Introduction to MRI data processing

MaRBEL educational
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Who am I?

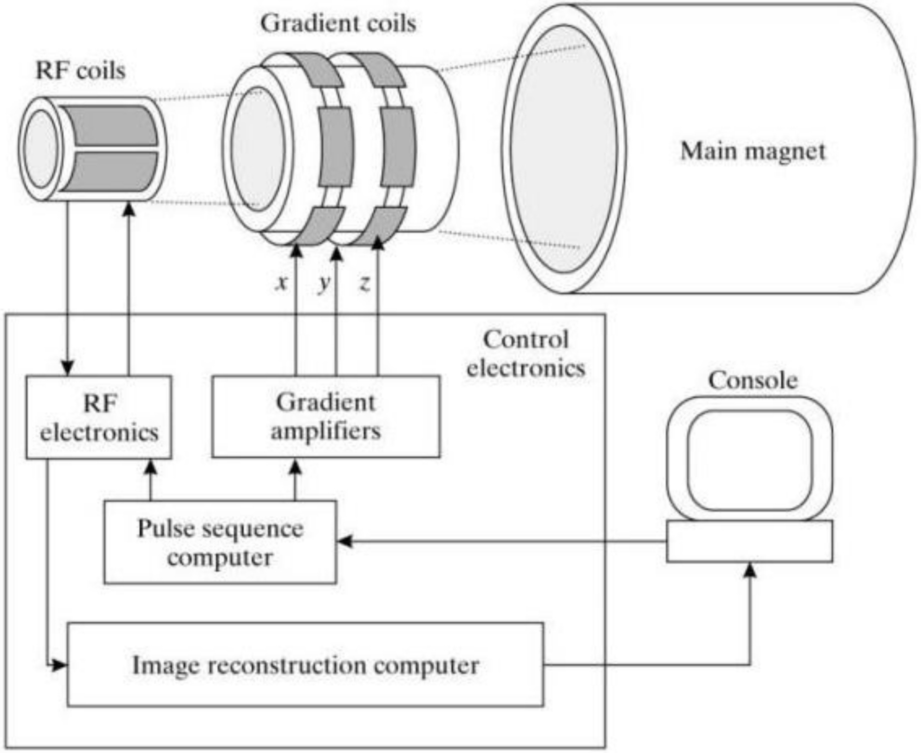
- Master in Electrical Engineering, then PhD. in Engineering
- Now FRS-FNRS Research Director & Professor
- Research and interest in “neuroimaging methods”
  $\rightarrow$ data processing of brain images (MRI and PET) and
  electro-physiological data (M/EEG)
- Linked to:
  - “GIGA CRC human imaging” research units
  - “GIGA in vivo imaging” technical platform.
  - Department of Electrical Engineering & Computer Science

Program

- MRI “flavours”
- MRI data processing
  - Within-/between-subject processing
  - Subject-/reference-space
  - Statistical inference
- “Vanilla fMRI protocol” example
- Take home message

MR scanner

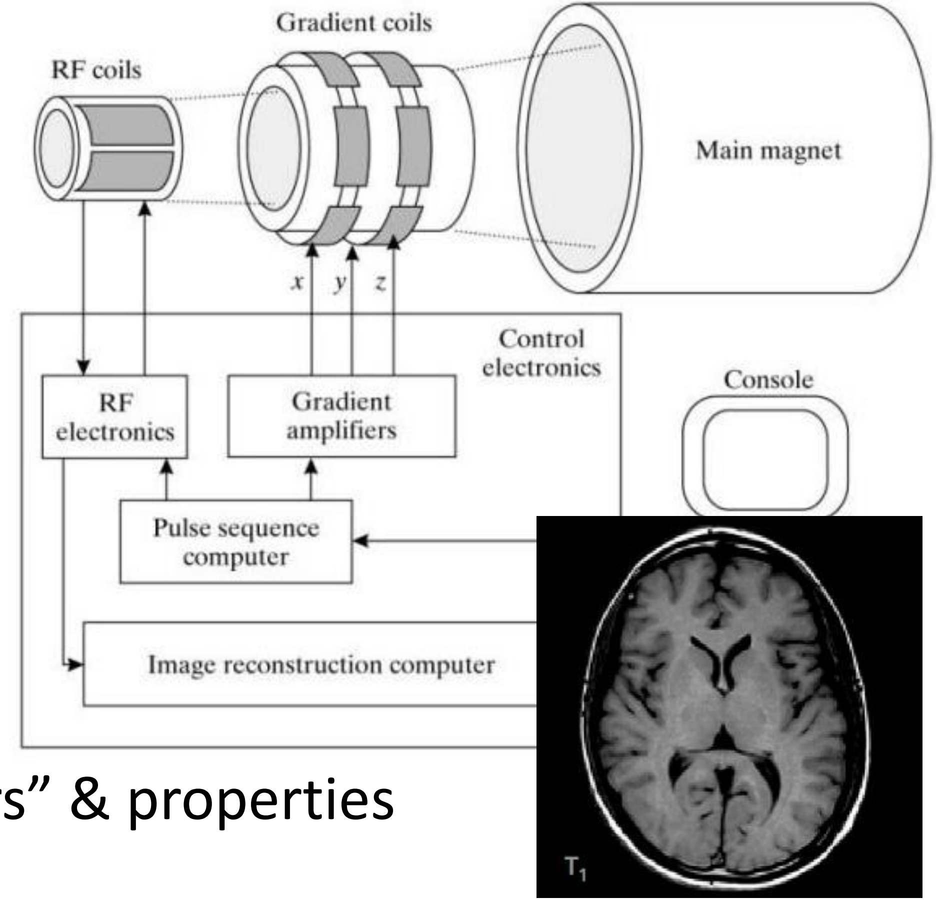
- big magnet
  → e.g. 1.5, 3 or 7T
- antenna, aka. RF coil
  → emit/receive RF signal
- gradient coils
  → small linear changes
- electronics & computer
  → control & image reconstruction



MR imaging

Image obtained according to

- *Pulse sequence*
  - RF emission & reception
    → signal *weighting*
  - linear magnetic gradient (in mT/m)
    → local variation of *frequency* & *phase*
    → spatial encoding
- *Image reconstruction*



➔ images with “different flavours” & properties

MRI "flavours"

Signal intensity "linked" to tissue properties

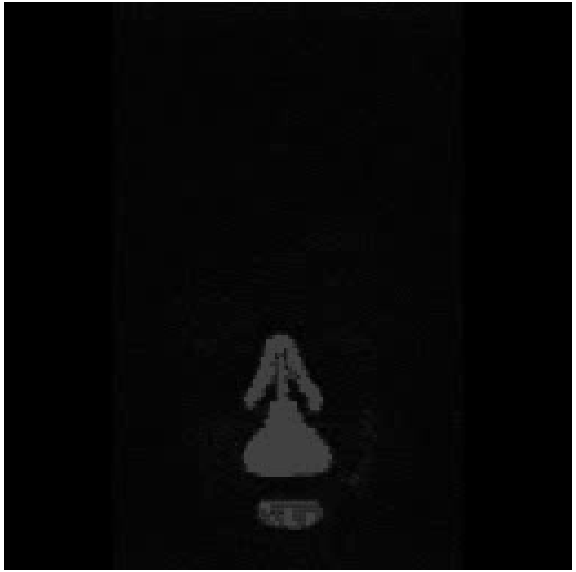
- Anatomical MRI
- Functional MRI
- Diffusion-weighted MRI
- Quantitative MRI
- CEST/QSM/spectroscopy/…

