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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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Director: Christian Barillot, Co-director: Pierre Maurel



Outline

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

Context

Contributions

Conclusions and future work

Outline

Context

Brain function
From group to
patient-specific
analyses

Contributions

Overview
Materials
Imaging protocol
Validation
State of the art
Heteroscedastic
GLM
Methods
Results
A contrario
Methods
Results

Conclusions and future work

Contributions
Discussion

Context

Brain function

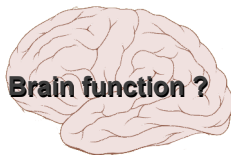
From group to patient-specific analyses

Contributions

Conclusions and future work

Brain function

Two views of brain function:



[Raichle 2010]

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

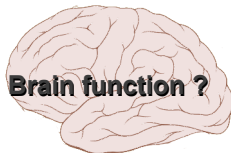
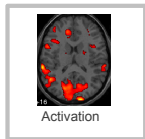
Contributions

Discussion

Brain function

Two views of brain function:

Task-evoked activity

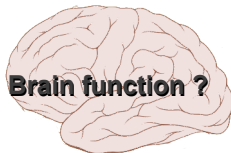
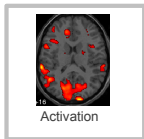


[Raichle 2010]

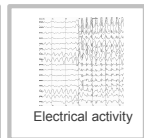
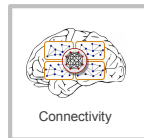
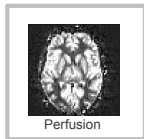
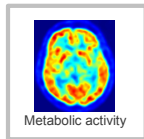
Brain function

Two views of brain function:

Task-evoked activity



Intrinsic brain function

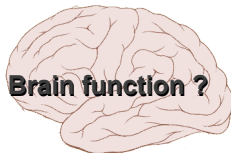


[Raichle 2010]

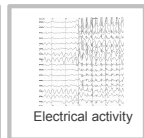
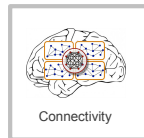
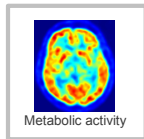
Brain function

Two views of brain function:

Task-evoked activity



Intrinsic brain function



[Raichle 2010]

Brain perfusion

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

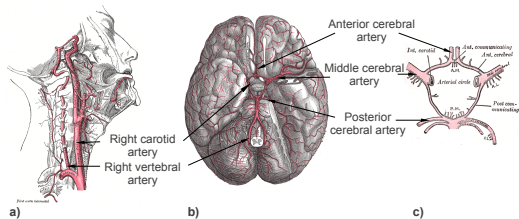
Methods

Results

Conclusions and future work

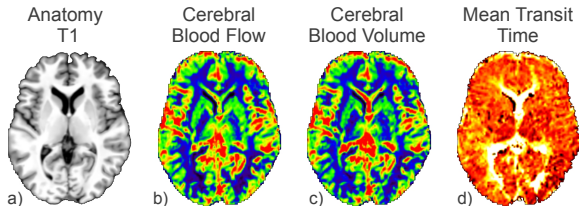
Contributions

Discussion



Blood supply to the brain

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

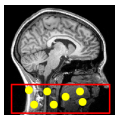


Example of perfusion parameters

Arterial Spin Labelling (ASL)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet



Labelling

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

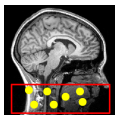
Discussion

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet



Labelling



Delay

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

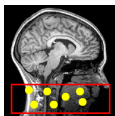
Methods

Results

Conclusions and future work

Contributions

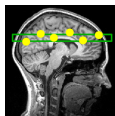
Discussion



Labelling



Delay



Readout

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

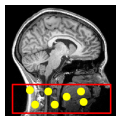
Methods

Results

Conclusions and future work

Contributions

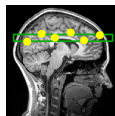
Discussion



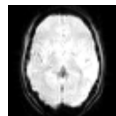
Labelling



Delay



Readout



Label

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

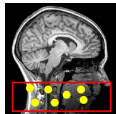
Methods

Results

Conclusions and future work

Contributions

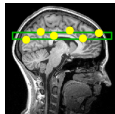
Discussion



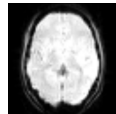
Labelling



Delay



Readout



Label



Readout

[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

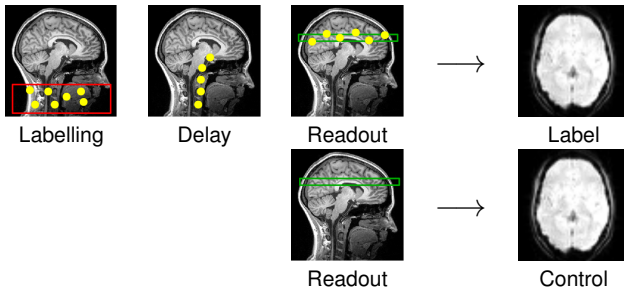
Methods

Results

Conclusions and future work

Contributions

Discussion



[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

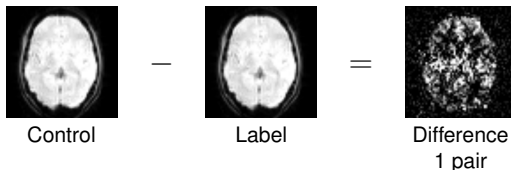
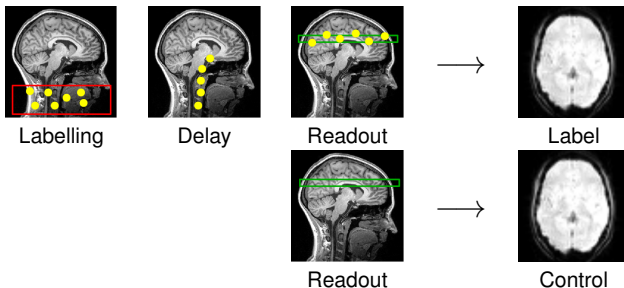
Methods

Results

Conclusions and future work

Contributions

Discussion



[Detre et al., MRM 1992]

Arterial Spin Labelling (ASL)

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

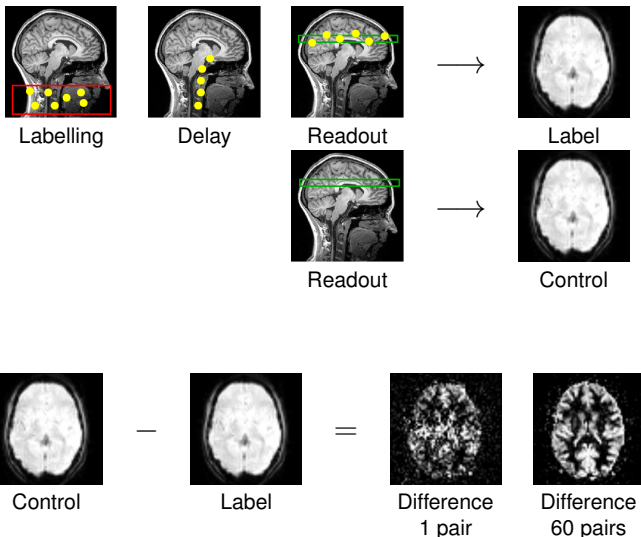
Methods

Results

Conclusions and future work

Contributions

Discussion



[Detre et al., MRM 1992]

Group analyses: definition (1/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

