



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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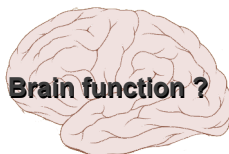
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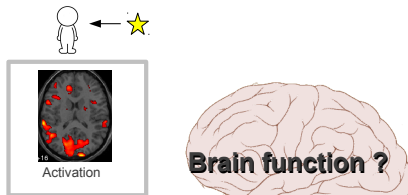
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[Raichle 2010]

Brain function

Two views of brain function:

Task-evoked activity



[Raichle 2010]

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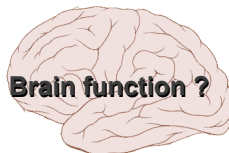
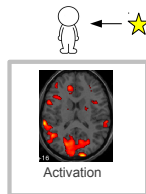
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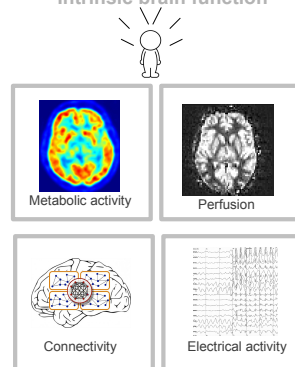
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Intrinsic brain function



[Raichle 2010]

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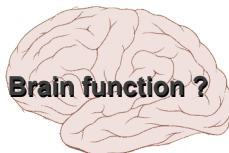
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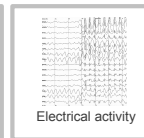
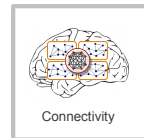
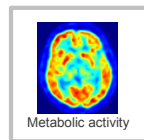
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Intrinsic brain function



[Raichle 2010]

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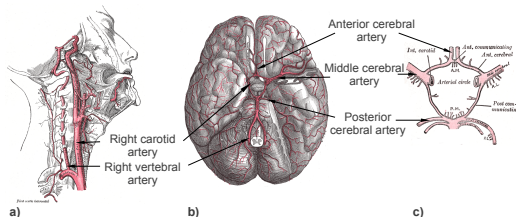
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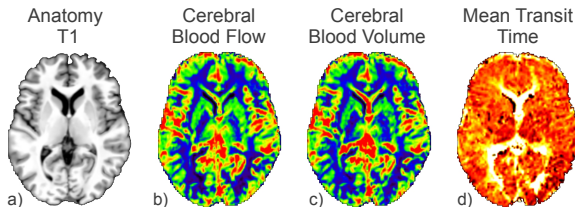
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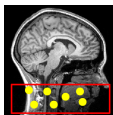
Blood supply to the brain

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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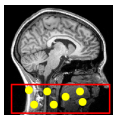
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[Detre et al., MRM 1992]

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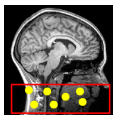
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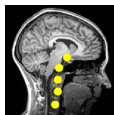
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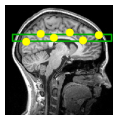
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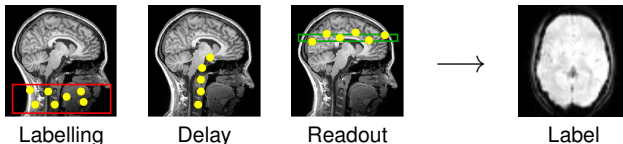
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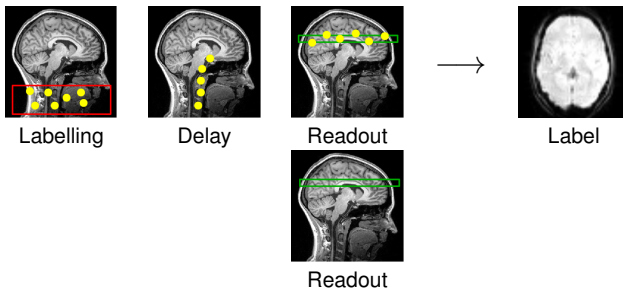
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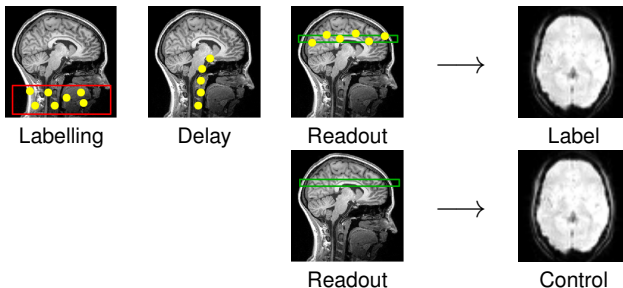
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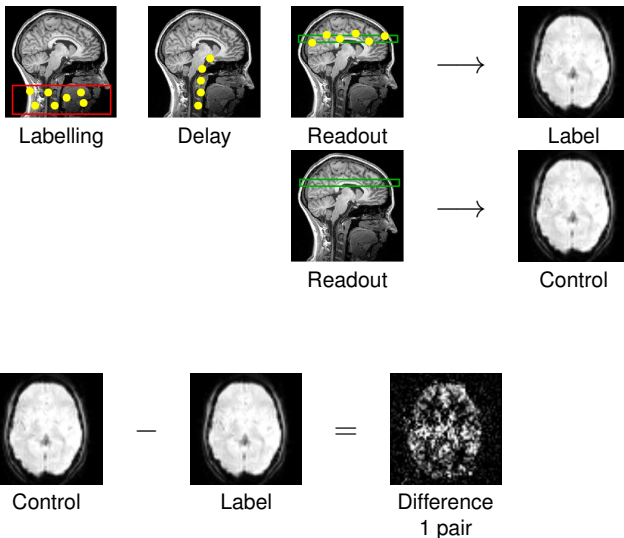
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[Detre et al., MRM 1992]

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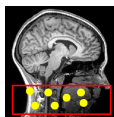
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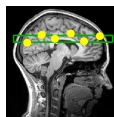
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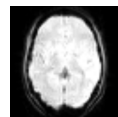
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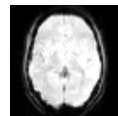
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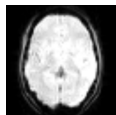
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Label

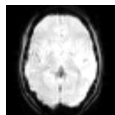


Control



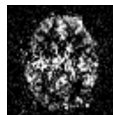
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—



Label

=



Difference
1 pair



Difference
60 pairs

[Detre et al., MRM 1992]

Group analyses: definition (1/2)

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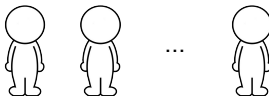
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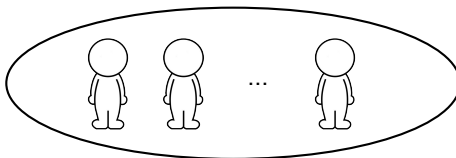
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Group analyses: definition (1/2)

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



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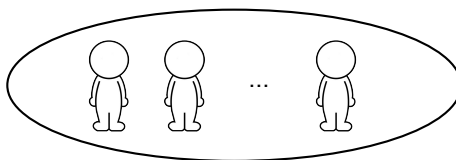
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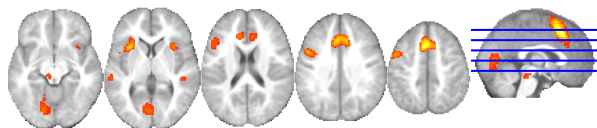
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Group analyses: definition (1/2)

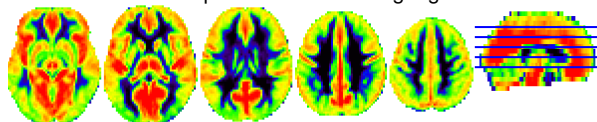
Within-group analyses identify common patterns across a group of subjects.