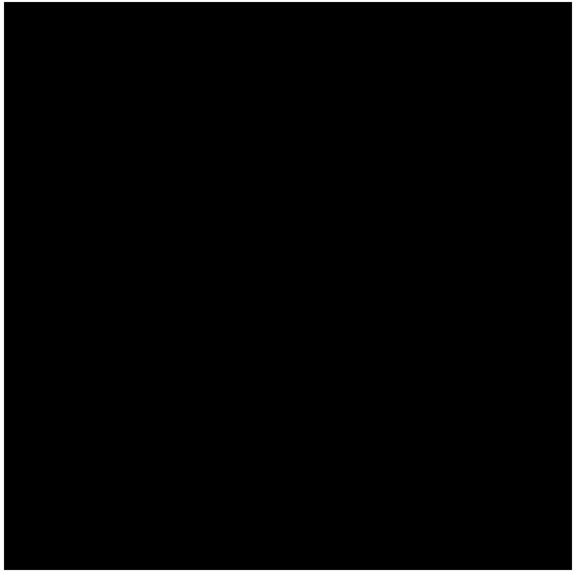
Anatomical MRI

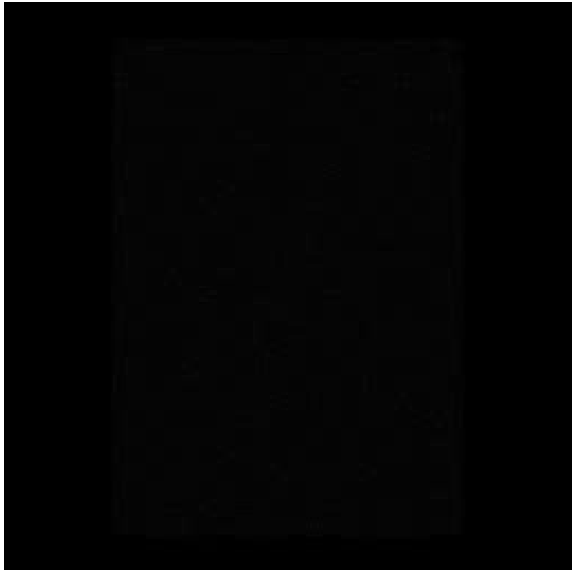
Characteristics (typical)

- Voxel size,
  - at 3T, 1mm $\rightarrow$ $1mm^3$
  - at 7T, .5-.8mm $\rightarrow$ $.25\text{-}.5mm^3$
- Acquisition time:
  a few minutes
- Contrast between GM, WM, CSF, “other tissues”

Anatomical MRI







Anatomical MRI

Characteristics (typical)

- Voxel size,
  - at 3T, ~1mm → ~$1mm^3$
  - at 7T, .5-.8mm → .25-.$5mm^3$
- Acquisition time: a few minutes
- Contrast between GM, WM, CSF, “other tissues”

Applications

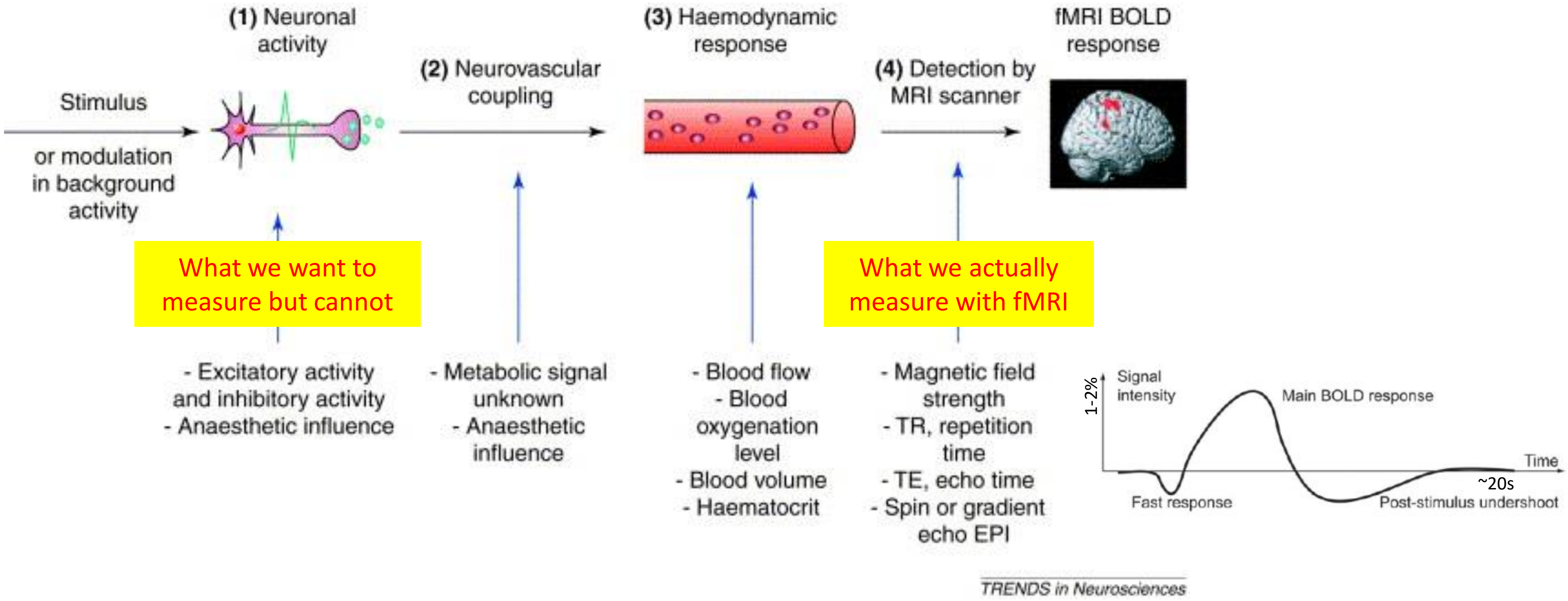
- Morphometric study
- Lesion detection
- Anatomical reference
- Inter-subject anatomical alignment
- …

Functional MRI

Characteristics (typical)

- Voxel size,
  - at 3T, 2-3mm → 8-27mm^3
  - at 7T, 1-2mm → 1-8mm^3
- Acquisition time, from 1 to 3 seconds/image (but continuous acquisition over 5-30 minutes)
- Signal intensity variation according to neuronal activation time course

Of neurons, blood & haemoglobin



Interpretation:

Image (slightly) brighter where & when (but delay!) neurons are active.