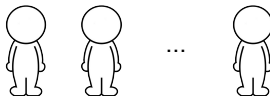
Methods

Results

Conclusions and
future work

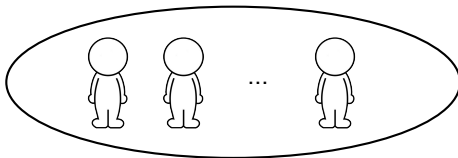
Contributions

Discussion



Group analyses: definition (1/2)

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



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

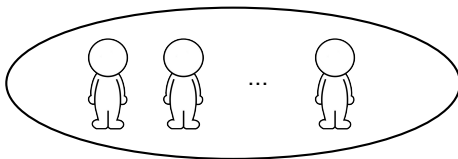
Conclusions and
future work

Contributions

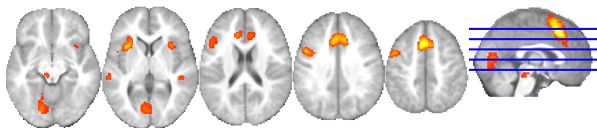
Discussion

Group analyses: definition (1/2)

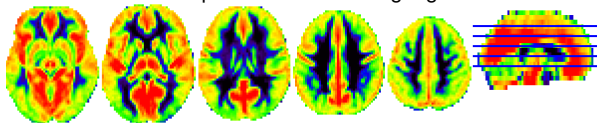
Within-group analyses identify common patterns across a group of subjects.



Examples



Group activation for a language task.



Group cerebral blood flow.

Group analyses: definition (2/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

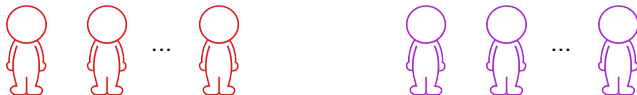
Methods

Results

Conclusions and
future work

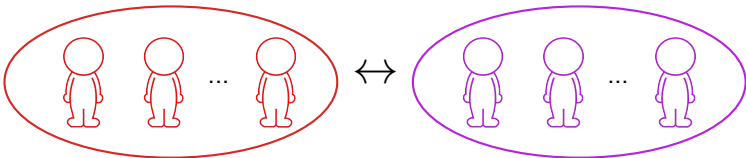
Contributions

Discussion



Group analyses: definition (2/2)

Between-group analyses identify differences at the group level.



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

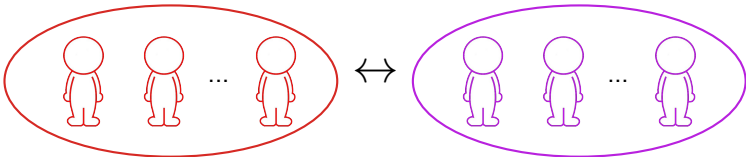
Conclusions and
future work

Contributions

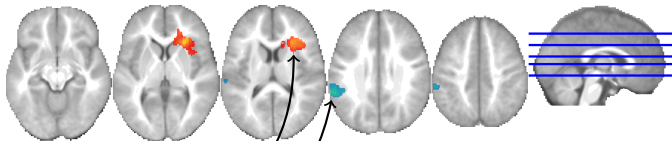
Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

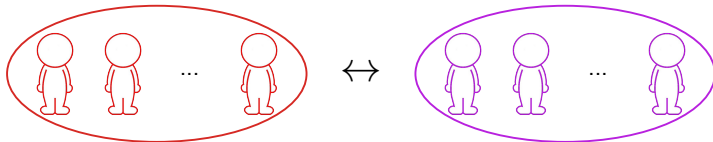
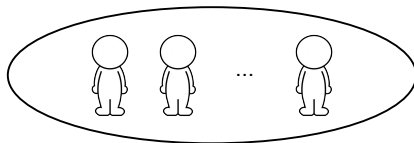
Methods

Results

Conclusions and
future work

Contributions

Discussion



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)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

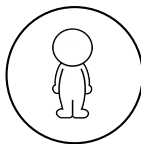
Contributions

Discussion



Patient-specific analyses: definition (1/2)

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



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

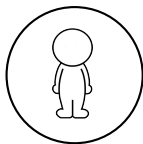
Conclusions and
future work

Contributions

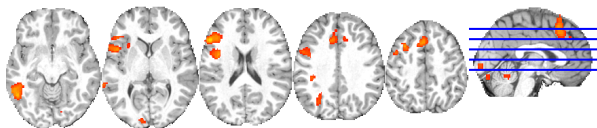
Discussion

Patient-specific analyses: definition (1/2)

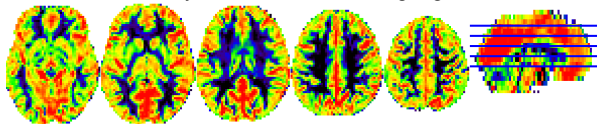
Patient-specific analyses identify patterns of brain function in a single subject.



Examples



Subject activation for a language task.



Cerebral blood flow.

Patient-specific analyses: definition (2/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

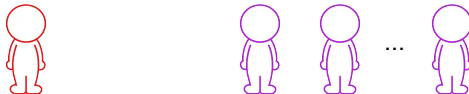
Methods

Results

Conclusions and
future work

Contributions

Discussion

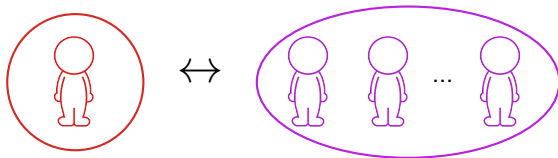


Patient-specific analyses: definition (2/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

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



Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

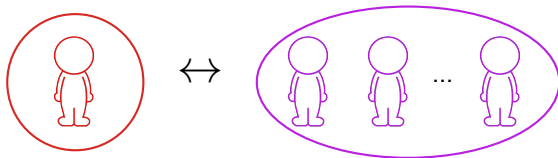
Conclusions and
future work

Contributions

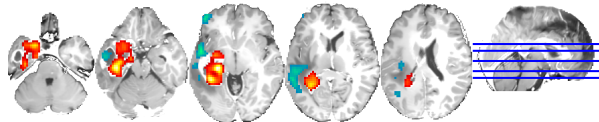
Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

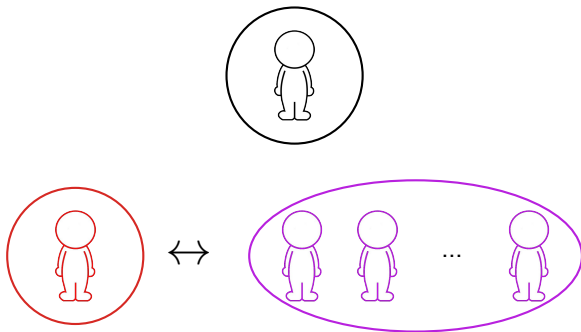
Methods

Results

Conclusions and
future work

Contributions

Discussion



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.

