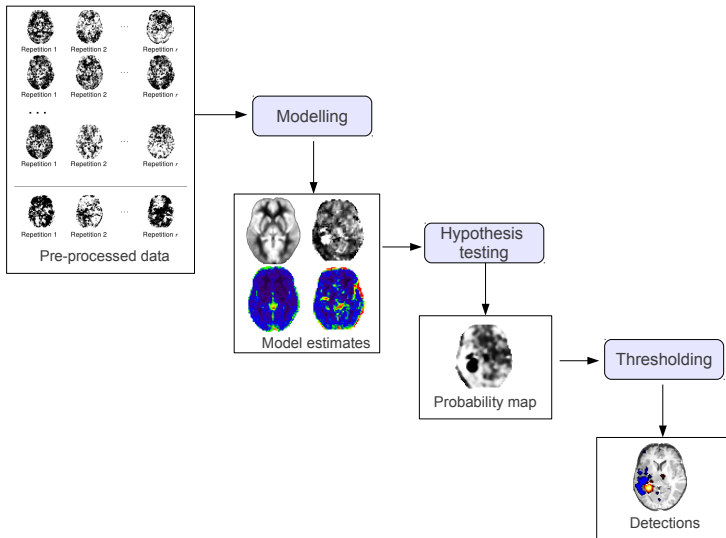
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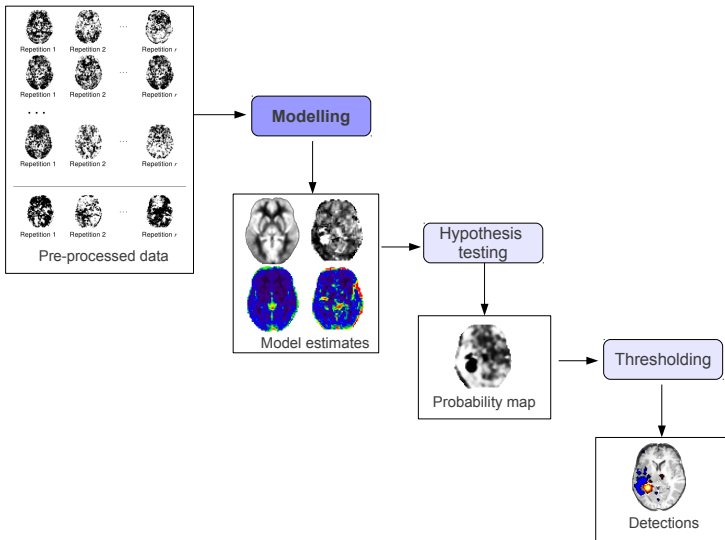
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# Modelling: subject level

## General Linear Model: subject level



Repetition 1



Repetition 2

...



Repetition  $r$

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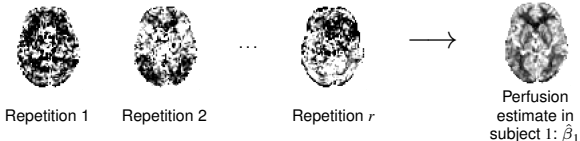
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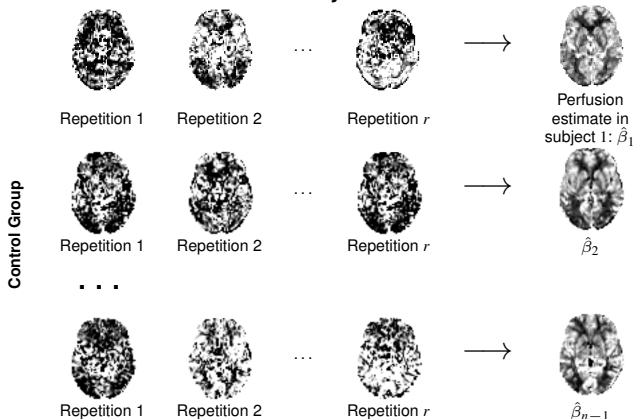
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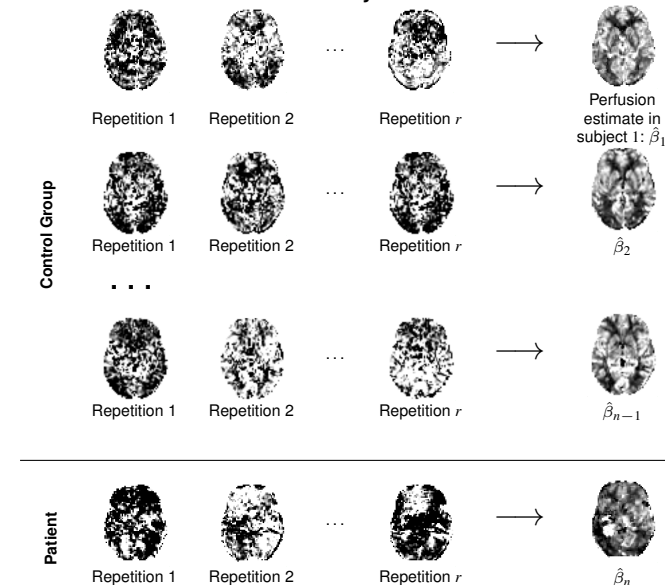
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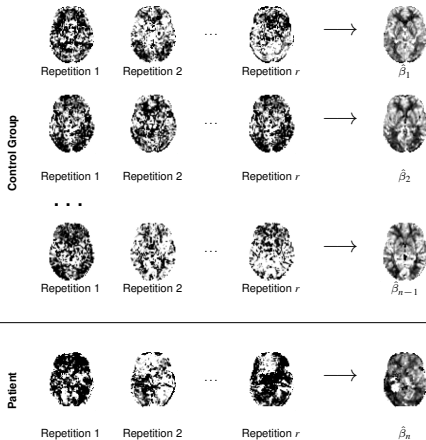
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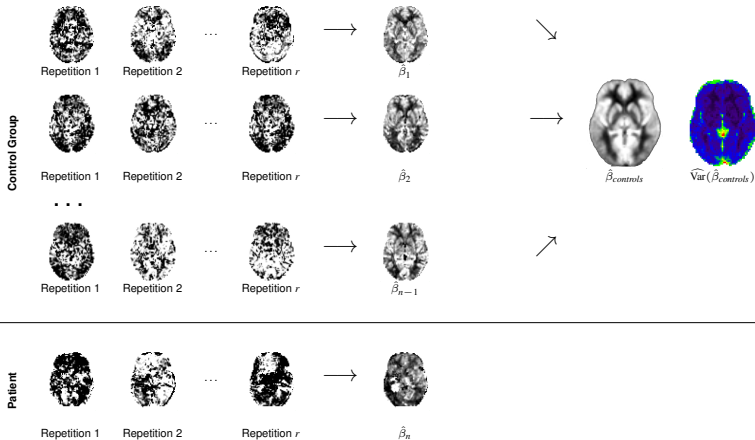
## General Linear Model: group level.