Examples

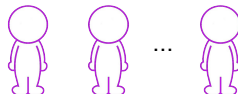


Group activation for a language task.



Group cerebral blood flow.

Group analyses: definition (2/2)



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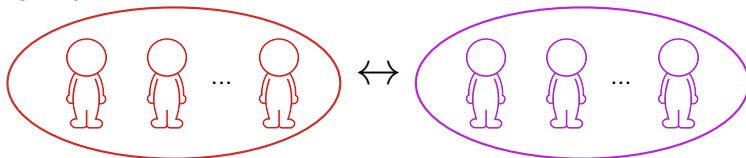
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Group analyses: definition (2/2)

Between-group analyses identify differences at the group level.



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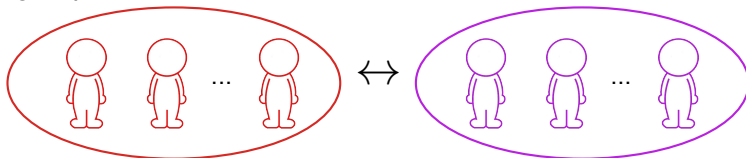
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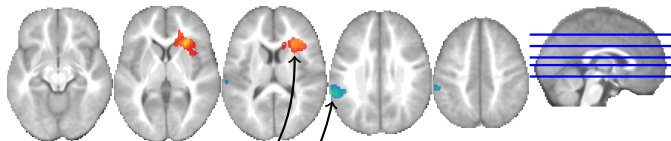
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Between-group analyses identify differences at the group level.



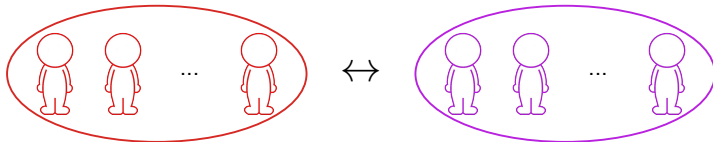
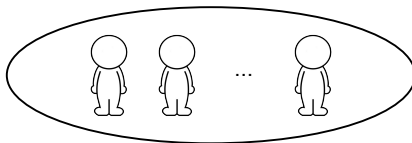
Example



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



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.

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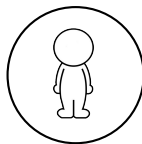
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Patient-specific analyses: definition (1/2)

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



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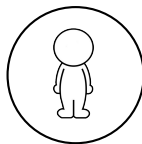
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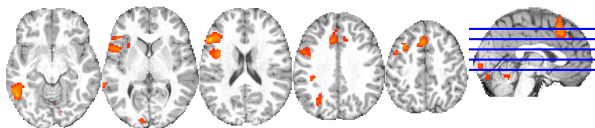
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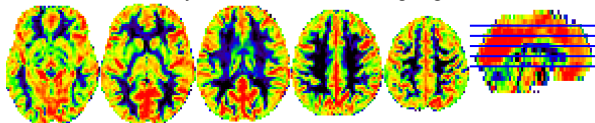
Patient-specific analyses identify patterns of brain function in a single subject.



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Subject activation for a language task.



Cerebral blood flow.

Patient-specific analyses: definition (2/2)

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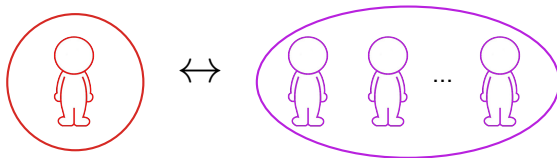
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Patient-specific analyses: definition (2/2)

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



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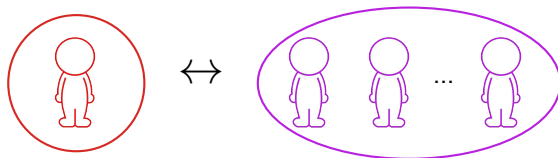
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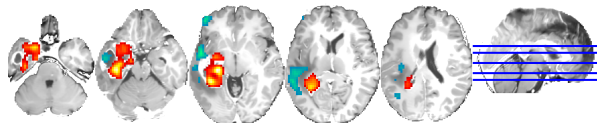
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Patient-specific analyses: definition (2/2)

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

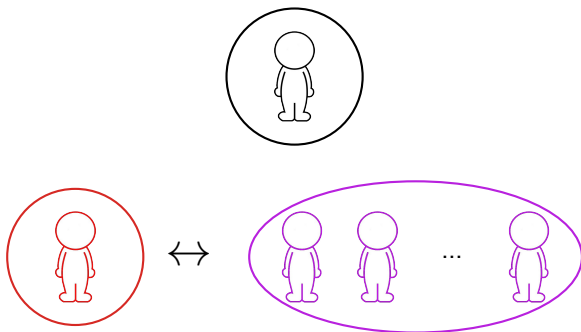


Examples



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

Patient-specific analyses



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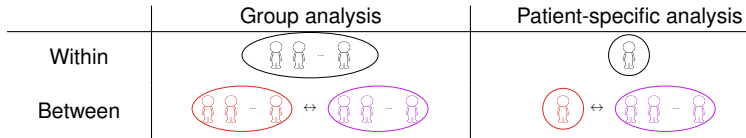
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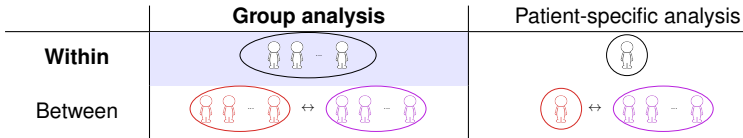
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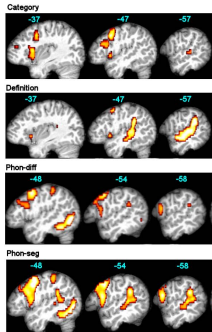
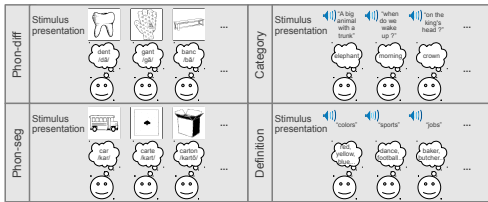
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A panel of 4 fMRI tasks for language mapping in children.