Arthurs & Boniface, 2002, *Trends in Neurosciences*

Functional MRI

Characteristics (typical)

- Voxel size,
  - at 3T, 2-3mm → $8\text{-}27mm^3$
  - at 7T, 1-2mm → $1\text{-}8mm^3$
- Acquisition time, from 1 to 3 seconds/image (but continuous acquisition over 5-10 minutes)
- Signal intensity variation according to neuronal activation time course

Applications

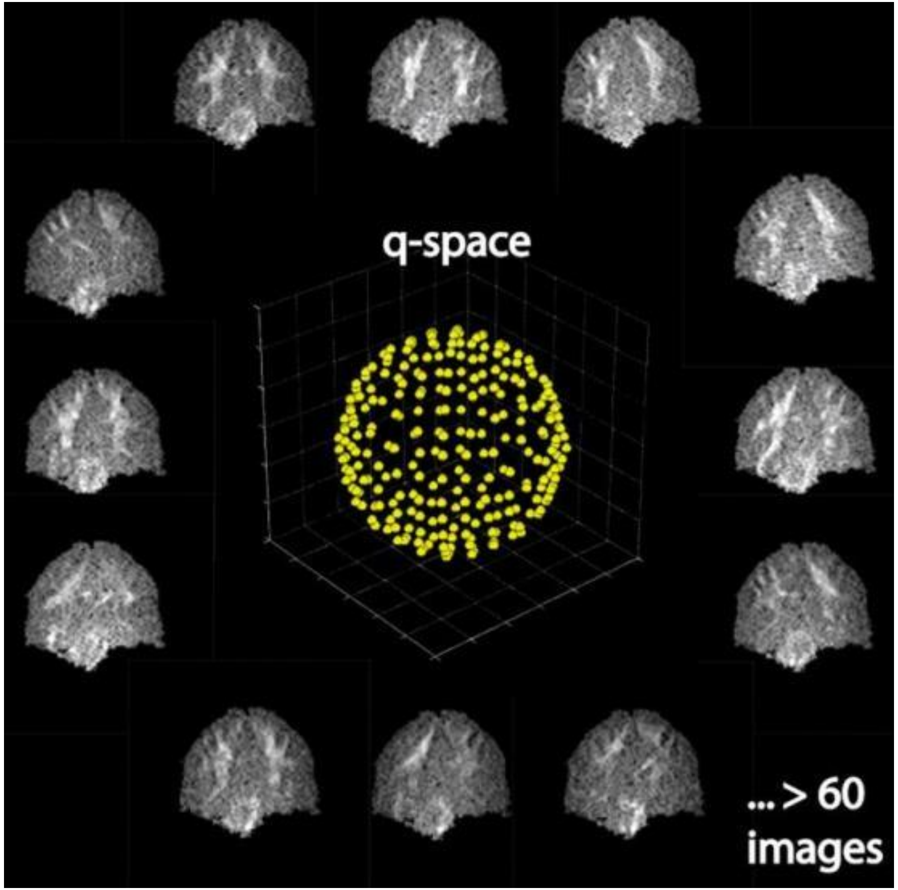
- Activation localisation
- Experimental manipulation of activation (age, fatigue, learning,…)
- Functional/effective connectivity analysis
- Brain activity decoding
- …

Diffusion-weighted MRI

Characteristics (typical)

- Voxel size,
  at 3T & 7T, 2-3mm → 8-27mm^3
- Acquisition time, from 1 to 3 seconds/image (but need 20+ images)
- Signal intensity decrease according to diffusion of (free) water in direction “poked”

Diffusion-weighted MRI



https://radiopaedia.org/articles/diffusion-weighted-imaging-2

Diffusion-weighted MRI

Characteristics (typical)

- Voxel size,
  at 3T & 7T, 2-3mm $\rightarrow$ 8-27mm^3
- Acquisition time, from 1 to 3 seconds/image (but need 20+ images)
- Signal intensity variation according to diffusion of (free) water in direction “poked”

Applications

- Model water diffusion,
  i.e. proxy to axon orientation & density
- WM properties, e.g. tissue integrity
- Anatomical WM connectivity
- Correlation and group comparison analysis
- …

Quantitative MRI

Characteristics (typical)

- Voxel size,
  - at 3T, .8-1mm $\rightarrow$ .5-1mm^3
  - at 7T, .5-.8mm $\rightarrow$ .13-.5mm^3
- Acquisition time: 10 to 30 minutes (for whole protocol)
- Multiple series of
  - T1-/PD-/MT-weighted images
  - B0/B1 maps

  ➔ quantification of tissue properties

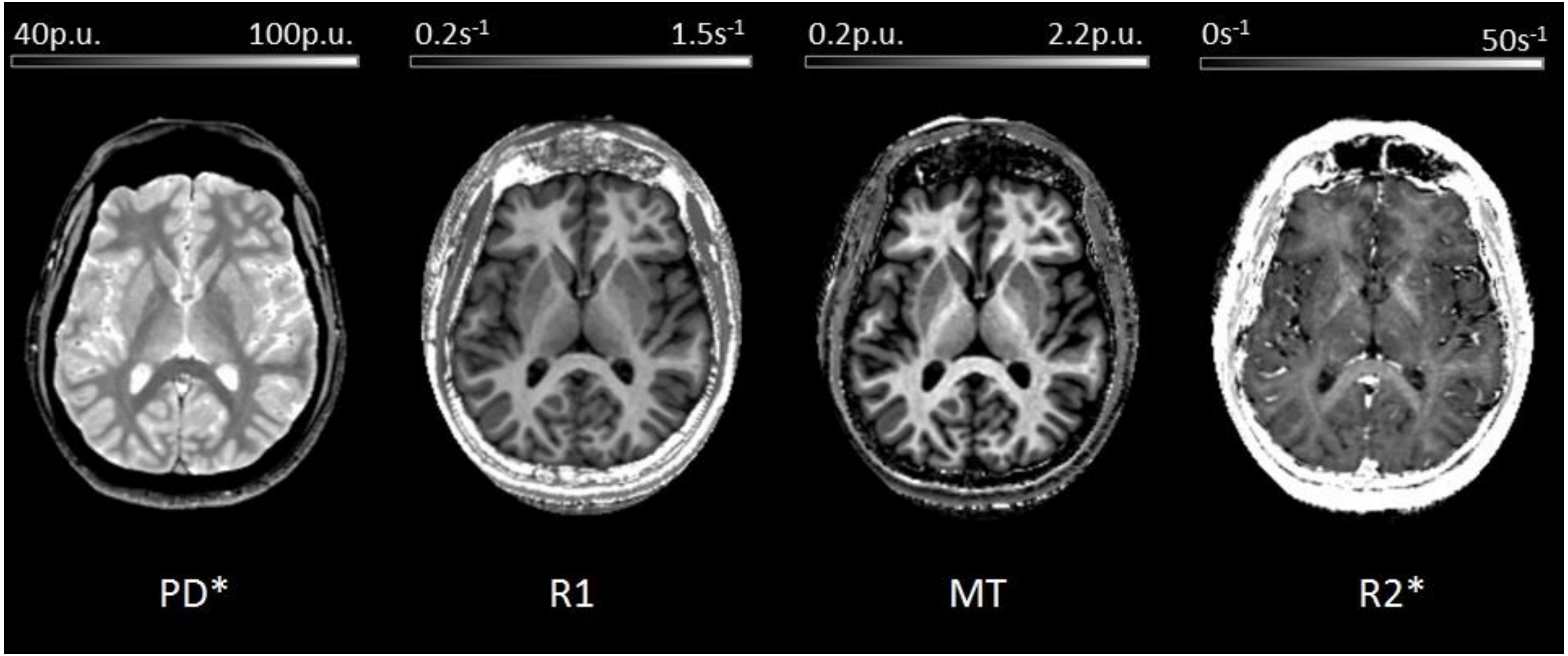
Quantitative MRI interpretation

Water Content

Water Content; Macromolecules, e.g. myelin; Iron

Macromolecules e.g. myelin

Iron



Weiskopf *et al.*, https://doi.org/10.1038/s42254-021-00326-1

Quantitative MRI

Characteristics (typical)