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

Contributions

Discussion

Outline

Context

Contributions

Overview

Materials

State of the art

General Linear Model: homoscedastic and
heteroscedastic models

A contrario approach

Conclusions and future work

Contributions: overview

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

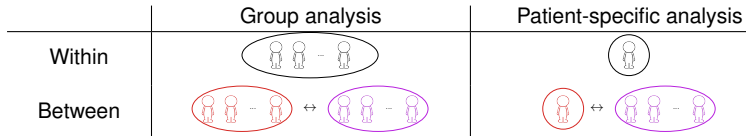
Methods

Results

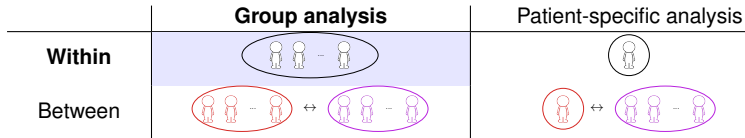
Conclusions and future work

Contributions

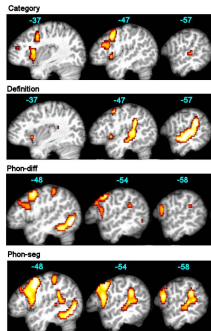
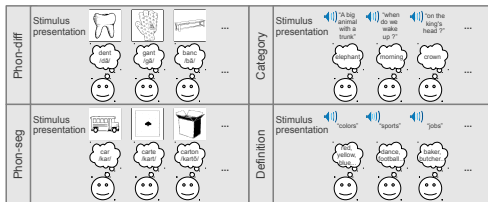
Discussion



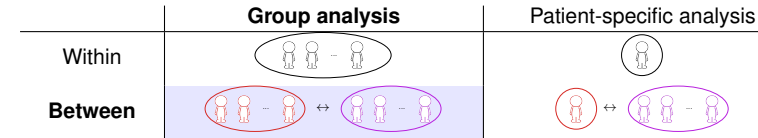
Contributions: overview



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

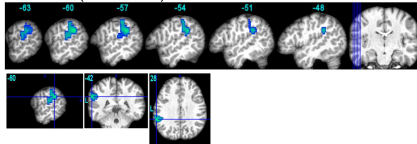


Contributions: overview

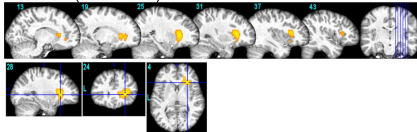


Atypical activity and lateralisation of brain function in children diagnosed with typical specific language impairment.

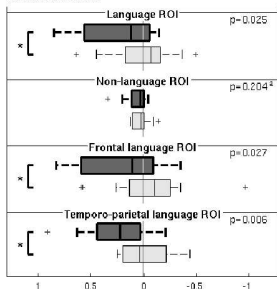
Definition task (Control > T-SLI)



PhonDiff task (T-SLI > Control)



Combined Tasks



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

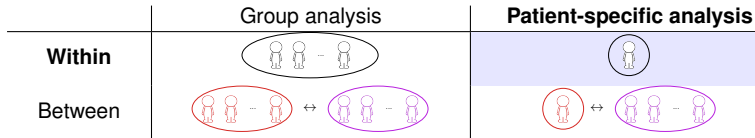
Results

Conclusions and future work

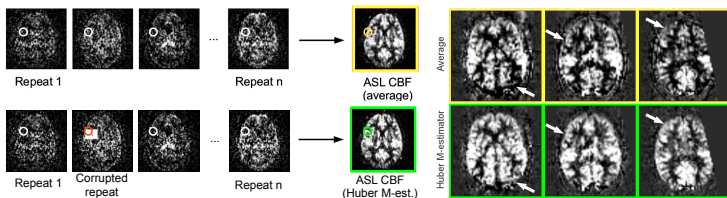
Contributions

Discussion

Contributions: overview



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



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

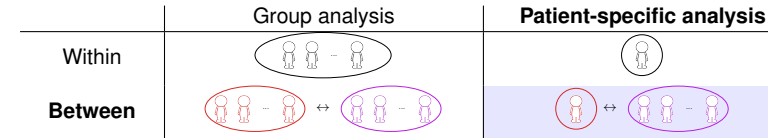
Results

Conclusions and future work

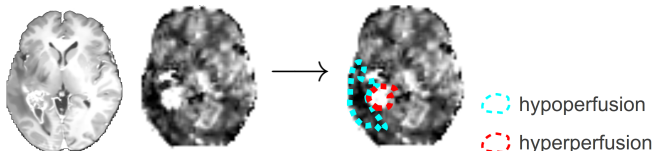
Contributions

Discussion

Contributions: overview



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



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

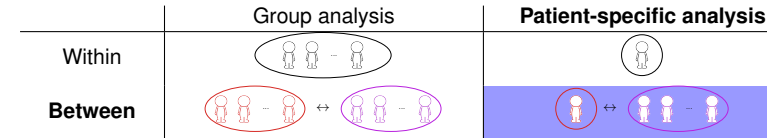
Results

Conclusions and
future work

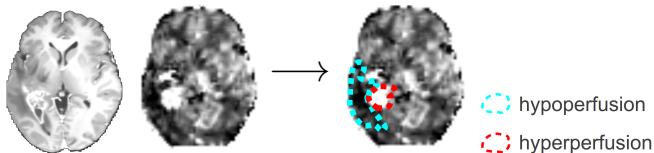
Contributions

Discussion

Contributions: overview



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



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

Contributions

Discussion

Materials

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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

Imaging protocol:

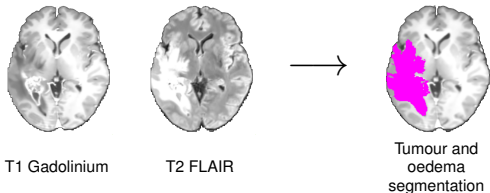
- ▶ PICORE Q2TIPS Pulsed ASL, 60 repetitions
- ▶ MPRAGE T1 3D
- ▶ T2 FLAIR

For the patients only:

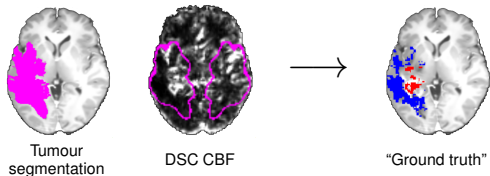
- ▶ T1 3D Gadolinium
- ▶ Dynamic Susceptibility Contrast imaging (DSC)

Validation: Ground Truth

1. Segmentation of the tumour:



2. Combination with T2 perfusion information:



3. Visual assessment and manual corrections by a clinician.

State of the art

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

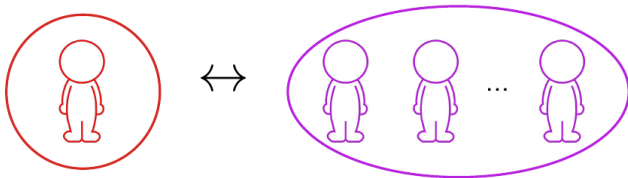
Methods

Results

Conclusions and future work

Contributions

Discussion



State of the art

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

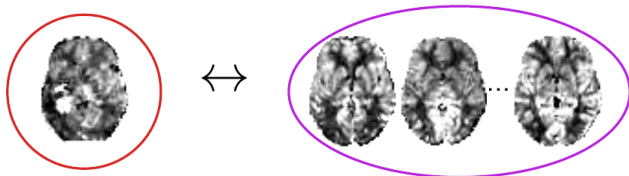
Methods

Results

Conclusions and future work

Contributions

Discussion



State of the art

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

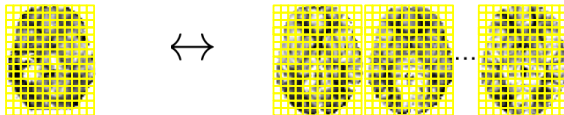
Methods

Results

Conclusions and future work

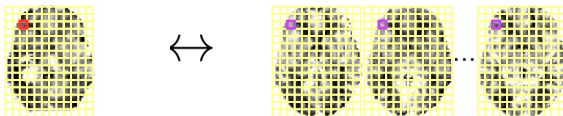
Contributions

Discussion



State of the art

Massively univariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

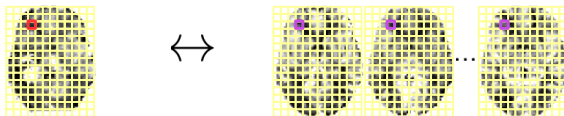
Conclusions and future work

Contributions

Discussion

State of the art

Massively univariate approaches:



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

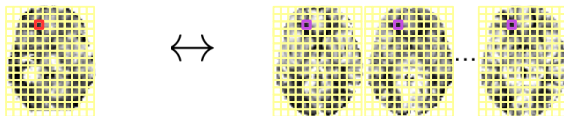
Conclusions and future work

Contributions

Discussion

State of the art

Massively univariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

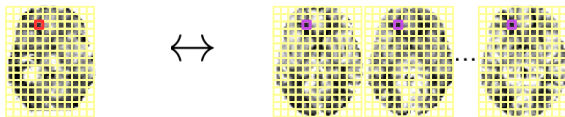
Conclusions and
future work

Contributions

Discussion

State of the art

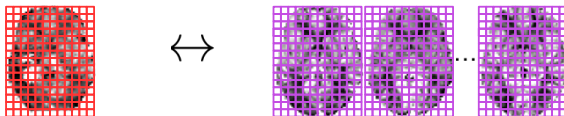
Massively univariate approaches:



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

State of the art

Multivariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

Context

Brain function
From group to
patient-specific
analyses

Contributions

Overview
Materials
Imaging protocol
Validation

State of the art

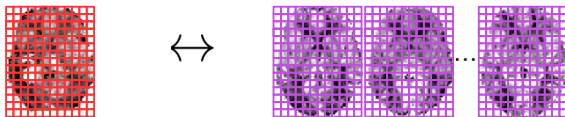
Heteroscedastic
GLM
Methods
Results
A contrario
Methods
Results

Conclusions and
future work

Contributions
Discussion

State of the art

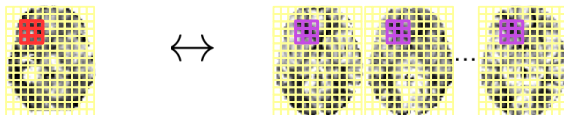
Multivariate approaches:



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

State of the art

Locally multivariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

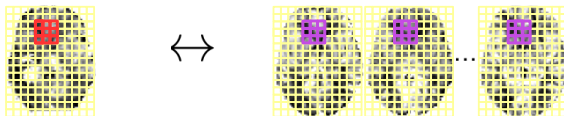
Conclusions and future work

Contributions

Discussion

State of the art

Locally multivariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

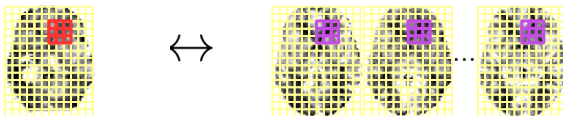
Conclusions and future work

Contributions

Discussion

State of the art

Locally multivariate approaches:



From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

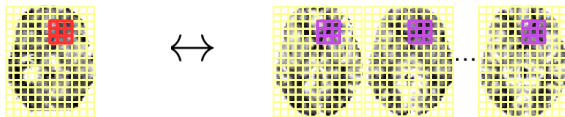
Conclusions and future work

Contributions

Discussion

State of the art

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.

Univariate / Multivariate - overview

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

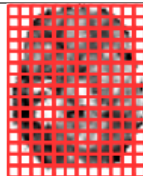
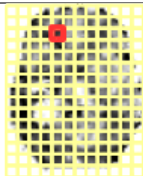
Results

Conclusions and future work

Contributions

Discussion

Massively univariate Locally multivariate Multivariate



Comput. efficiency

++

+ / -

-

Cross-voxels info.

-

+

++

Univariate / Multivariate - overview

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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

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

Univariate / Multivariate - overview

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

	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.

Univariate / Multivariate - overview

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

	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.

Standard statistics: overview

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

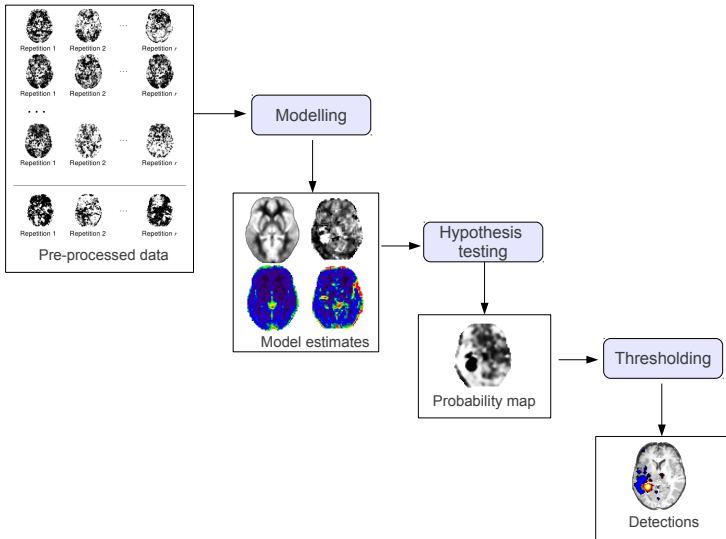
Methods

Results

Conclusions and future work

Contributions

Discussion



Standard statistics: overview

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

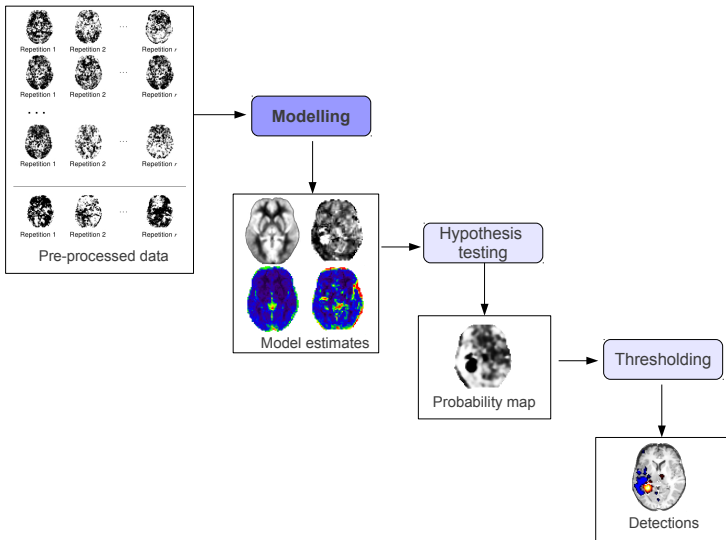
Methods

Results

Conclusions and future work

Contributions

Discussion



Modelling: subject level

General Linear Model: subject level



Repetition 1



Repetition 2

...