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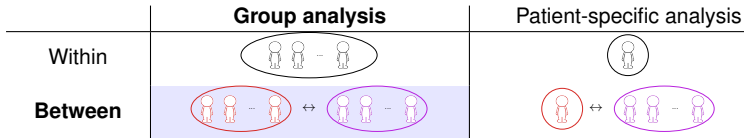
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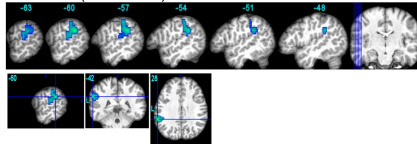
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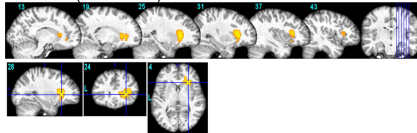


Atypical activity and lateralisation of brain function in children diagnosed with typical specific language impairment.

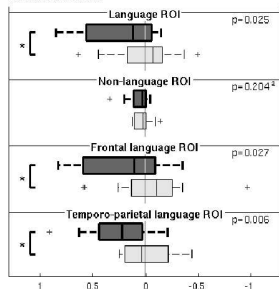
Definition task (Control > T-SLI)



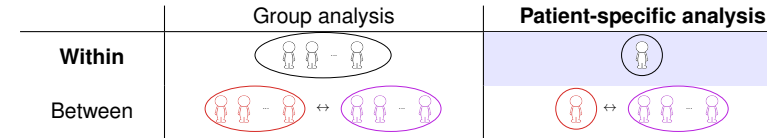
PhonDiff task (T-SLI > Control)



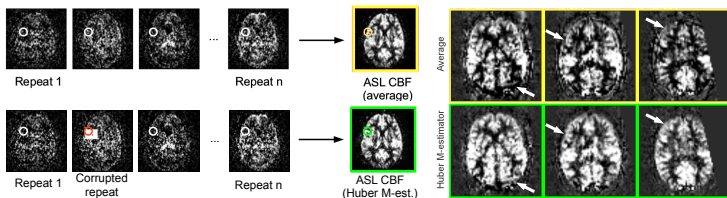
Combined Tasks



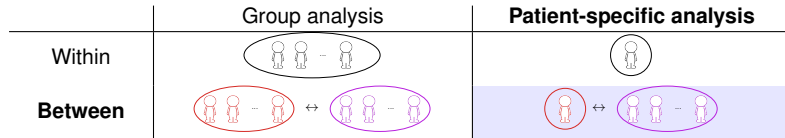
Contributions: overview



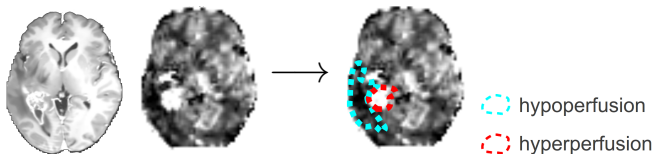
Robust Estimation of the Cerebral Blood Flow in Arterial Spin Labelling.



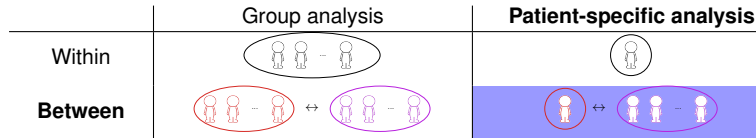
Contributions: overview



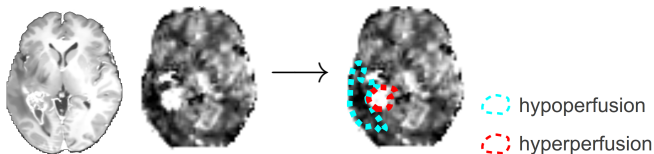
Objective: Quantitative identification of voxelwise patient-specific perfusion abnormalities.



Contributions: overview



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.

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)

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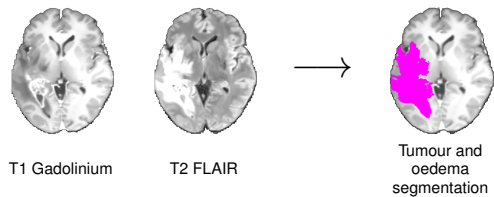
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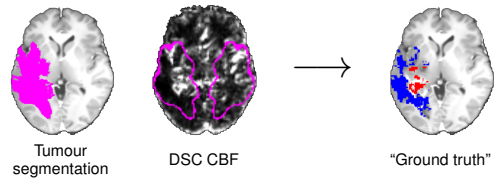
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Validation: Ground Truth

1. Segmentation of the tumour:



2. Combination with T2 perfusion information:



3. Visual assessment and manual corrections by a clinician.

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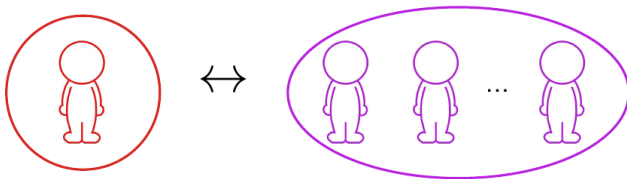
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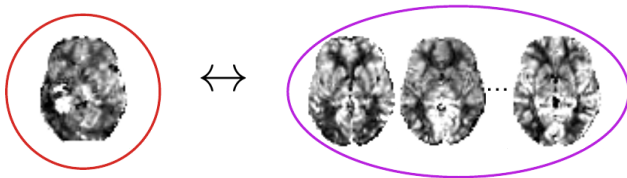
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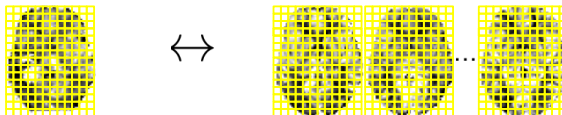
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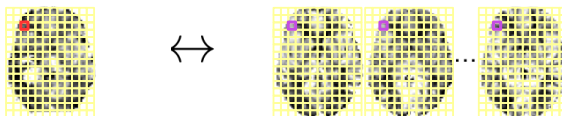
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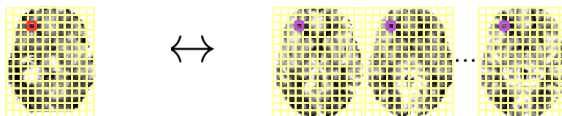
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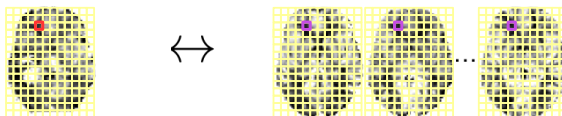
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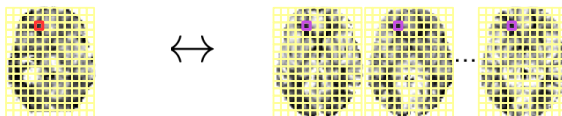
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Massively univariate approaches:



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

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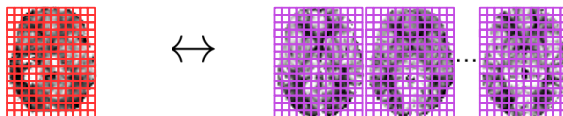
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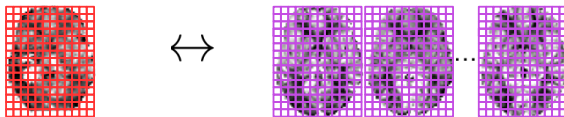
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Multivariate approaches:



- ✓ 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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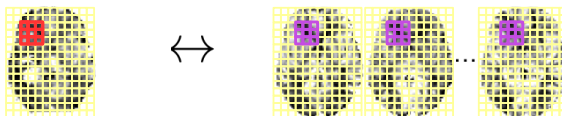
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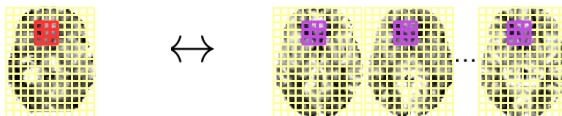
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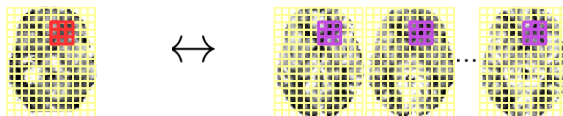
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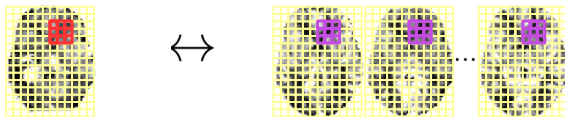
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Locally multivariate approaches:



- ✓ 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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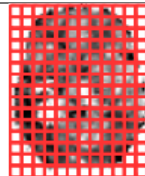
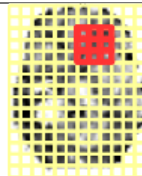
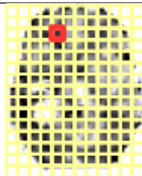
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Massively univariate Locally multivariate Multivariate



Comput.
efficiency

++

+ / -

-

Cross-
voxels
info.

-

+

++

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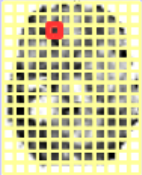
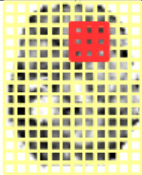
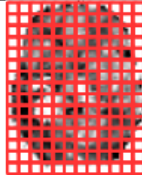
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	Massively univariate	Locally multivariate	Multivariate
			
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

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

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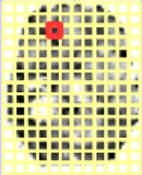
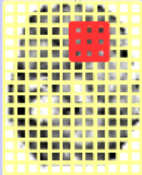
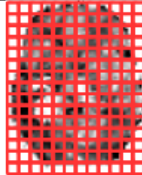
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	Massively univariate	Locally multivariate	Multivariate
			
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

1. The massively univariate GLM: **homoscedastic and heteroscedastic models.**
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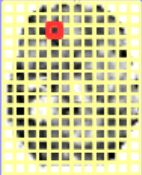
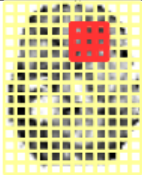
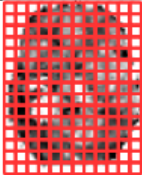
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	Massively univariate	Locally multivariate	Multivariate
			
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

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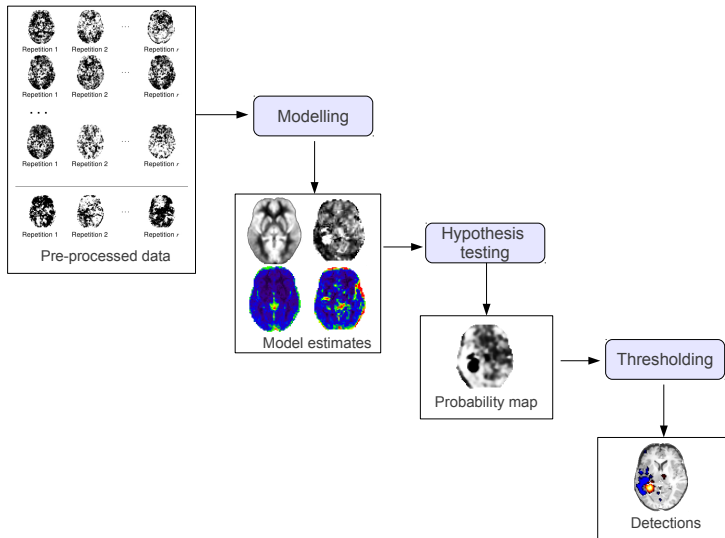
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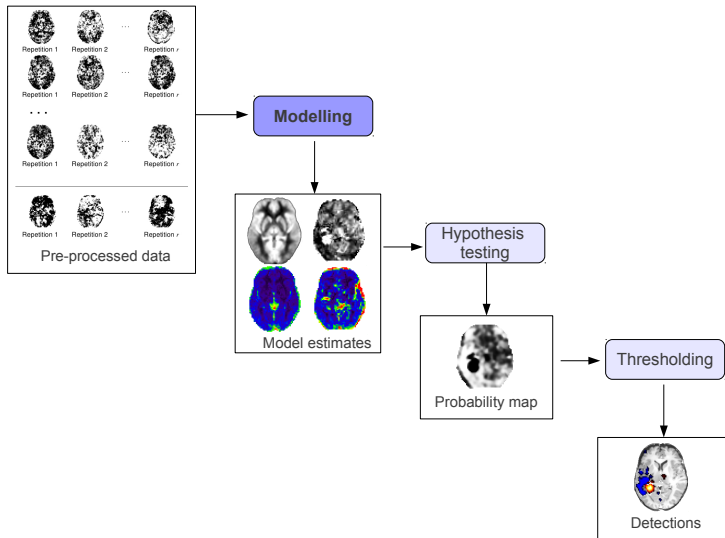
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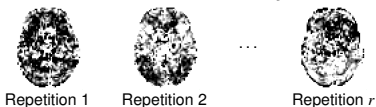
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Modelling: subject level