- Voxel size,
  - at 3T, .8-1mm → .5-1mm^3
  - at 7T, .5-.8mm → .13-.5mm^3
- Acquisition time: 10 to 30 minutes (for whole protocol)
- Multiple series of
  - T1-/PD-/MT-weighted images
  - B0/B1 maps

  ➔ quantification of tissue properties

Applications

- Tissue property analysis, e.g. correlation, difference, longitudinal changes,…
- Lesion detection & characterization
- Morphometric study
- Multi-scanner/centre study
- …

Other sequences…

- Chemical Exchange Saturation Transfer (CEST) MRI
  ➔ molecular/metabolite concentration mapping
- Quantitative Susceptibility Mapping (QSM) MRI
  ➔ iron deposit & calcification mapping
- MRI Spectroscopy
  ➔ (chemical) metabolism & other nuclei mapping
- …

Program

- MRI “flavours”
- MRI data processing
  - Within- /between-subject processing
  - Subject-/reference-space
  - Statistical inference
- “Vanilla fMRI protocol” example
- Take home message

Research in neuroscience

Neuroscientific question about the brain

- Acquire data from “many” subjects
- Grouping
  - single group ?
    ➔ within group activation, regression with continuous variable,…
  - 2 or more groups ? ➔ group comparisons, regression, interaction,…
- Sessions
  - 1 session ➔ cross-sectional study
  - sessions at t_0, t_1, t_2,… ➔ longitudinal study

Within AND between subject processing

Within-/between-subject

Within-subject, i.e. using data from a single-subject

- Spatial processing:

SS

  - Image alignment & "coregistration"
  - Artifacts detection & correction
  - Segmentation & "spatial normalisation" (=warp into reference space)

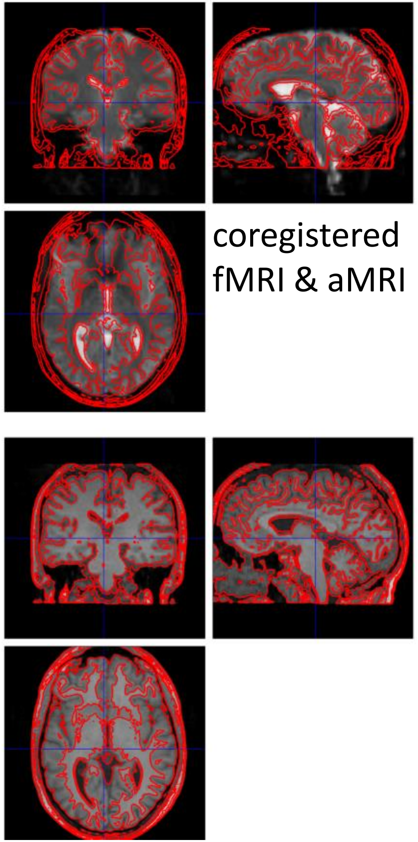
SS or RS

  - smoothing
- Modelling
  - Create parametric "map of interest"
  - Statistical inference
- **In subject-space (SS) , reference-space (RS) or either one.**

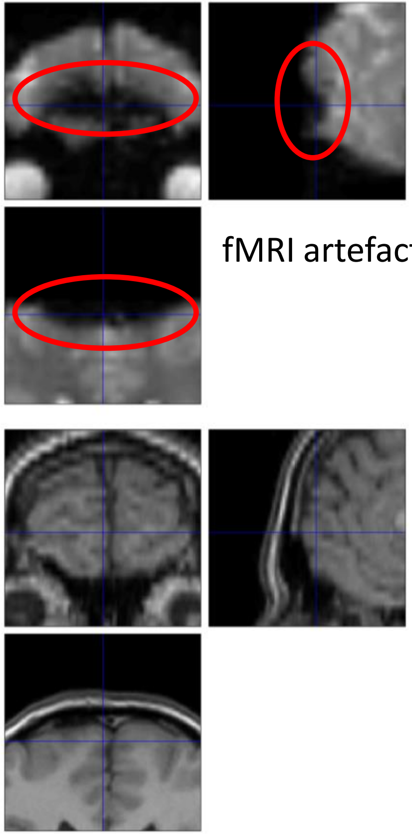
Spatial processing: within-subject

- "Rigid-body" transformation
  - Intra-modality, e.g. fMRI series, *realignment*
  - Inter-modality, e.g. (mean) fMRI and aMRI, *coregistration*
- Elastic transformation
  - Segmentation & "spatial normalisation" → typically aMRI
  - Image deformation correction, i.e. "unwarping" → fMRI & DW-MRI
    ("Field mapping" or "Top-Up" but needs extra data!)
- Smoothing, i.e. reduce variability → maps for statistical analysis

Spatial processing: within-subject

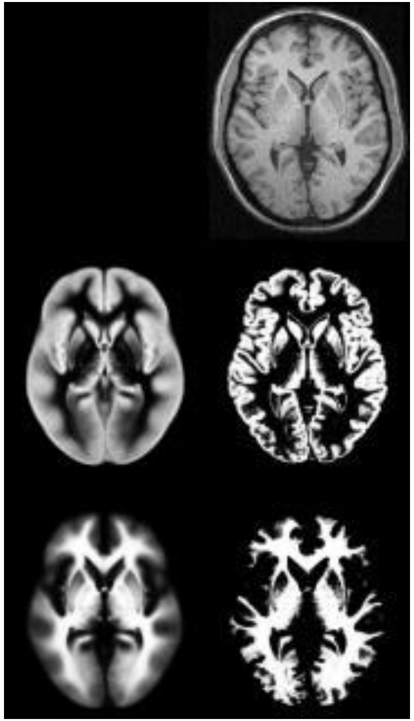


coregistered fMRI & aMRI

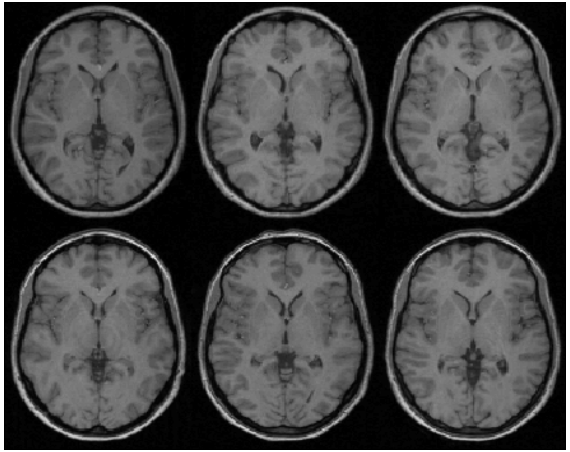


fMRI artefact

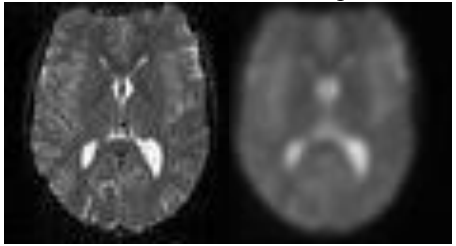
1 subject's normalized & segmented aMRI + TPMs