Repetition r

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

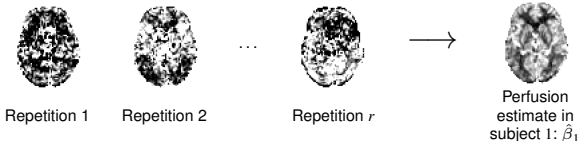
Conclusions and future work

Contributions

Discussion

Modelling: subject level

General Linear Model: subject level



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

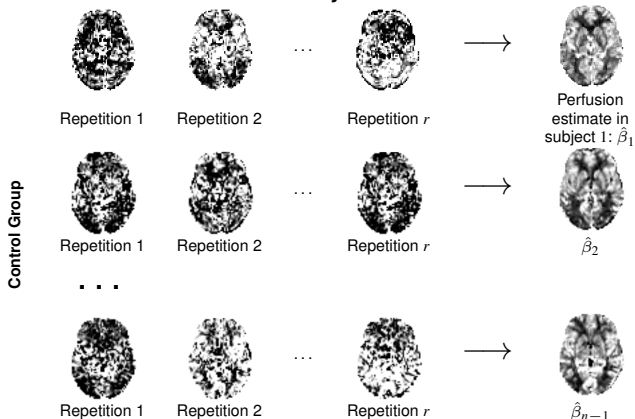
Conclusions and future work

Contributions

Discussion

Modelling: subject level

General Linear Model: subject level



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

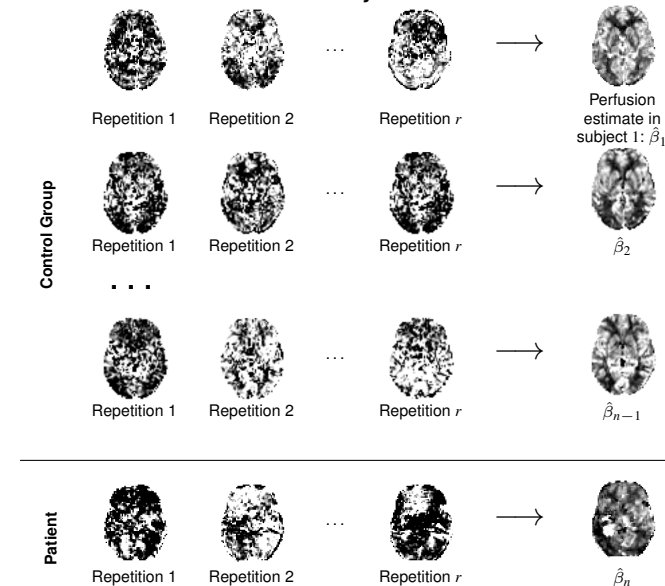
Conclusions and future work

Contributions

Discussion

Modelling: subject level

General Linear Model: subject level



From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

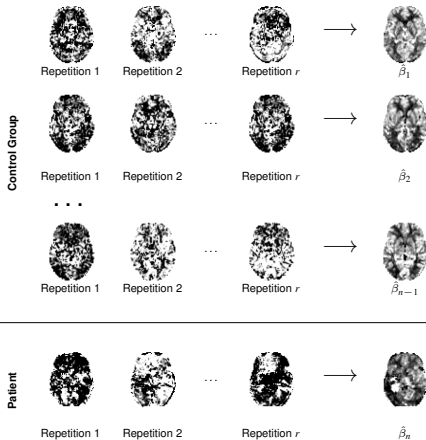
Conclusions and future work

Contributions

Discussion

Modelling: group level

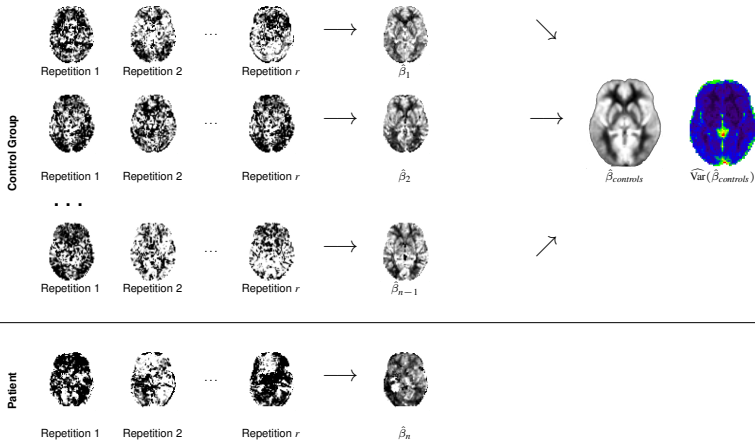
General Linear Model: group level.



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

Modelling: group level

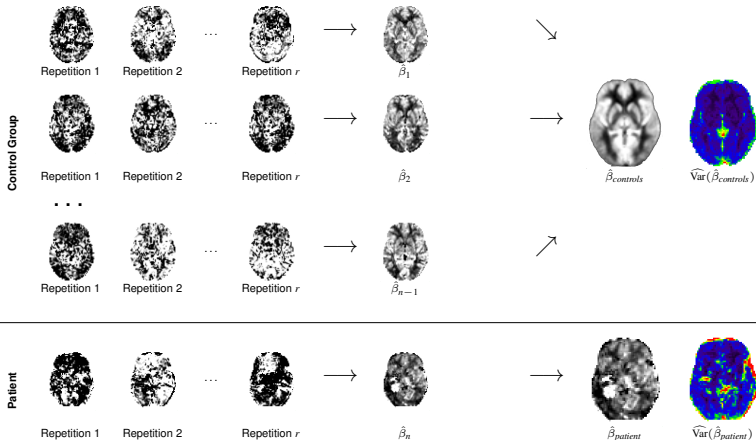
General Linear Model: group level.



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

Modelling: group level

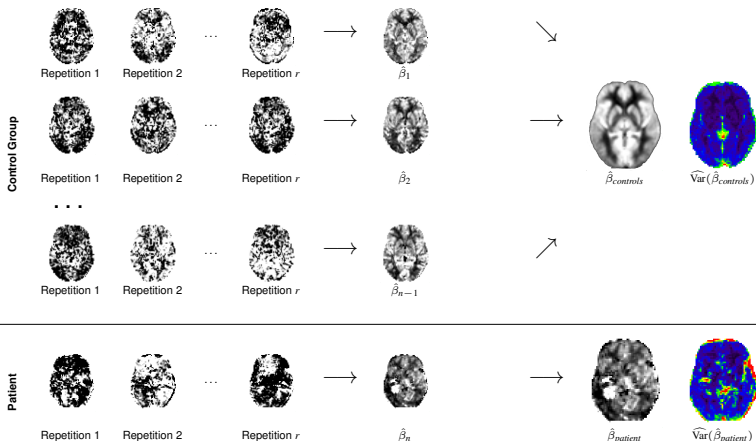
General Linear Model: group level.



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.

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

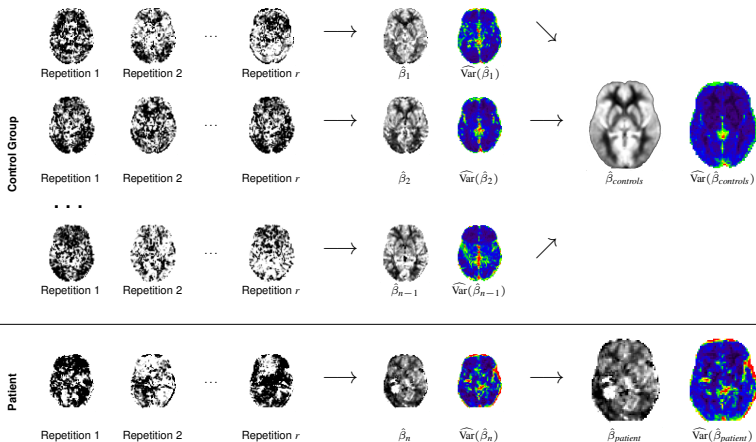
Conclusions and future work

Contributions

Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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/