General Linear Model: subject level



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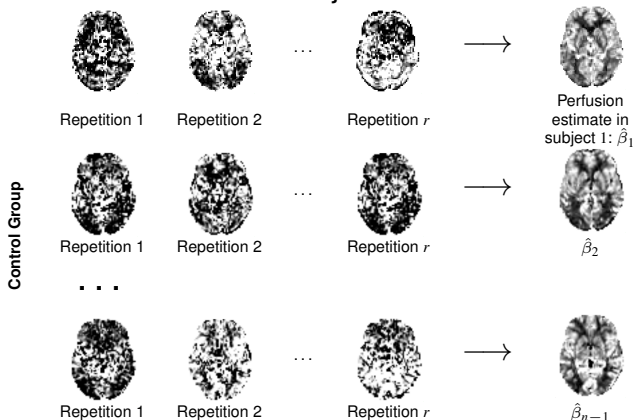
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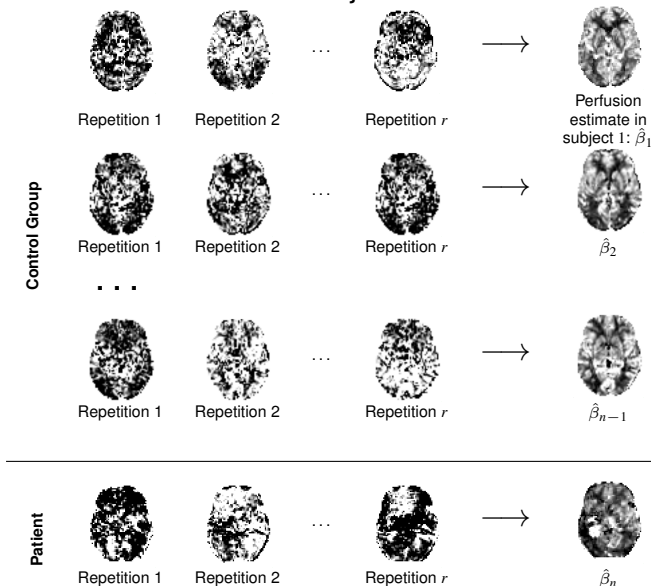
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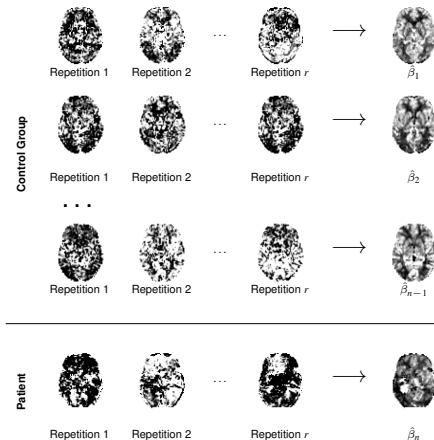
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Modelling: group level

General Linear Model: group level.



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

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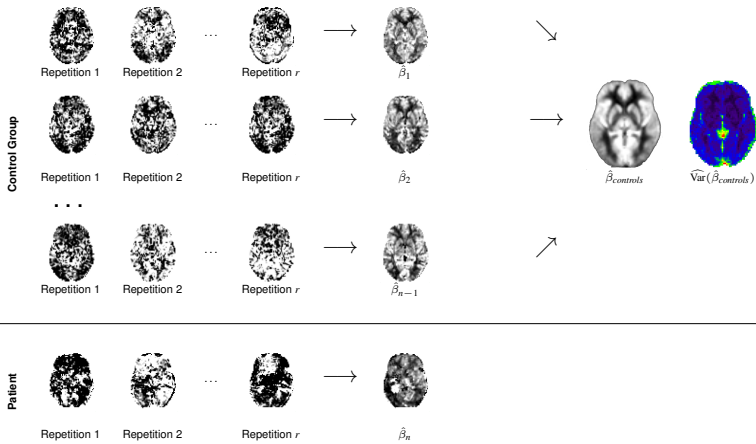
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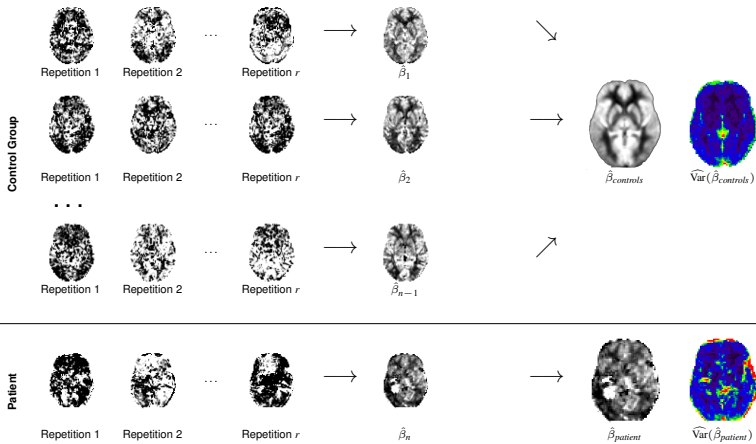
General Linear Model: group level.



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

Modelling: group level

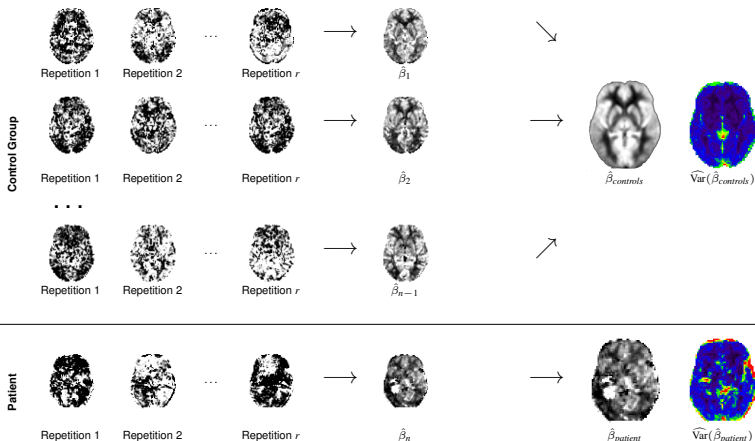
General Linear Model: group level.



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

Modelling: group level

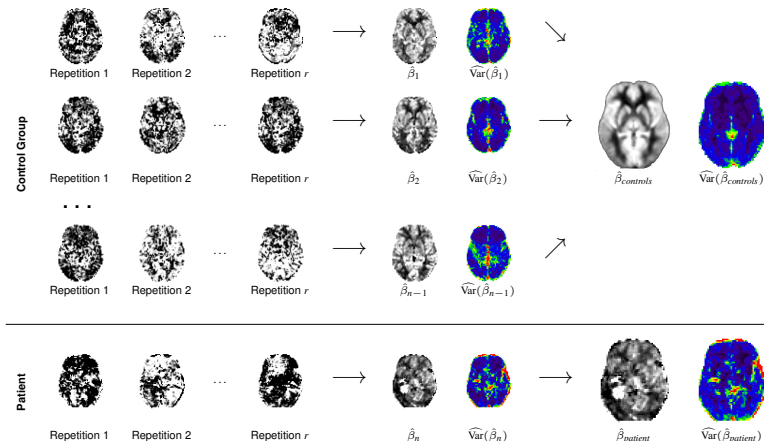
General Linear Model: group level. The **homoscedastic model**:



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

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

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 (SPM¹)
- ▶ The heteroscedastic approach (FSL², AFNI³).