6 subjects' normalized aMRI



fMRI smoothing



Within-/between-subject

Between-subject, i.e. using data from all subjects

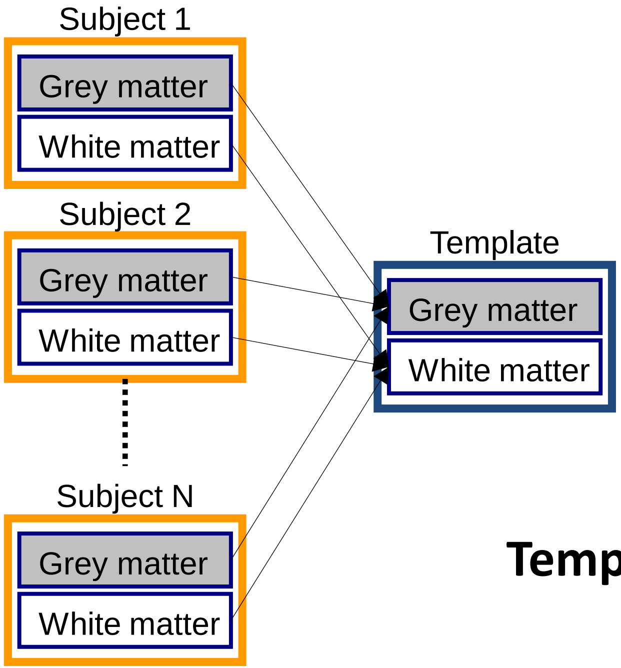
- Spatial processing
  - Warping individual maps into “group average” reference space
- Modelling
  - Group-level model
  - Statistical inference
- **In reference-space (RS)**

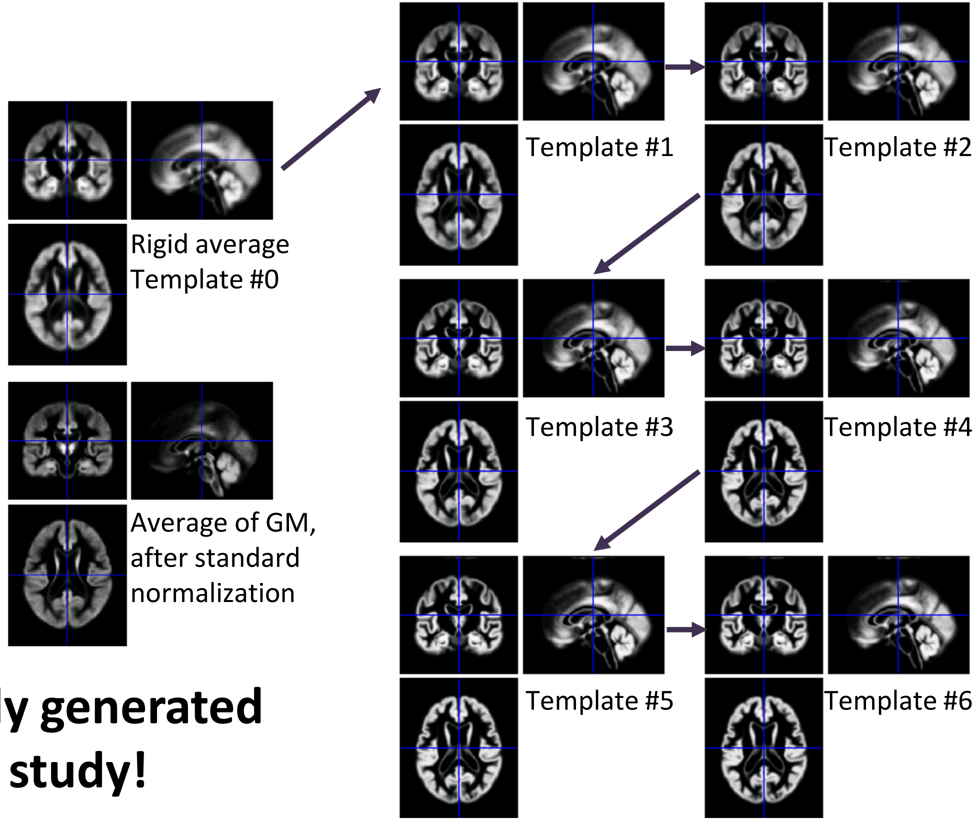
  → Atlas and standardized coordinates

  → Multi-subject analysis

Spatial processing: between-subject

- More flexible elastic , i.e. diffeomorphic, transformation
  → typically segmented aMRI
  for *VBM analysis*





Template implicitly generated from data in study!

Modelling: within-subject fMRI

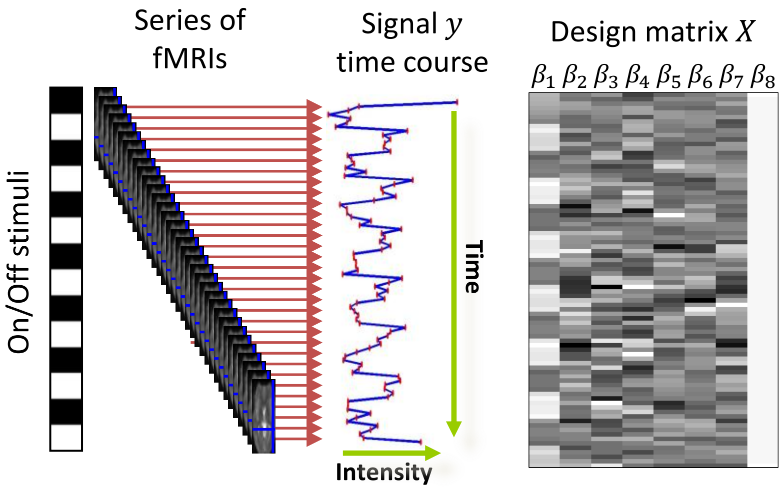
fMRI time-series modelling, i.e. General Linear Model (GLM)

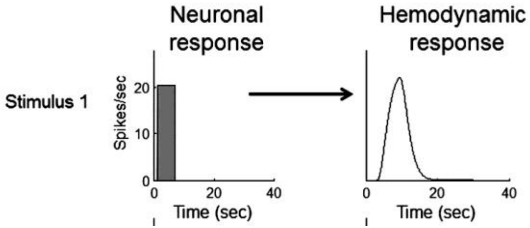
- Model the signal (variance) based on $y = X\beta + e$
  - experimental protocol, e.g. stimuli, conditions, actions,…
  - confounding effects, e.g. haemodynamic response, movement,…
- Model the noise distribution C_i : noise level + autocorrelation signal $e_i \sim N(0, C_i)$
- Estimate the model parameters $\hat{\beta}$
- Build **effect of interest** $\longrightarrow$ linear contrast of parameters $c^T\hat{\beta}$
- Statistical inference of contrast value, with t-/F-test
  $\longrightarrow$ **objectively detect “effect of interest”**