Two sources of variation: the **between-subject** variance and the **within-subject** variance.

# Modelling: group level

## General Linear Model: group level.



Two sources of variation: the **between-subject** variance and the **within-subject** variance.

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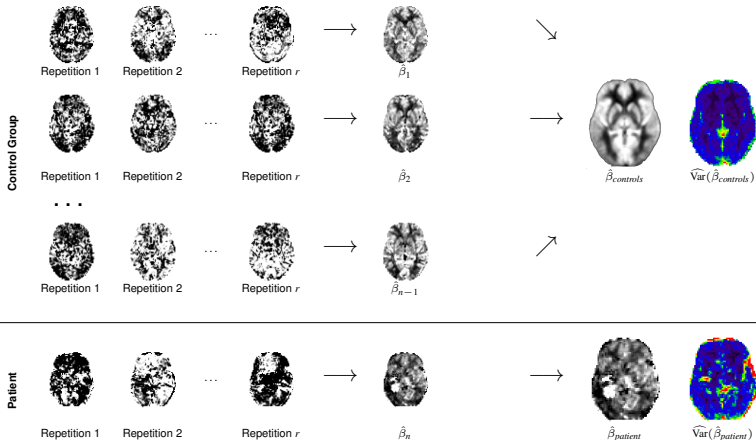
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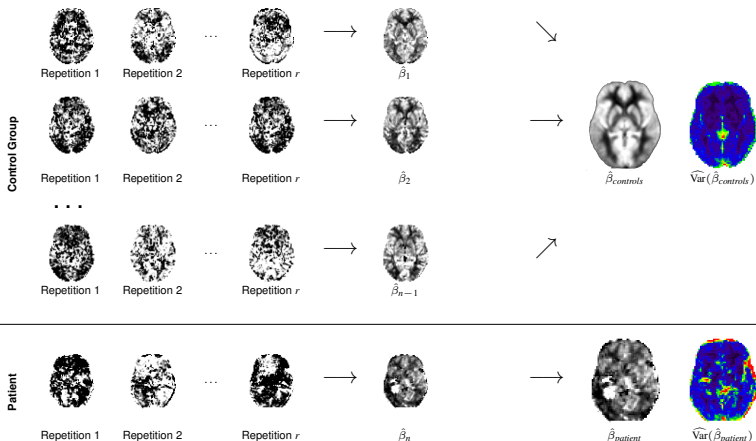
## General Linear Model: group level.



Two sources of variation: the **between-subject** variance and the **within-subject** variance.

# Modelling: group level

General Linear Model: group level. The **homoscedastic model**:



Two sources of variation: the **between-subject** variance and the **within-subject** variance.