Standard statistics: overview

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

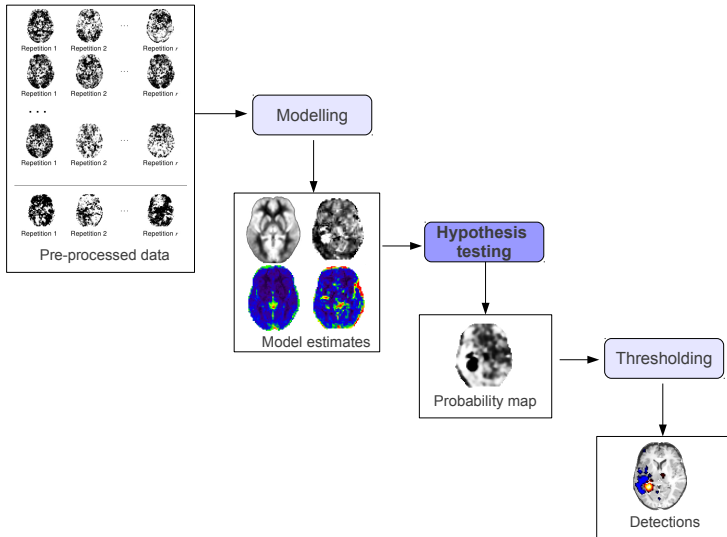
Methods

Results

Conclusions and future work

Contributions

Discussion



Standard statistics: overview

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

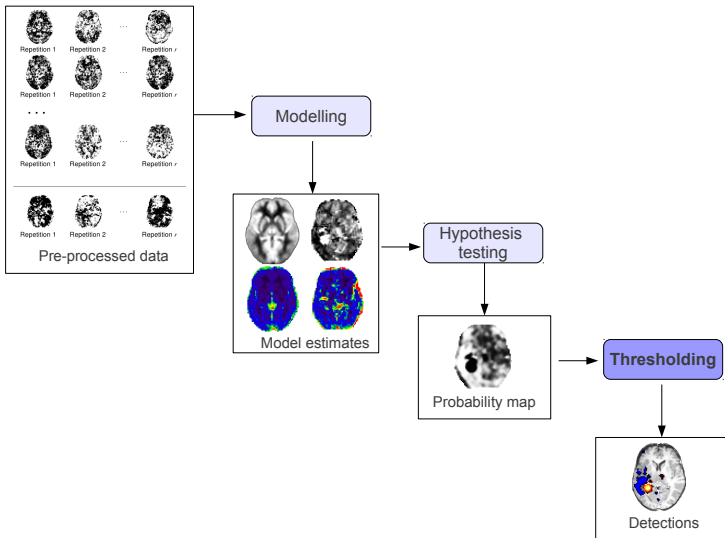
Methods

Results

Conclusions and future work

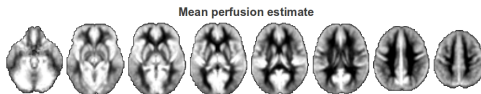
Contributions

Discussion

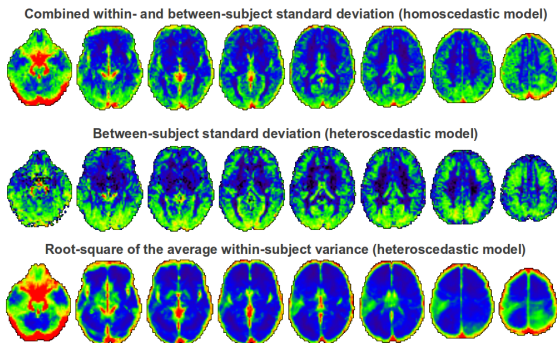


Results: Perfusion in the control group

Mean estimate



Standard deviation estimates



Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

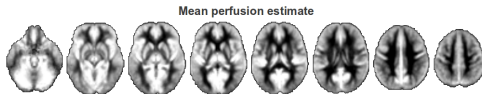
Conclusions and
future work

Contributions

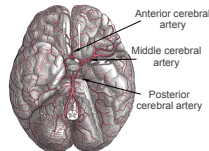
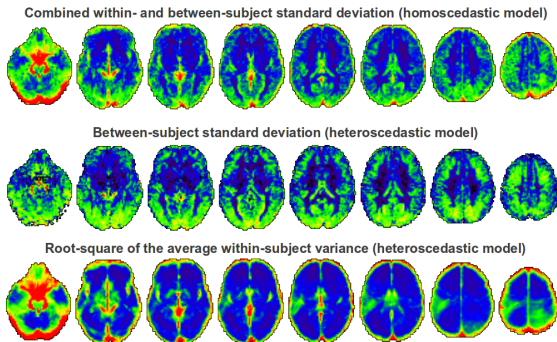
Discussion

Results: Perfusion in the control group

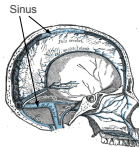
Mean estimate



Standard deviation estimates



Brain arteries



Brain veins

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

Contributions

Discussion

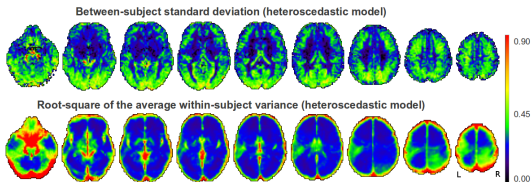
Assumptions of the homoscedastic model

- ▶ 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

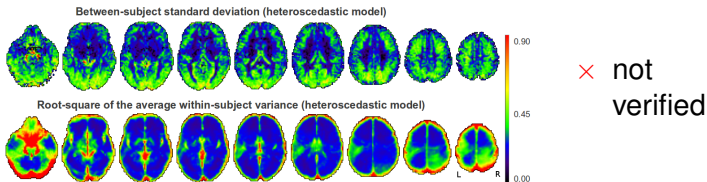
- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



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

Assumptions of the homoscedastic model

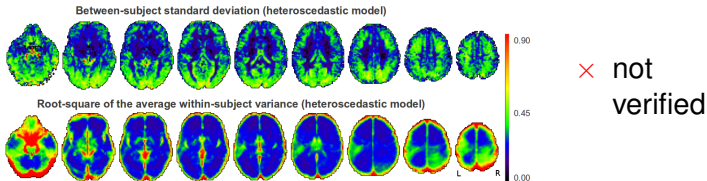
- ▶ Assumption 1: Within-subject variance negligible by comparison to the between-subject variance.



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

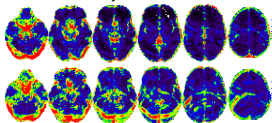
Assumptions of the homoscedastic model

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



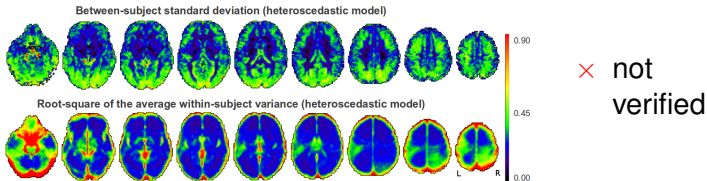
- ▶ Assumption 2: Within-subject variance roughly constant across subjects.