¹www.fil.ion.ucl.ac.uk/spm/

²fsl.fmrib.ox.ac.uk/fsl/fslwiki/

³afni.nimh.nih.gov/afni/

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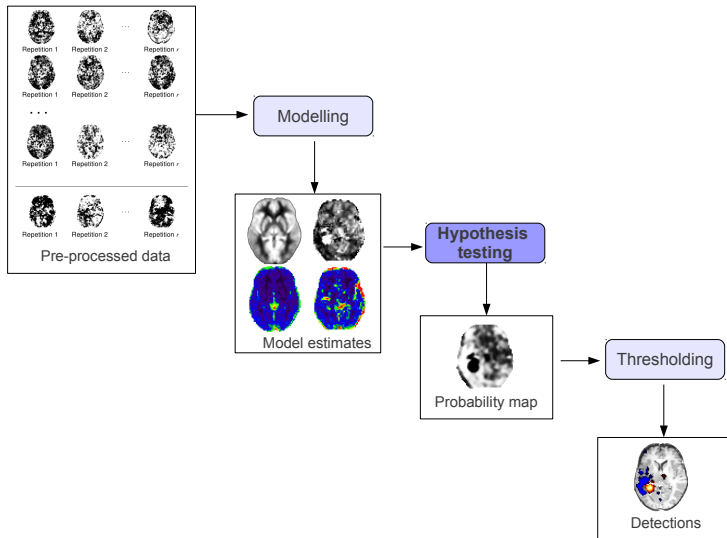
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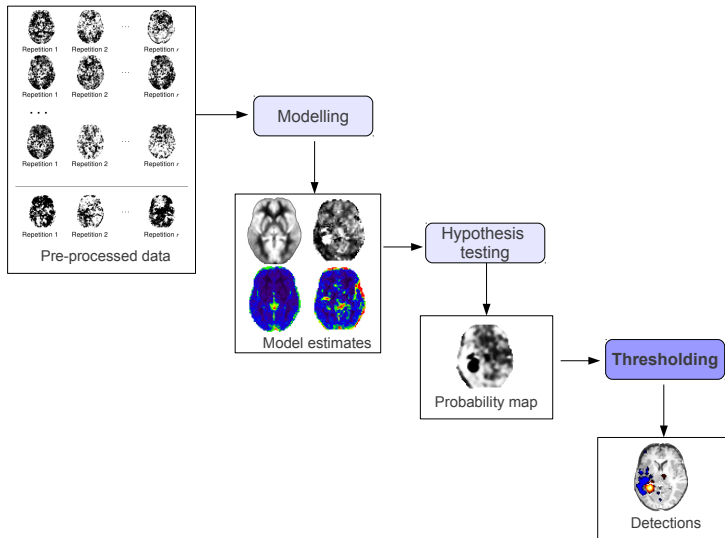
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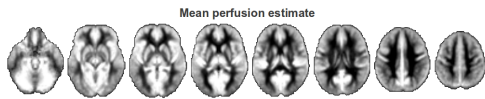
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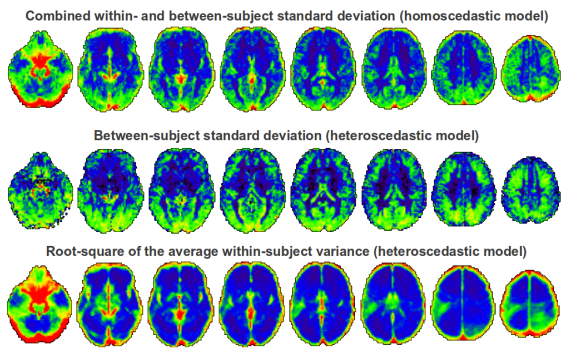


Results: Perfusion in the control group

Mean estimate

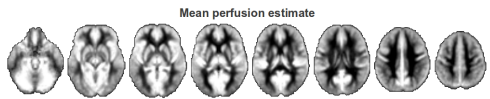


Standard deviation estimates

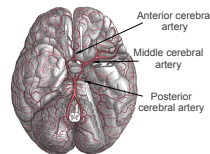
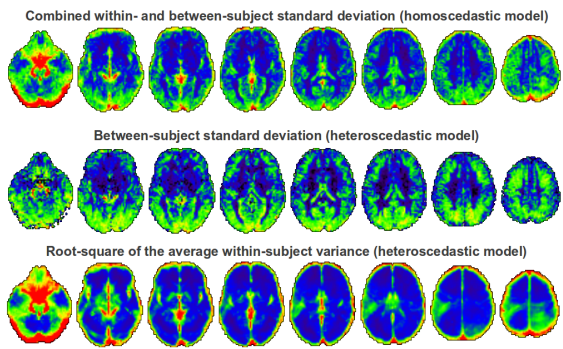


Results: Perfusion in the control group

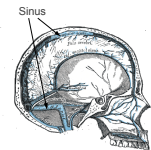
Mean estimate



Standard deviation estimates



Brain arteries



Brain veins

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.

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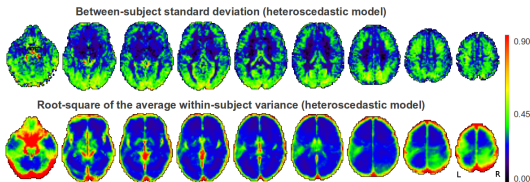
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Assumptions of the homoscedastic model

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

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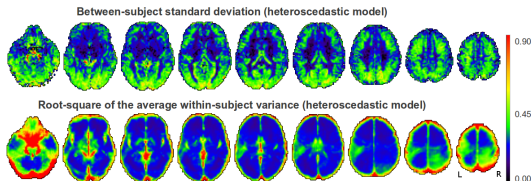
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Assumptions of the homoscedastic model

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



× not
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- Assumption 2: Within-subject variance roughly constant across subjects.

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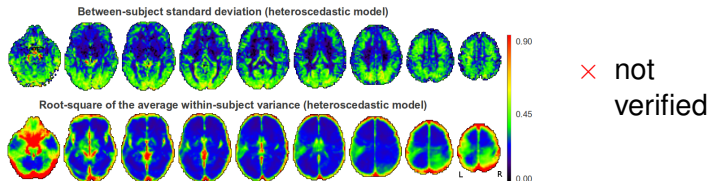
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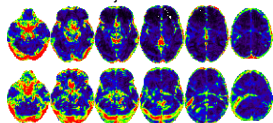
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- Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



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

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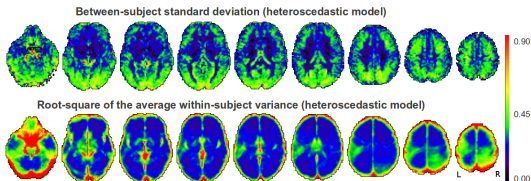
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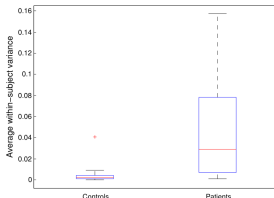
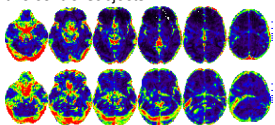
- Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



× not
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- Assumption 2: Within-subject variance roughly constant across subjects.