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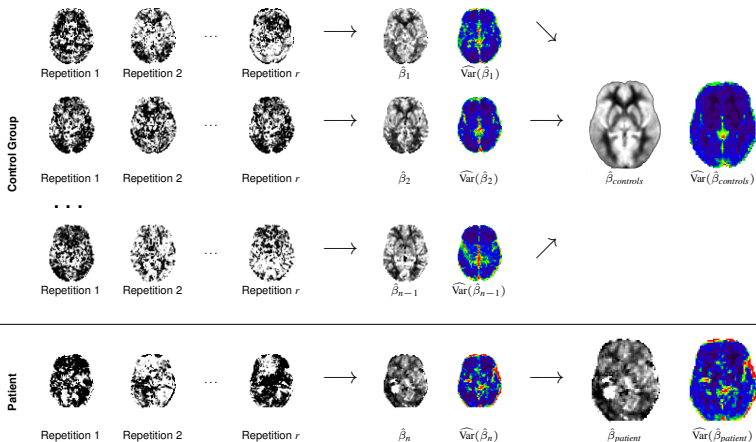
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# Modelling: group level

General Linear Model: group level. The **heteroscedastic model**:



Two sources of variation: the **between-subject** variance and the **within-subject** variance.



# Homoscedastic and heteroscedastic GLM

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The **homoscedastic model assumes** that the **within-subject variance** is:

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

# Homoscedastic and heteroscedastic GLM

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In functional MRI there is no consensus:

- ▶ Superiority of the heteroscedastic model, [Beckmann 2003, Mumford 2006, Thirion 2007].
- ▶ Validity of the homoscedastic model for one-sample t-tests in BOLD fMRI, [Mumford 2009].
- ▶ Invalidity of the homoscedastic model [Chen 2012].

Both approaches are in use in the neuroimaging community:

- ▶ The homoscedastic approach (SPM<sup>1</sup>)
- ▶ The heteroscedastic approach (FSL<sup>2</sup>, AFNI<sup>3</sup>).

---

<sup>1</sup>[www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)

<sup>2</sup>[fsl.fmrib.ox.ac.uk/fsl/fslwiki/](http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)

<sup>3</sup>[afni.nimh.nih.gov/afni/](http://afni.nimh.nih.gov/afni/)

# Standard statistics: overview

From Group to  
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Camille Maumet

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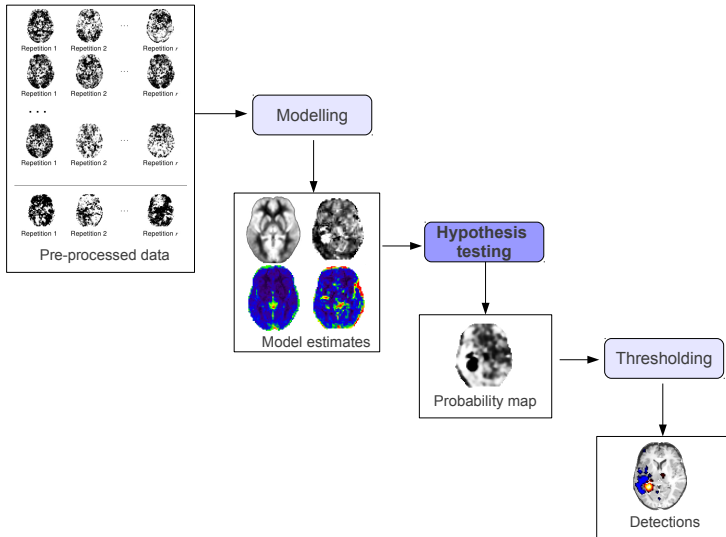
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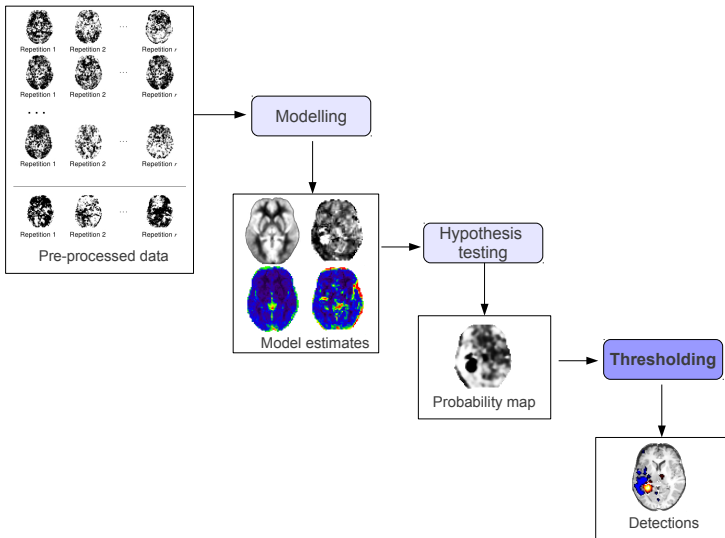
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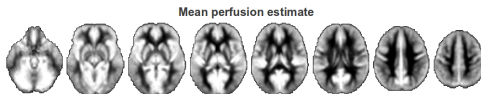
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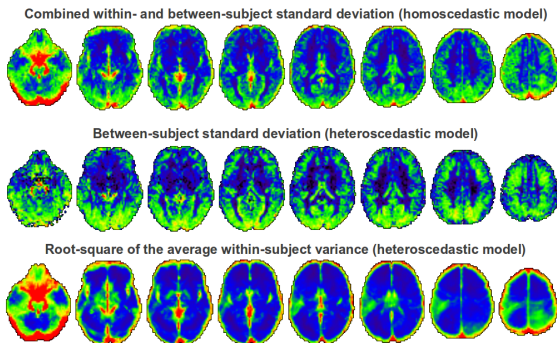