Within-subject standard deviation in two control subjects:

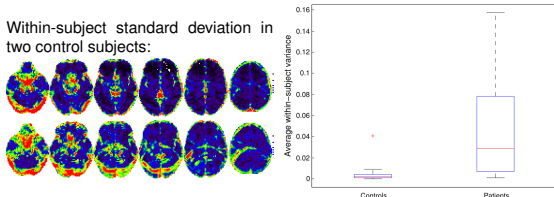


Assumptions of the homoscedastic model

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



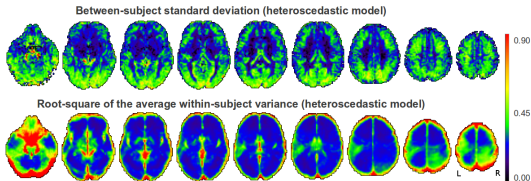
- ▶ Assumption 2: Within-subject variance roughly constant across subjects.



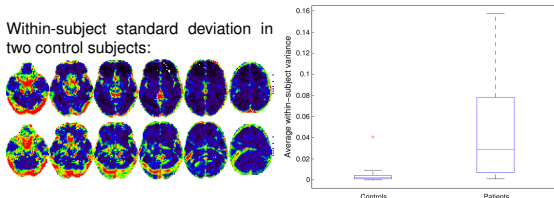
Using a metric from [Mumford 2009].

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.



Using a metric from [Mumford 2009].

Results: homoscedastic versus heteroscedastic GLM

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

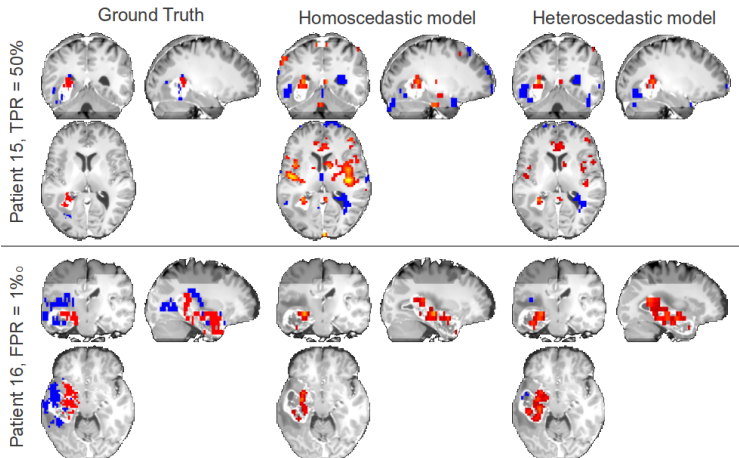
Methods

Results

Conclusions and future work

Contributions

Discussion



Results: homoscedastic versus heteroscedastic GLM

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

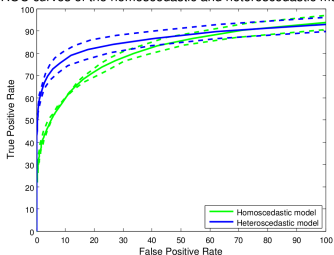
Results

Conclusions and future work

Contributions

Discussion

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

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

- ▶ 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

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

	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].

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

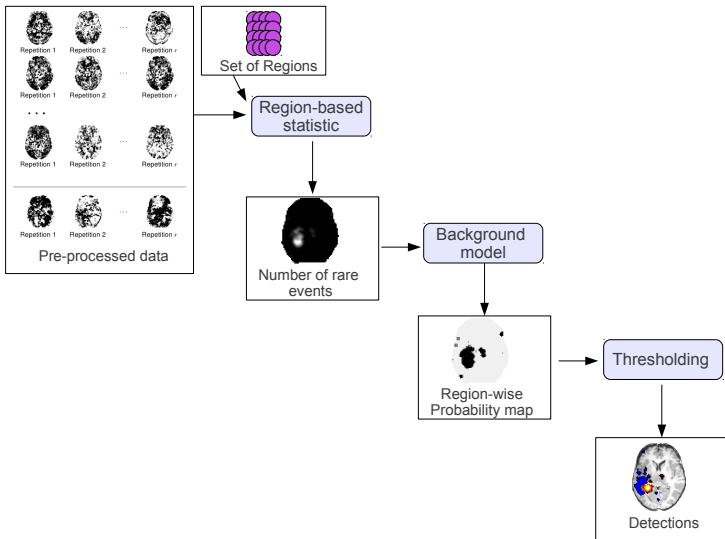
Methods

Results

Conclusions and
future work

Contributions

Discussion



A *contrario* approach

From the computer vision community [Desolneux 2003].

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

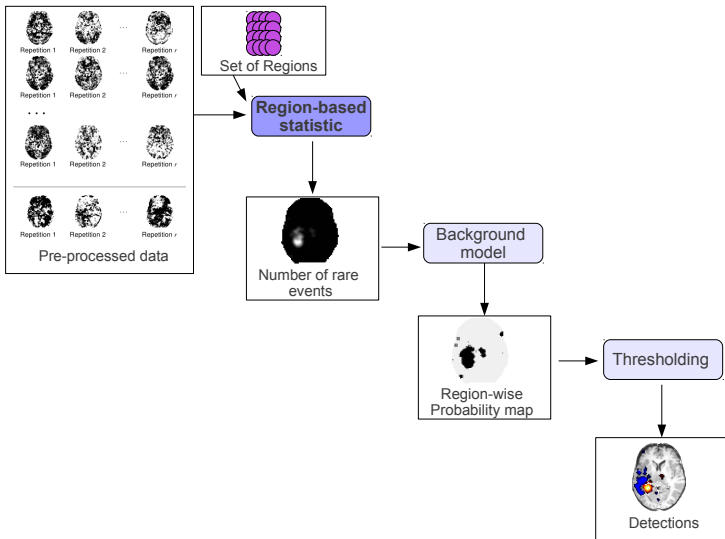
Methods

Results

Conclusions and
future work

Contributions

Discussion



A *contrario* approach

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

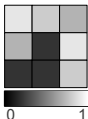
Results

Conclusions and
future work

Contributions

Discussion

Rare event count per sphere as region-based statistic:



1. Voxel-based
probability

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

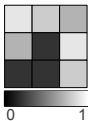
Results

Conclusions and future work

Contributions

Discussion

Rare event count per sphere as region-based statistic:



1. Voxel-based
probability



2. Thresholding

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

A *contrario* approach

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

Methods

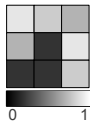
Results

Conclusions and future work

Contributions

Discussion

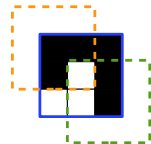
Rare event count per sphere as region-based statistic:



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].

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

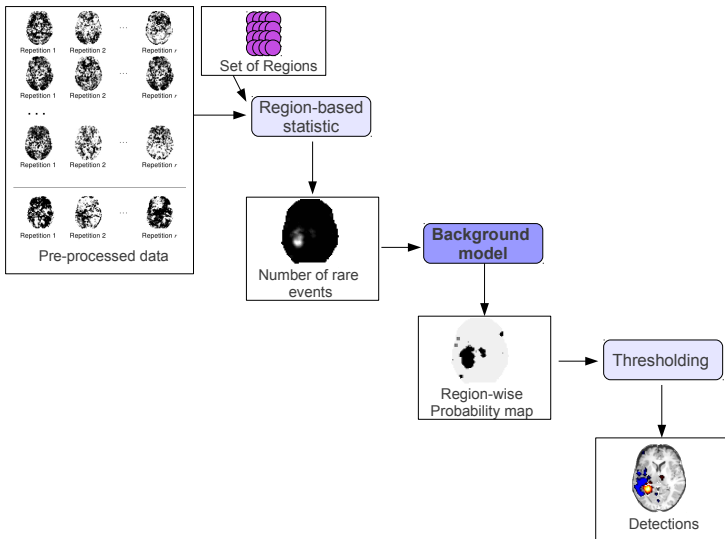
Methods

Results

Conclusions and
future work

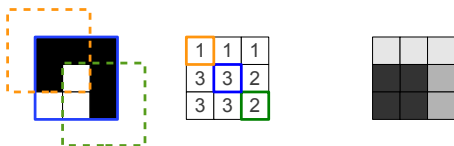
Contributions

Discussion



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.