Modelling: within-subject fMRI

$$y = X\beta + e$$

$$e_i \sim N(0, C_i)$$



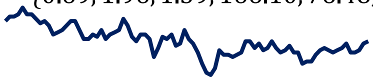


$$\hat{\beta} = (X^T C^{-1} X)^{-1} X^T C^{-1} y$$

$$\hat{\beta} \sim N(\beta, \sigma^2 (X^T C^{-1} X)^{-1})$$

$\hat{\beta}_1 = 3.9831$

$\hat{\beta}_{2-7} = \{0.69, 1.96, 1.39, 166.10, 76.48, -64.82\}$



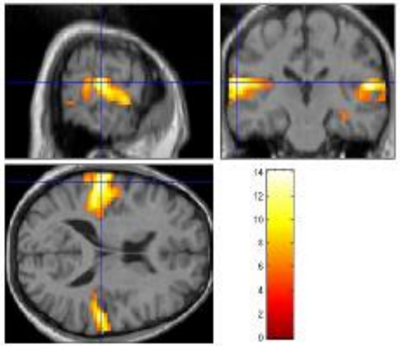
$\hat{\beta}_8 = 131.0040$

$\varepsilon =$

T-test on effect of interest

$$t = \frac{c^T \hat{\beta}}{\sqrt{\mathrm{var}(c^T \hat{\beta})}}$$

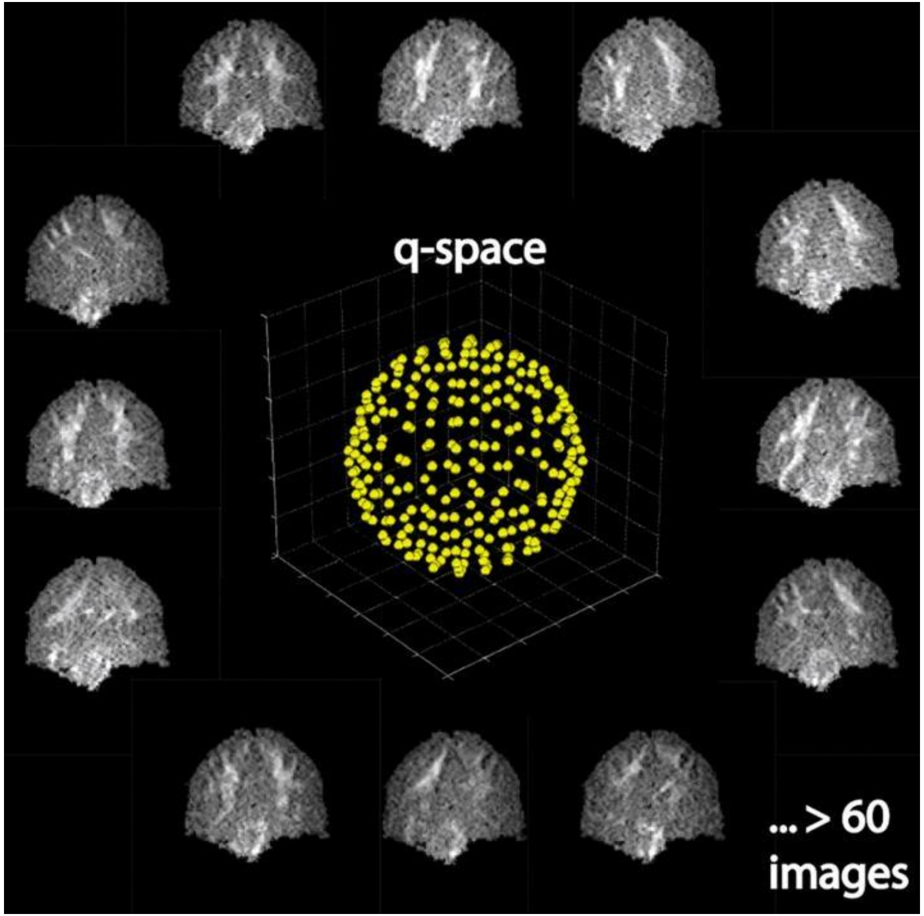
Height threshold T = 3.2057 {p<0.001}



Diffusion-weighted MRI

20+ images acquired

- No gradient = reference signal
- With gradient to dephase-rephase signal
  ➔ signal loss due to water-diffusion
- 1 image = 1 diffusion direction ‘poked’

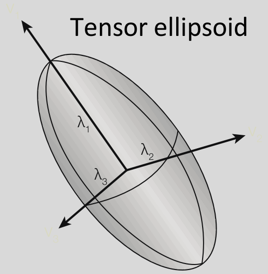


https://radiopaedia.org/articles/diffusion-weighted-imaging-2

Modelling: within-subject DW-MRI

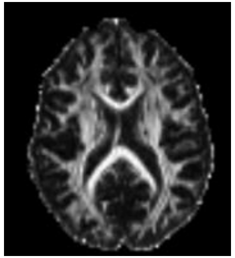
Fit tensor model to DWI data, i.e. **DTI**

- 6 parameters per voxel, i.e. 3D ellipsoid



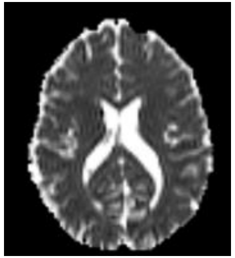
$$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