# Results: Perfusion in the control group

## Mean estimate



## Standard deviation estimates



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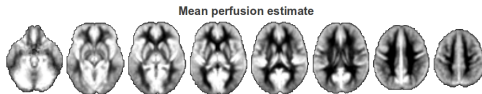
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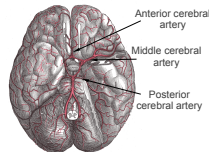
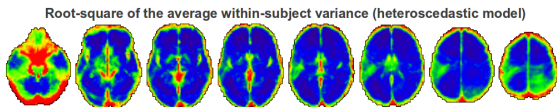
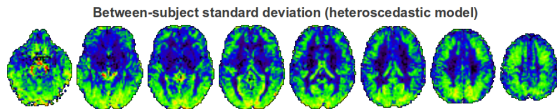
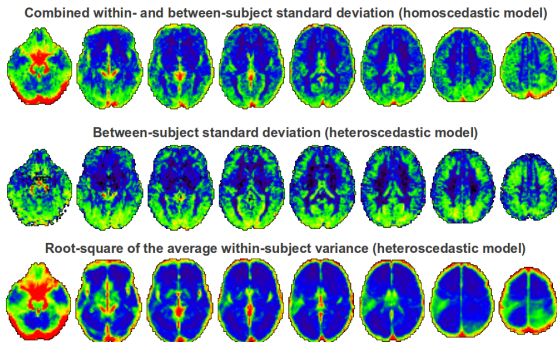
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# Results: Perfusion in the control group

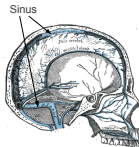
## Mean estimate



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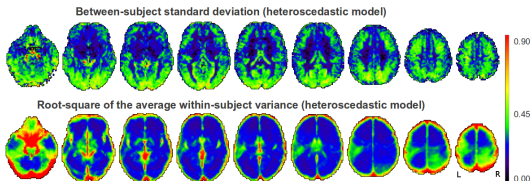
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# Assumptions of the homoscedastic model

- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.
  
- ▶ Assumption 2: Within-subject variance roughly constant across subjects.

# Assumptions of the homoscedastic model

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

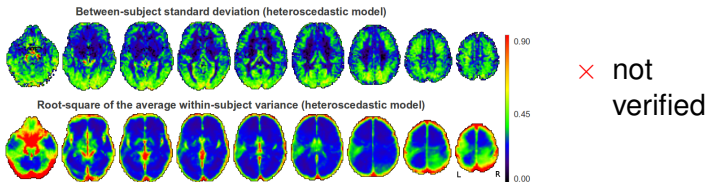


- ▶ Assumption 2: Within-subject variance roughly constant across subjects.



# Assumptions of the homoscedastic model

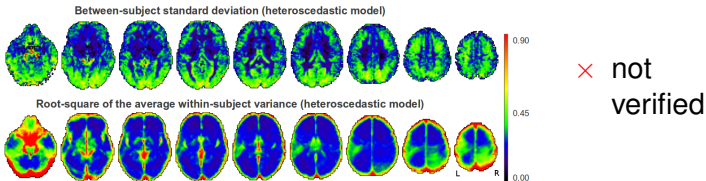
- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



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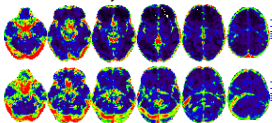
# Assumptions of the homoscedastic model

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



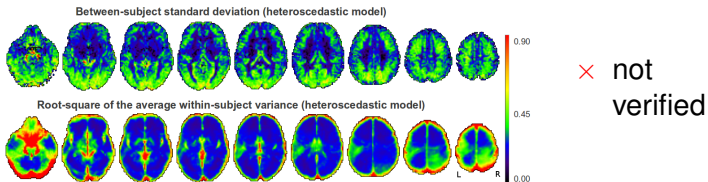
- ▶ Assumption 2: Within-subject variance roughly constant across subjects.