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

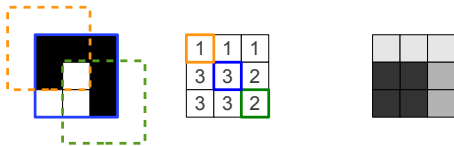
Conclusions and
future work

Contributions

Discussion

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 independance 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].

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

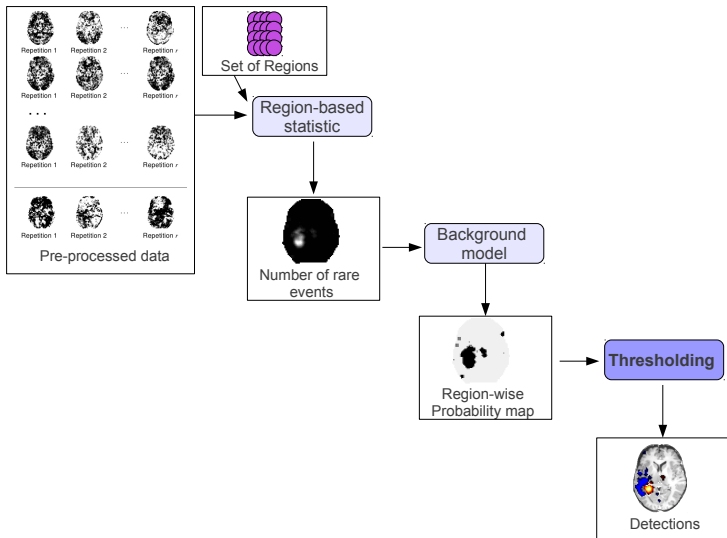
Methods

Results

Conclusions and
future work

Contributions

Discussion



A *contrario* approach: thresholding

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function
From group to
patient-specific
analyses

Contributions

Overview
Materials
Imaging protocol
Validation
State of the art
Heteroscedastic
GLM
Methods
Results
A contrario

Methods

Results

Conclusions and future work

Contributions
Discussion

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*

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function
From group to
patient-specific
analyses

Contributions

Overview
Materials
Imaging protocol
Validation

State of the art
Heteroscedastic
GLM

Methods
Results

A contrario

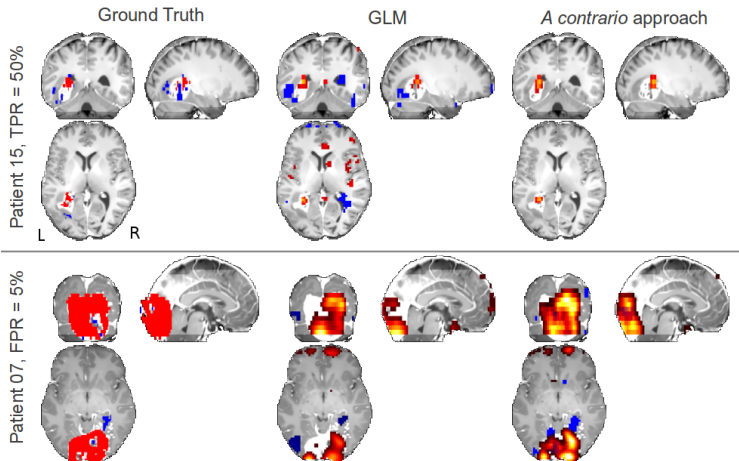
Methods

Results

Conclusions and
future work

Contributions

Discussion



Results: *a contrario*

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

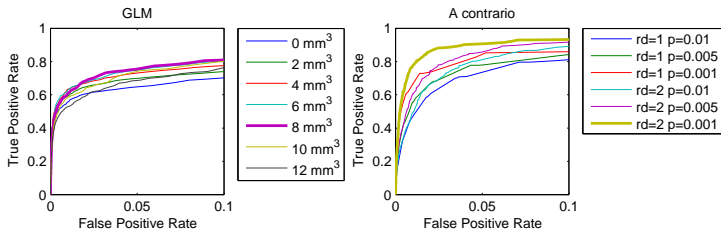
Methods

Results

Conclusions and future work

Contributions

Discussion



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

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	0.87

Area under the ROC curves

Results: *a contrario*

Checking the test validity

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

Methods

Results

A contrario

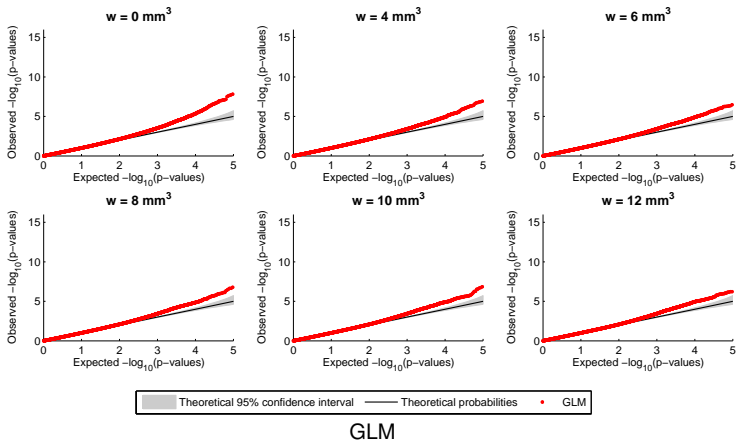
Methods

Results

Conclusions and future work

Contributions

Discussion



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

Results: *a contrario*

From Group to Patient-Specific Analysis of Brain Function

Camille Maumet

Context

Brain function

From group to patient-specific analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic GLM

GLM

Methods

Results

A contrario

Methods

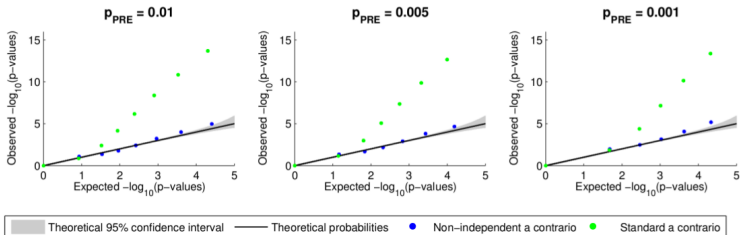
Results

Conclusions and future work

Contributions

Discussion

Checking the test validity



A contrario

Conclusion: *a contrario*

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

- ▶ 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.

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and
future work

Contributions

Discussion

Outline

Context

Contributions

Conclusions and future work

Contributions

Discussion

Contributions(1/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

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.

Contributions(1/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

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.

Contributions(1/2)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

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

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic

GLM

Methods

Results

A contrario

Methods

Results

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)

From Group to
Patient-Specific
Analysis of Brain
Function

Camille Maumet

Context

Brain function

From group to
patient-specific
analyses

Contributions

Overview

Materials

Imaging protocol

Validation

State of the art

Heteroscedastic
GLM

Methods

Results

A contrario

Methods

Results

Conclusions and future work

Contributions

Discussion

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