Fractional anisotropy



Reflects directionality of diffusion

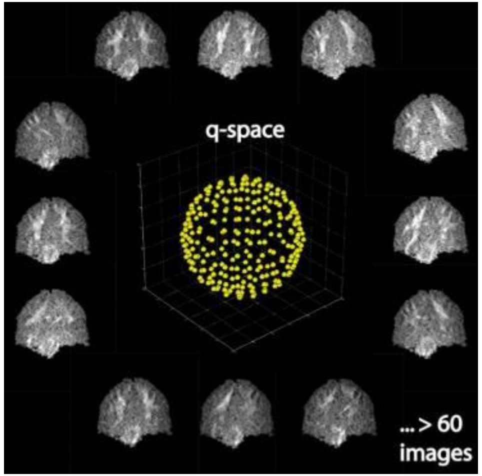
Mean diffusivity

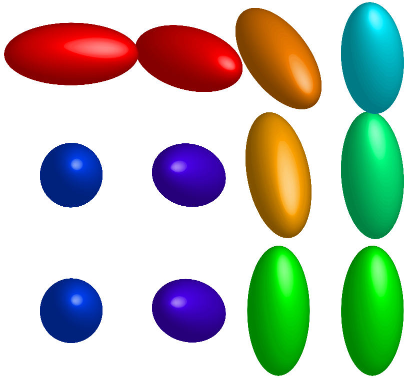


Reflects strength of diffusion

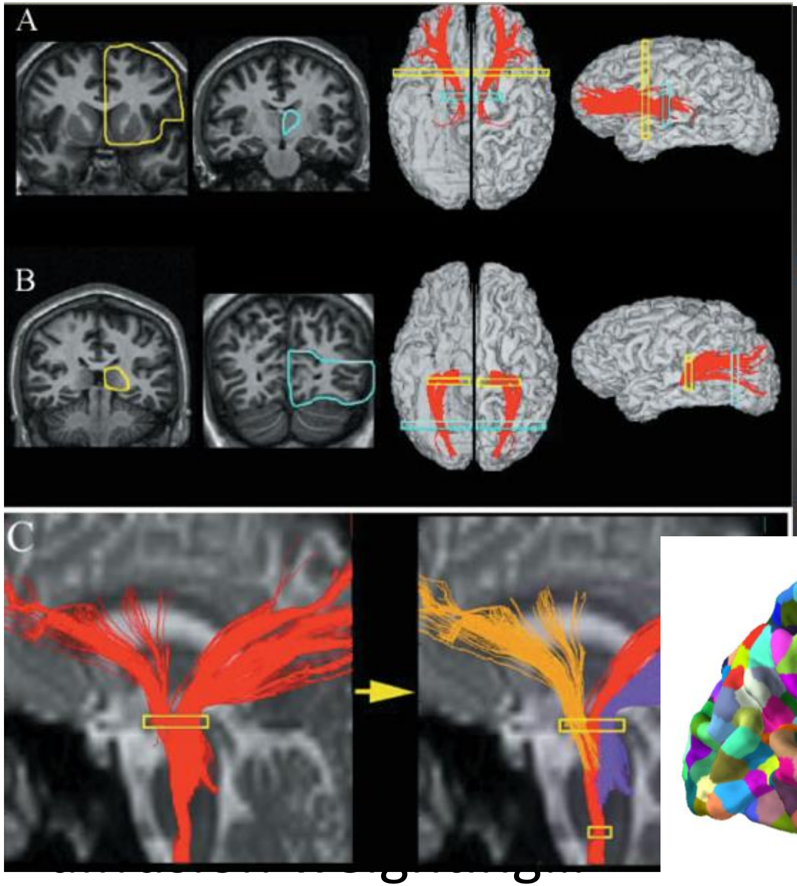
- Derive scalar map(s)
  ➔ “interpretable” values

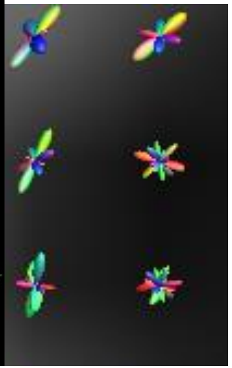
- Fiber tracking

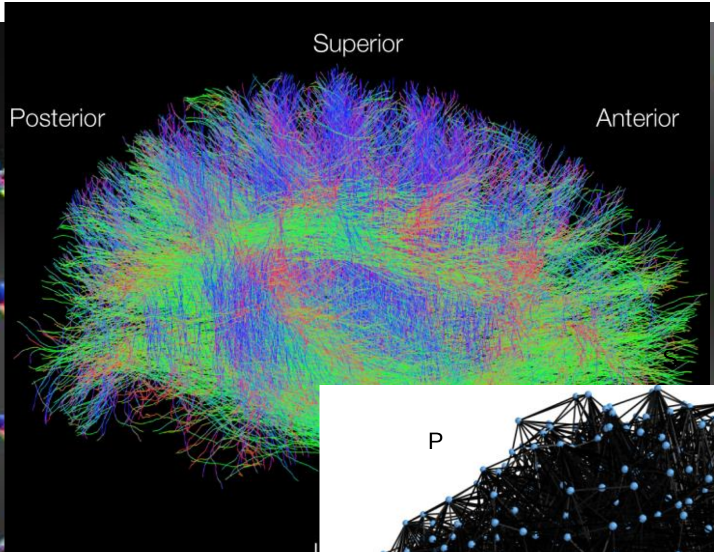


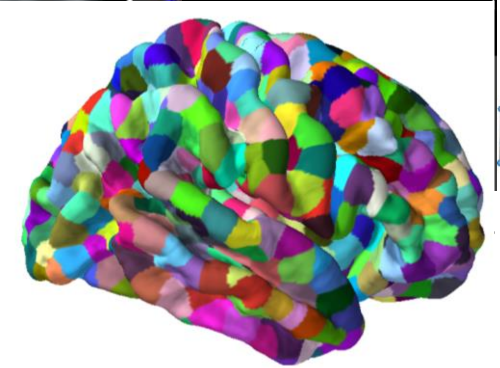


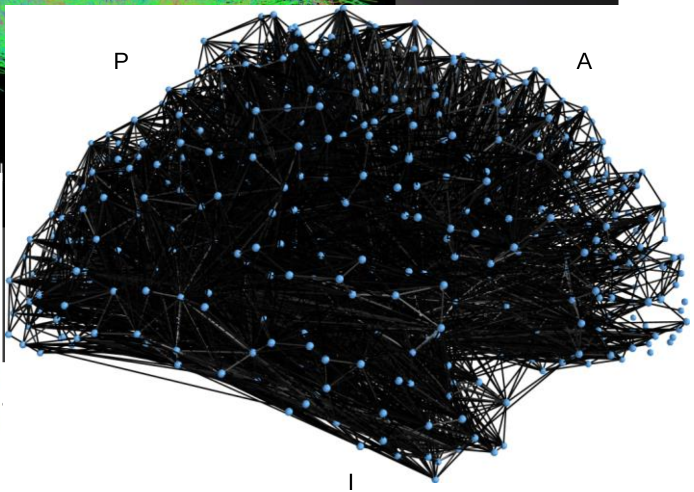
Fiber orientation distributions & connectomics