Within-subject standard deviation in
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Using a metric from [Mumford 2009].

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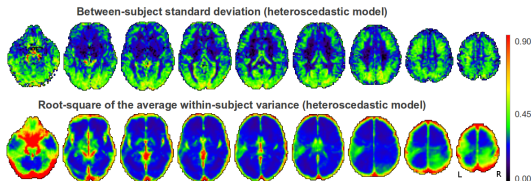
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Assumptions of the homoscedastic model

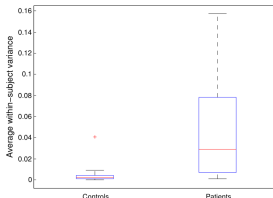
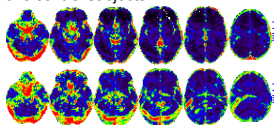
- Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



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Within-subject standard deviation in
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Using a metric from [Mumford 2009].

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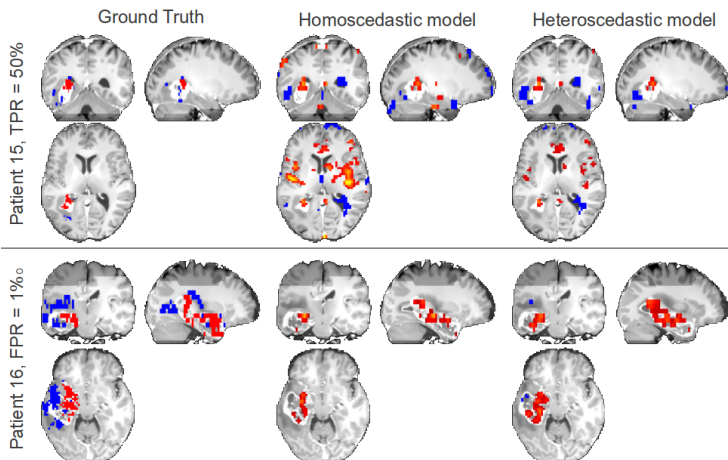
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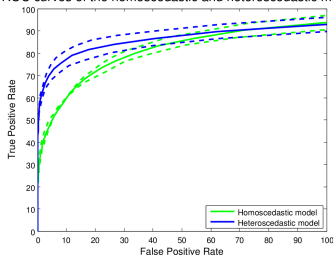
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ROC curves of the homoscedastic and heteroscedastic models



ROC curves for perfusion abnormality detections.

Homoscedastic model						
FWHM (mm ³)	0	4	6	8	10	12
ROC Area	0.46	0.49	0.49	0.49	0.48	0.48

Heteroscedastic model						
FWHM (mm ³)	0	4	6	8	10	12
ROC Area	0.63	0.70	0.72	0.72	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](#)].

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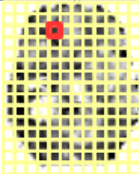
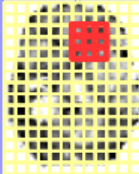
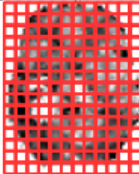
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	Massively univariate	Locally multivariate	Multivariate
			
Comput. efficiency	++	+ / -	-
Cross-voxels info.	-	+	++

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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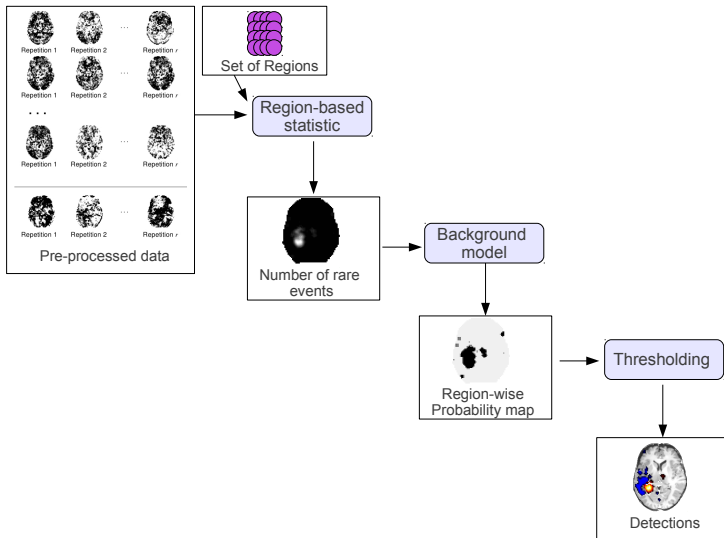
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A *contrario* approach

From the computer vision community [Desolneux 2003].

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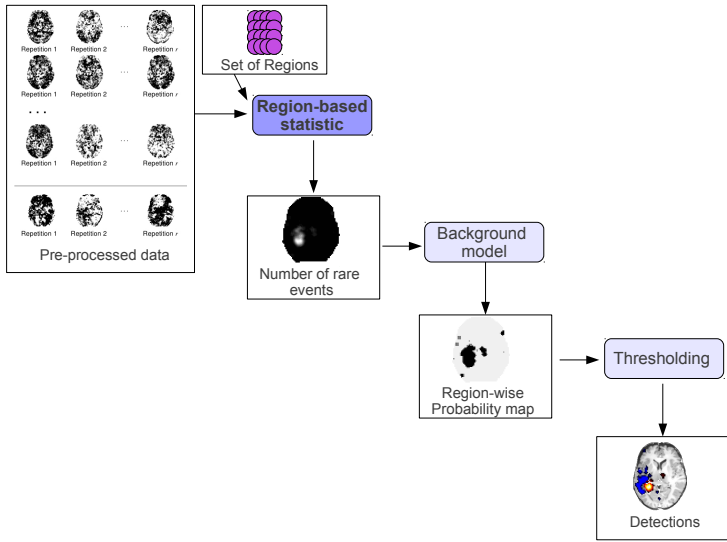
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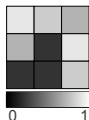
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A *contrario* approach

Rare event count per sphere as region-based statistic:



1. Voxel-based
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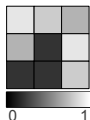
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A *contrario* approach

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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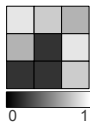
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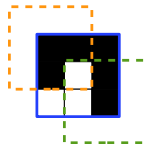
Rare event count per sphere as region-based statistic:



1. Voxel-based
probability



2. Thresholding



3. Rare event count per region

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

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A contrario approach

From the computer vision community [Desloneux 2003].