Within-subject standard deviation in two control subjects:

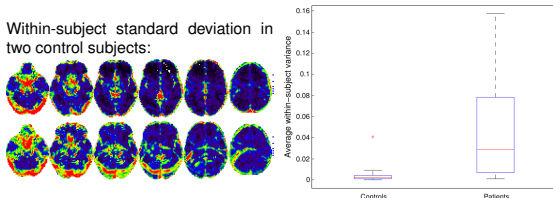


# Assumptions of the homoscedastic model

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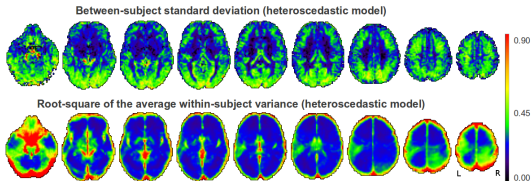
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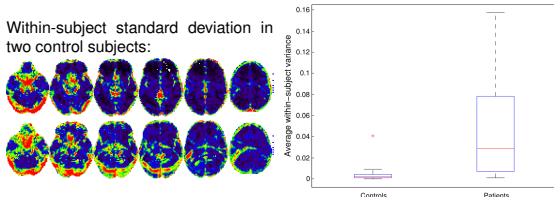
Using a metric from [Mumford 2009].

# Assumptions of the homoscedastic model

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



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Using a metric from [Mumford 2009].

# Results: homoscedastic versus heteroscedastic GLM

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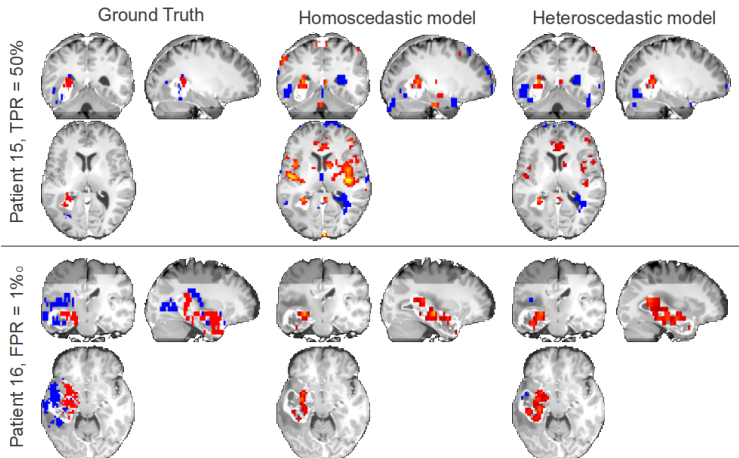
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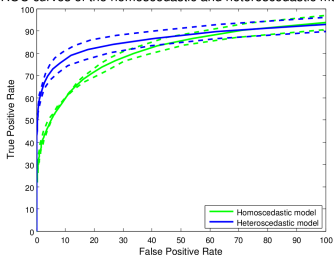
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ROC curves of the homoscedastic and heteroscedastic models



ROC curves for perfusion abnormality detections.

	Homoscedastic model					
FWHM (mm <sup>3</sup> )	0	4	6	8	10	12
ROC Area	0.46	<b>0.49</b>	<b>0.49</b>	<b>0.49</b>	0.48	0.48

	Heteroscedastic model					
FWHM (mm <sup>3</sup> )	0	4	6	8	10	12
ROC Area	0.63	0.70	<b>0.72</b>	<b>0.72</b>	0.69	0.65

Area under the ROC curve.

# Conclusion: homoscedastic versus heteroscedastic GLM

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- ▶ The assumption of homoscedasticity is violated in ASL studies.
- ▶ **Modelling heteroscedasticity is essential** in the detection of patient-specific perfusion abnormalities with ASL.

Related publication: [[Maumet et al., NeuroImage 2013](#)].

# Univariate / Multivariate - overview

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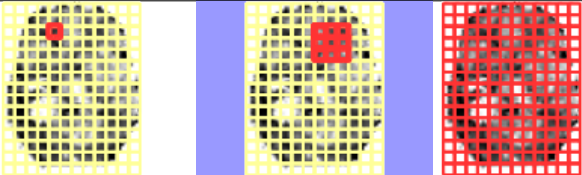
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	Massively univariate	Locally multivariate	Multivariate
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++



1. The massively univariate GLM: **homoscedastic and heteroscedastic models.**
2. The ***a contrario*** approach as a new locally multivariate procedure.



# A *contrario* approach

From the computer vision community [Desolneux 2003].

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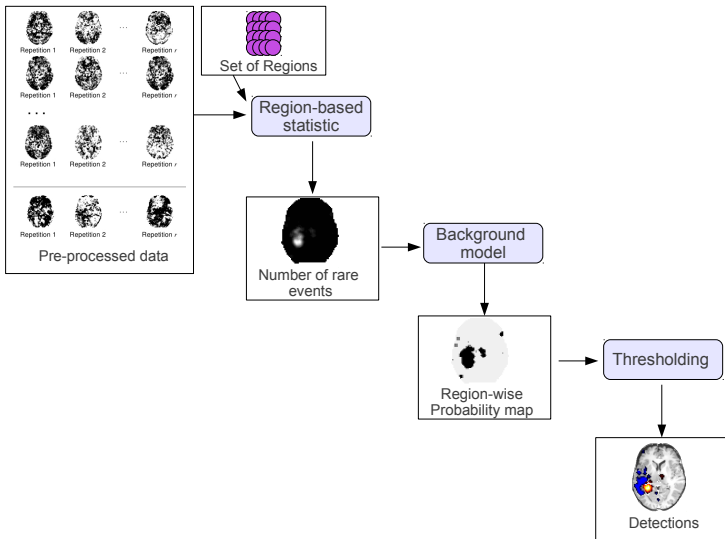
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From the computer vision community [Desolneux 2003].

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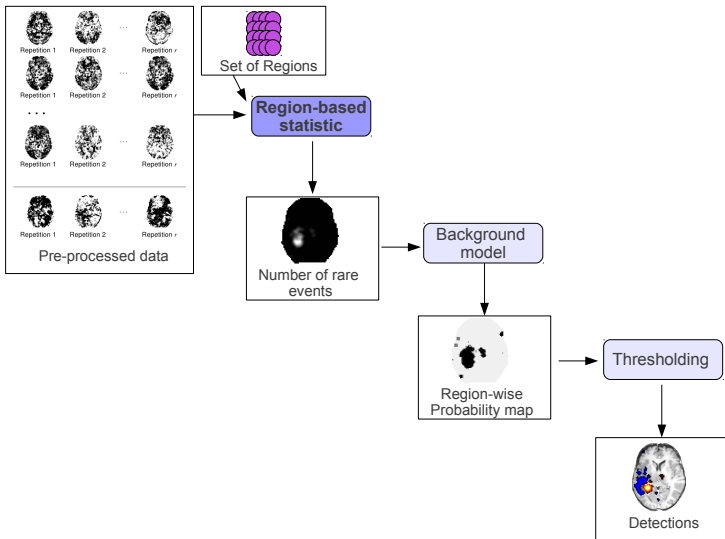
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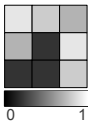
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Rare event count per sphere as region-based statistic:



1. Voxel-based  
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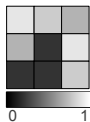
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Rare event count per sphere as region-based statistic:



1. Voxel-based  
probability



2. Thresholding

$$k_{(v)} = \begin{cases} 1, & \text{if } \pi_v^{GLM} \leq p_{PRE}, \\ 0, & \text{otherwise.} \end{cases}$$

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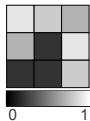
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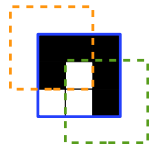
Rare event count per sphere as region-based statistic:



1. Voxel-based probability



2. Thresholding



3. Rare event count per region

1	1	1
3	3	2
3	3	2

$$k_{(v)} = \begin{cases} 1, & \text{if } \pi_v^{GLM} \leq p_{PRE}, \\ 0, & \text{otherwise.} \end{cases} \quad l_{(r)} = \sum_{v \in R} k_{(v)}$$

# A *contrario* approach

From the computer vision community [Desloneux 2003].

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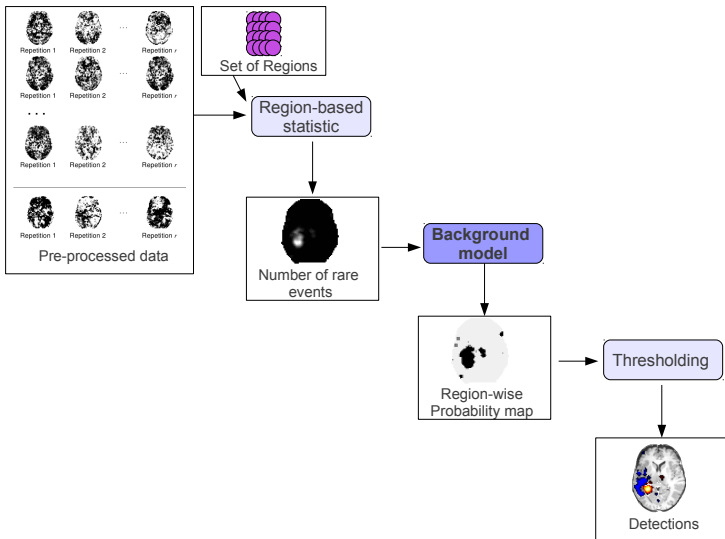
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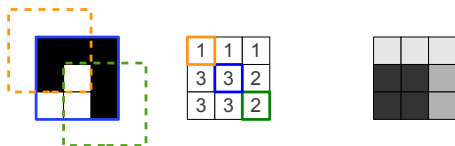
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# A *contrario* approach

From region-based statistic to region-based probability:



3. Rare event count per region

4. Region-based probability

$$L_{(r)} = \sum_{v \in R} K_{(v)} \quad \text{with} \quad K_{(v)} \sim \text{Bern}(p_{PRE})$$

The original *a contrario* approach assumes **white noise**, i.e. the events are **independent**:

$$\pi_{(r)} = \Pr(L_{(r)} \geq l_{(r)}), \quad \text{where} \quad L_{(r)} \sim \text{B}(e, p_{PRE}),$$

where  $e$  is the number of voxel per region.