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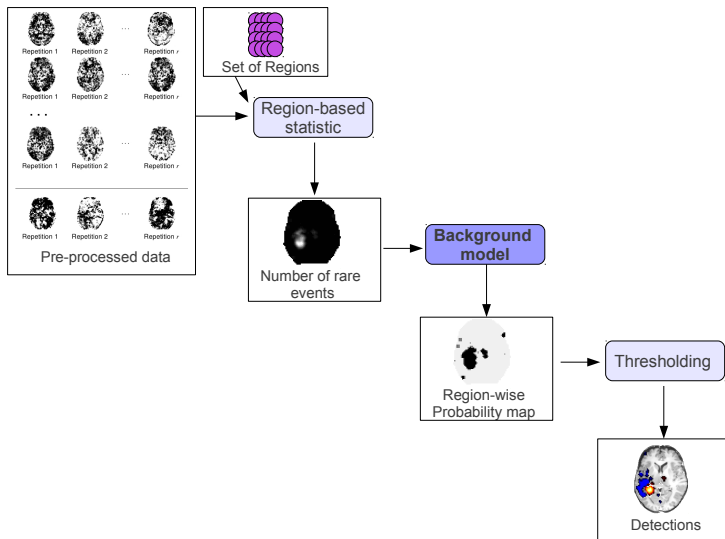
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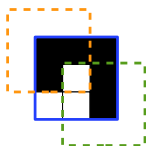
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A *contrario* approach

From region-based statistic to region-based probability:



1	1	1
3	3	2
3	3	2



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**:

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

where e is the number of voxel per region.

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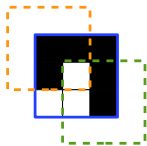
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From region-based statistic to region-based probability:



1	1	1
3	3	2
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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 independance assumption is therefore questionned.

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

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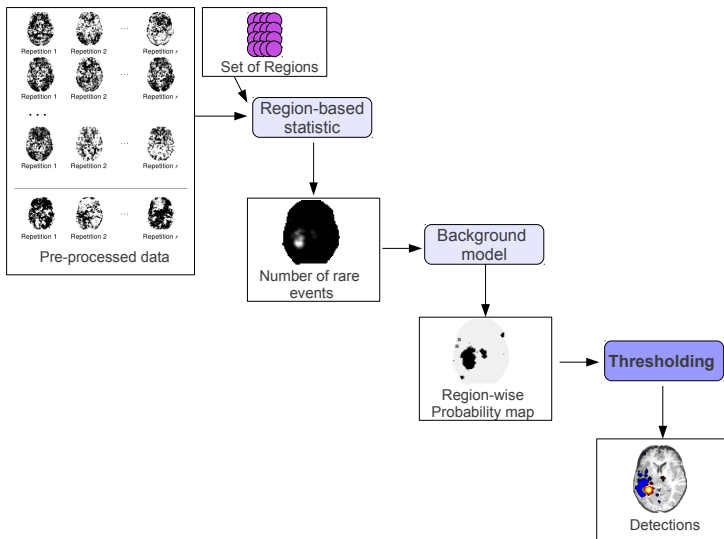
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A *contrario* approach: thresholding

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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 ϵ , 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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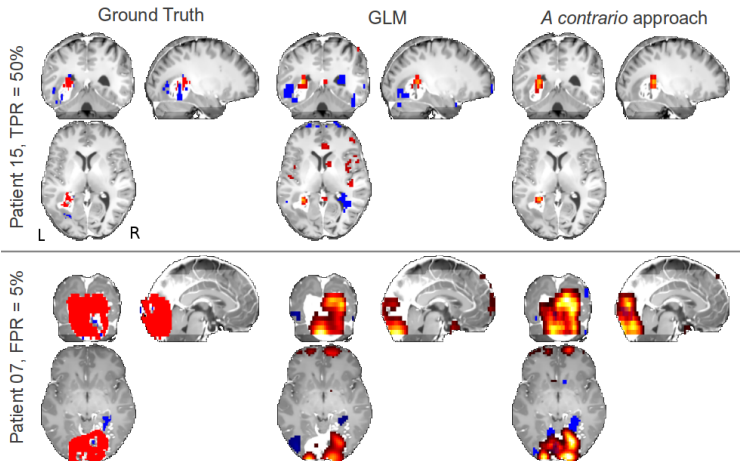
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Results: *a contrario*

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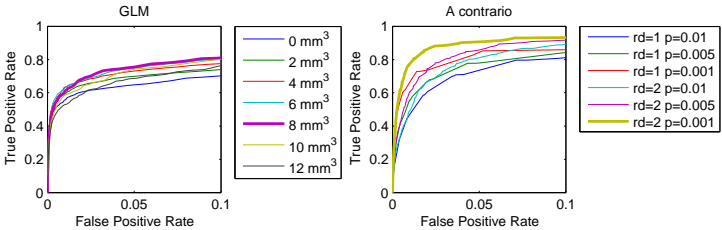
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Average ROC curves

GLM							
w	0	2	4	6	8	10	12
ROC area	0.63	0.67	0.70	0.72	0.73	0.70	0.65

<i>a contrario</i>						
	<i>rd</i> = 1			<i>rd</i> = 2		
<i>p</i> _{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	0.87

Area under the ROC curves

Results: *a contrario*

Checking the test validity

Camille Maumet

Context

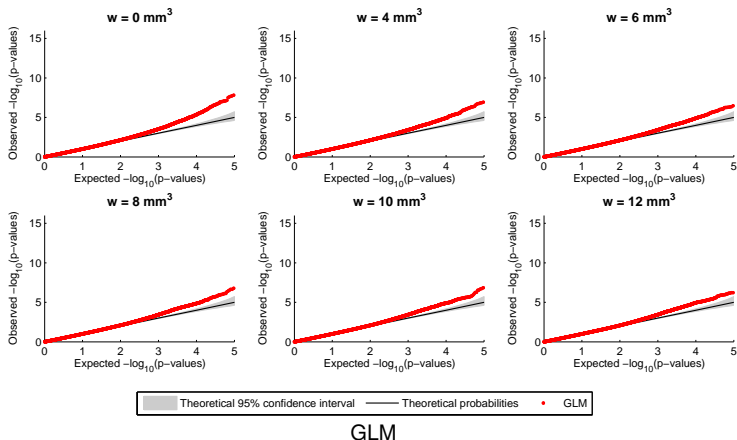
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- Invalidity of the GLM.
- This invalidity was also observed in voxel-based morphometry [Scarpazza 2013, Viviani 2007].

Results: *a contrario*

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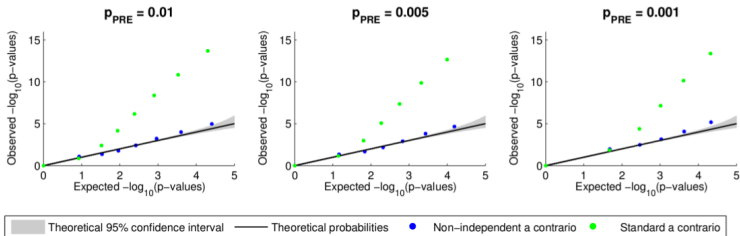
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- ▶ The *a contrario* approach outperforms the standard General Linear Model.
- ▶ Non-independent probabilities provide more valid statistics in the context of MRI data analysis.

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

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Contributions(1/2)

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:

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 - ▶ **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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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.

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Contributions (2/2)

Camille Maumet

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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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Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

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Conclusions and future work

Contributions

Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

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Q & A