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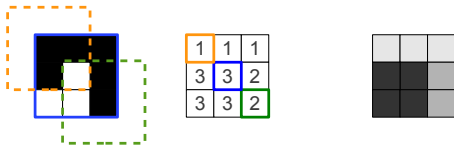
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# A contrario approach

From region-based statistic to region-based probability:



3. Rare event count per region

4. Region-based  
probability

$$L(r) = \sum_{v \in R} K(v) \quad \text{with} \quad K(v) \sim \text{Bern}(p_{PRE})$$

**In MRI**, spatial **autocorrelation of the noise** has been described (e.g. [Chumbley 2009]) and the independence assumption is therefore questioned.

We proposed a **non-independent probability** based on the joint distribution of a multivariate Gaussian distribution.



# A *contrario* approach

From the computer vision community [Desloneux 2003].

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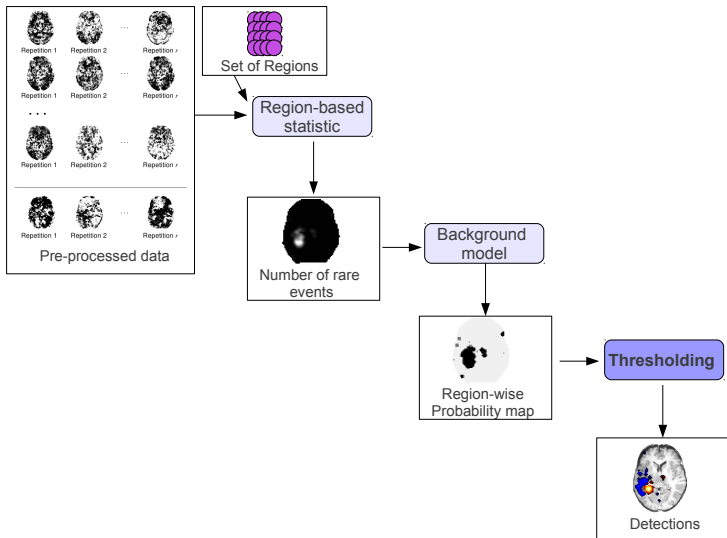
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# A *contrario* approach: thresholding

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The correction for multiple testing is usually done by computing the Number of False Alarms:

$$NFA_{(r)} = numReg \pi_{(r)},$$

and the detections are outlined with:

$$NFA_{(r)} < \epsilon.$$

where  $\epsilon$ , is the average number of false detections that are tolerated.

The NFA is related to Bonferroni correction [[Rousseau 2007](#)].

# Results: *a contrario*

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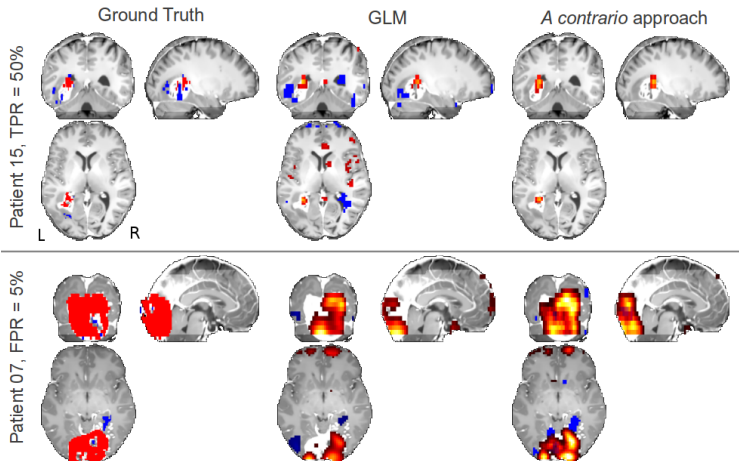
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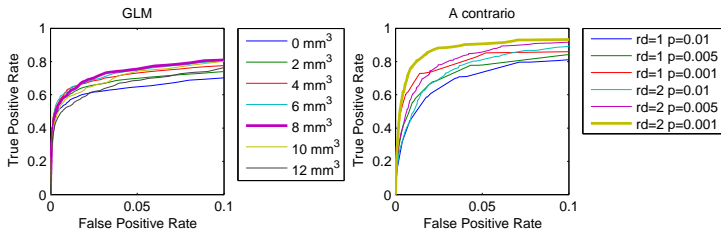
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Average ROC curves

## GLM

$w$	0	2	4	6	8	10	12
ROC area	0.63	0.67	0.70	0.72	<b>0.73</b>	0.70	0.65

## *a contrario*

	$rd = 1$			$rd = 2$		
$p_{PRE}$	0.01	0.005	0.001	0.01	0.005	0.001
ROC area	0.68	0.73	0.79	0.75	0.80	<b>0.87</b>

Area under the ROC curves

# Results: *a contrario*

## Checking the test validity

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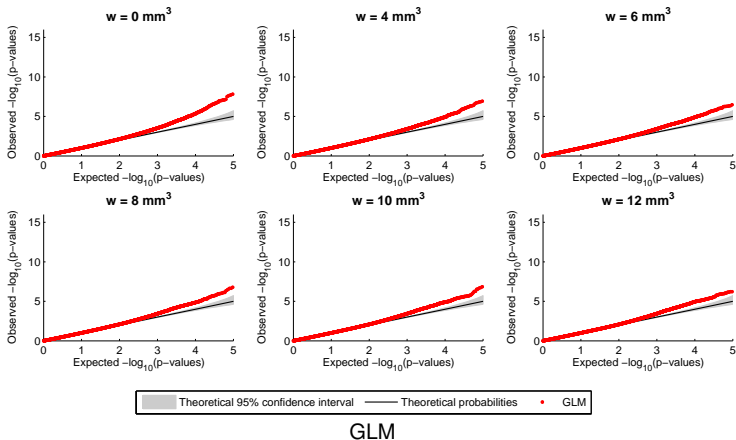
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- ▶ Invalidity of the GLM.
- ▶ This invalidity was also observed in voxel-based morphometry [Scarpazza 2013, Viviani 2007].

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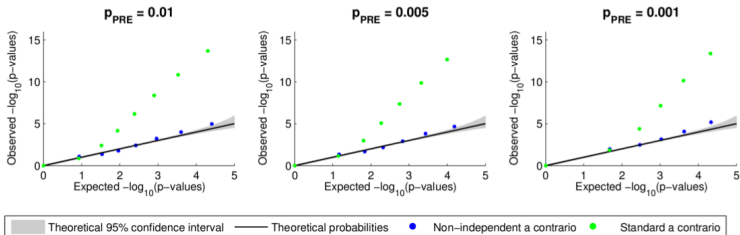
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- ▶ The *a contrario* approach outperforms the standard General Linear Model.
- ▶ Non-independent probabilities provide more valid statistics in the context of MRI data analysis.

Related publications: [[Maumet et al., ISBI 2012](#)], [[Maumet et al., MICCAI 2012](#)], a journal paper submitted to NeuroImage.

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## Patient-specific analysis in BOLD fMRI and ASL:

- ▶ Comparison of the homoscedastic and heteroscedastic GLM
  - ▶ **Heteroscedasticity of Arterial Spin Labelling** data.
  - ▶ **Modelling heteroscedasticity is essential** in the detection of patient-specific perfusion abnormalities with ASL.

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## Patient-specific analysis in BOLD fMRI and ASL:

- ▶ Comparison of the homoscedastic and heteroscedastic GLM
  - ▶ **Heteroscedasticity of Arterial Spin Labelling** data.
  - ▶ **Modelling heteroscedasticity is essential** in the detection of patient-specific perfusion abnormalities with ASL.
- ▶ The *a contrario* locally multivariate procedure
  - ▶ **Superiority** onto the massively univariate **GLM**.
  - ▶ **Two applications**: the detection of patient-specific perfusion abnormalities and the detection of activation patterns in task-evoked analyses.

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## Conclusions and future work

## Contributions

Discussion

## Patient-specific analysis in BOLD fMRI and ASL:

- ▶ Comparison of the homoscedastic and heteroscedastic GLM
  - ▶ **Heteroscedasticity of Arterial Spin Labelling** data.
  - ▶ **Modelling heteroscedasticity is essential** in the detection of patient-specific perfusion abnormalities with ASL.
- ▶ The *a contrario* locally multivariate procedure
  - ▶ **Superiority** onto the massively univariate **GLM**.
  - ▶ **Two applications**: the detection of patient-specific perfusion abnormalities and the detection of activation patterns in task-evoked analyses.
- ▶ Robust computation (using M-estimators) of cerebral blood flow maps from a series of Arterial Spin Labelling acquisitions.

# Contributions (2/2)

From Group to  
Patient-Specific  
Analysis of Brain  
Function

Camille Maumet

## Context

Brain function

From group to  
patient-specific  
analyses

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## Group analyses in BOLD functional MRI.

- ▶ An original panel of four tasks for language mapping in children.
- ▶ **Atypical patterns of activity and lateralisation** in children diagnosed with **specific language impairment**.

# Software

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autoMRI: SPM-based automation tools for anatomical and functional MRI data, Matlab scripts

- ▶ Used in other clinical projects.
- ▶ Registered at the APP.
- ▶ Open source (GPL), available on request.

**autoMRI**

# Discussion and future work (1/2)

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Atypical brain function in specific language impairment:

- ▶ Extend the preliminary results of the *a contrario* approach in fMRI to this context.
- ▶ Take advantage of ASL sequences.

Robust statistics to compute cerebral blood flow maps:

- ▶ Compare current results with other M-estimators and complementary robust approaches.

# Discussion and future work (2/2)

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## Arterial Spin Labelling

- ▶ More advanced ASL sequences, such as pseudo-continuous ASL with 3D readouts, provide a better signal-to-noise ratio.
- ▶ How does the conclusion on heteroscedasticity extend to these datasets ?

## The *a contrario* approach

- ▶ Provide a more thorough validation in BOLD fMRI.
- ▶ Extend the approach to group analyses.

# Questions

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# Q & A