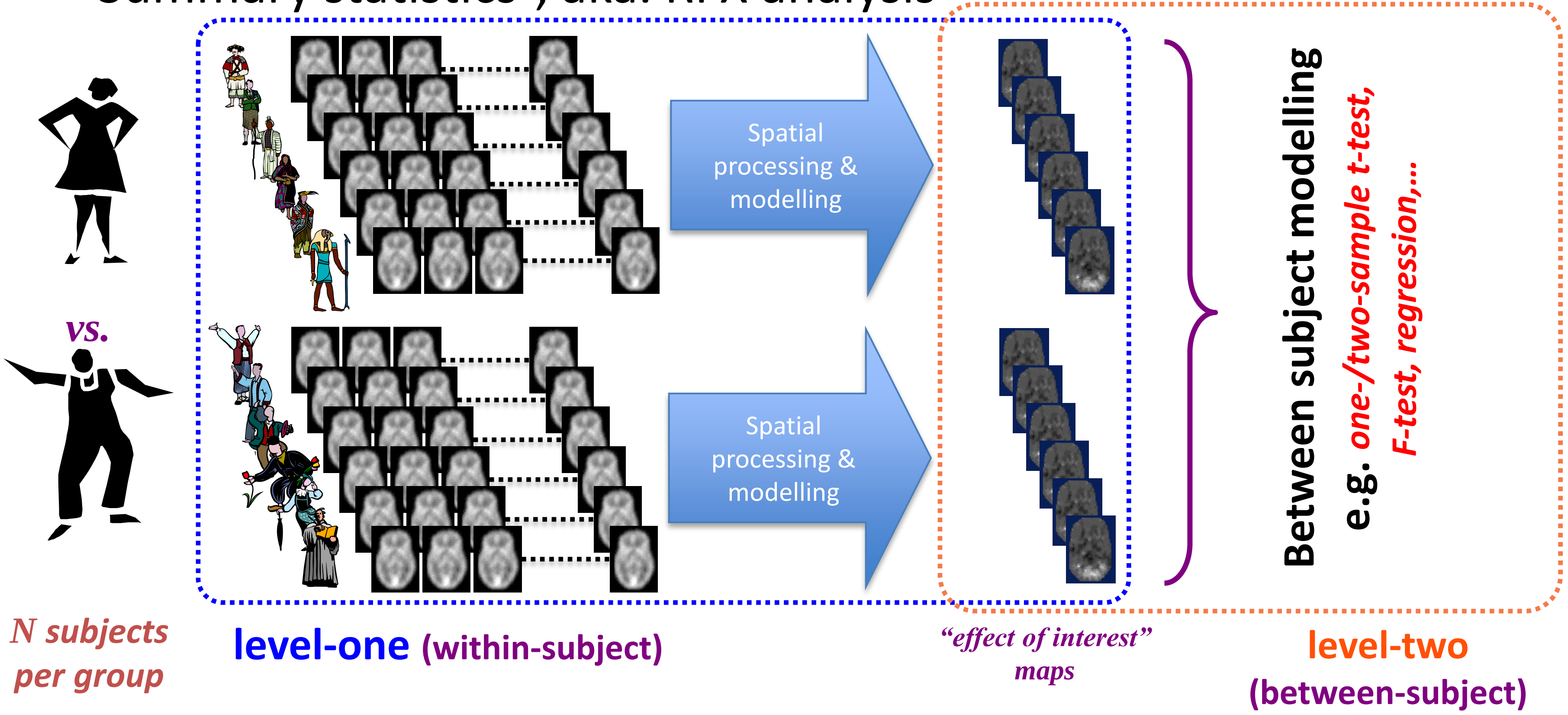




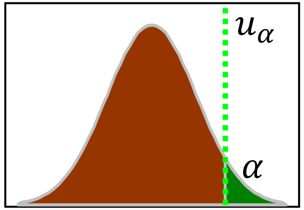


Modelling: between-subject analysis

"Summary statistics", aka. RFX analysis



Statistics: hypothesis testing & inference



Null Distribution of T

$$t = \frac{c^T\hat{\beta}}{\sqrt{\mathrm{var}(c^T\hat{\beta})}}$$

- Significance level α :

  Acceptable false positive rate α

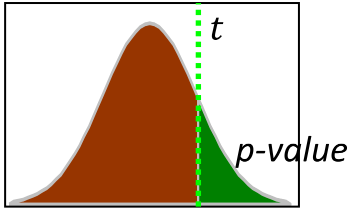
  ⇨ threshold u_α

  Threshold u_α controls the false positive rate $\alpha = p(T > u_\alpha | H_0)$

- Conclusion about the hypothesis:

  Reject the null hypothesis H_0 if $t > u_\alpha \rightarrow$ favour the alternative hypothesis H_A

- p-value: $p(T > t | H_0)$
  - *evidence against* H_0.
  - "chance of observing value more extreme than t under H_0.

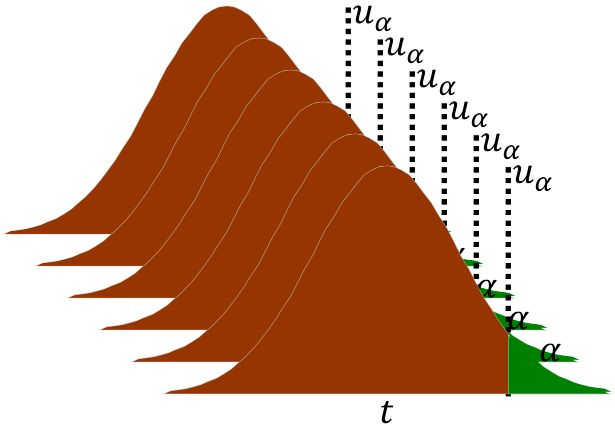


Null Distribution of T

$$y = X\beta + e$$

$$e \sim \mathcal{N}(0, C)$$

Statistics: multiple comparison problem



With 100000 voxels & $\alpha = .05$

$\Rightarrow$ **5000 false positive voxels**.

Need to

- define a H_0 for a *collection of tests*
- use *corrected p-values*.

Existing solutions

- "Family-wise error rate" (**FWER**) & "False discovery rate" (**FDR**)
- Should account for image smoothness, i.e. Bonferroni too conservative!
- Parametric vs non-parametric approaches

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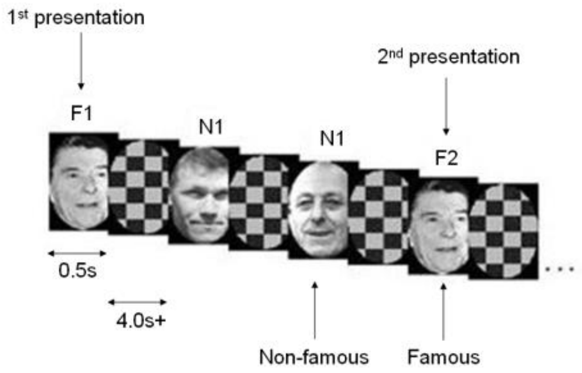
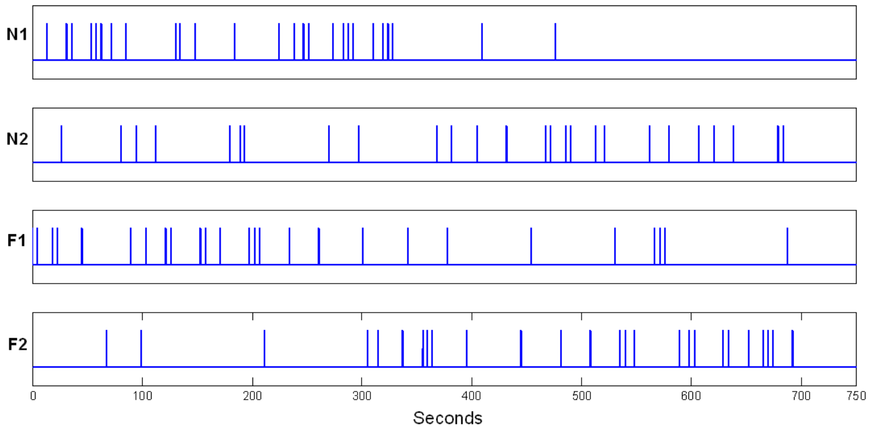
“Vanilla fMRI protocol” example



- 2x2 factorial design:
  - “famous” (F) vs “non-famous” (N) faces
  - first (1) vs repeated (2) presentation



- Timing of the presentations:
  - Same task for all subjects
- 12 subjects
  - ~350 fMRIs, TR = 2s
  - 1 anatomical MRI

https://www.fil.ion.ucl.ac.uk/spm/data/face_rep/

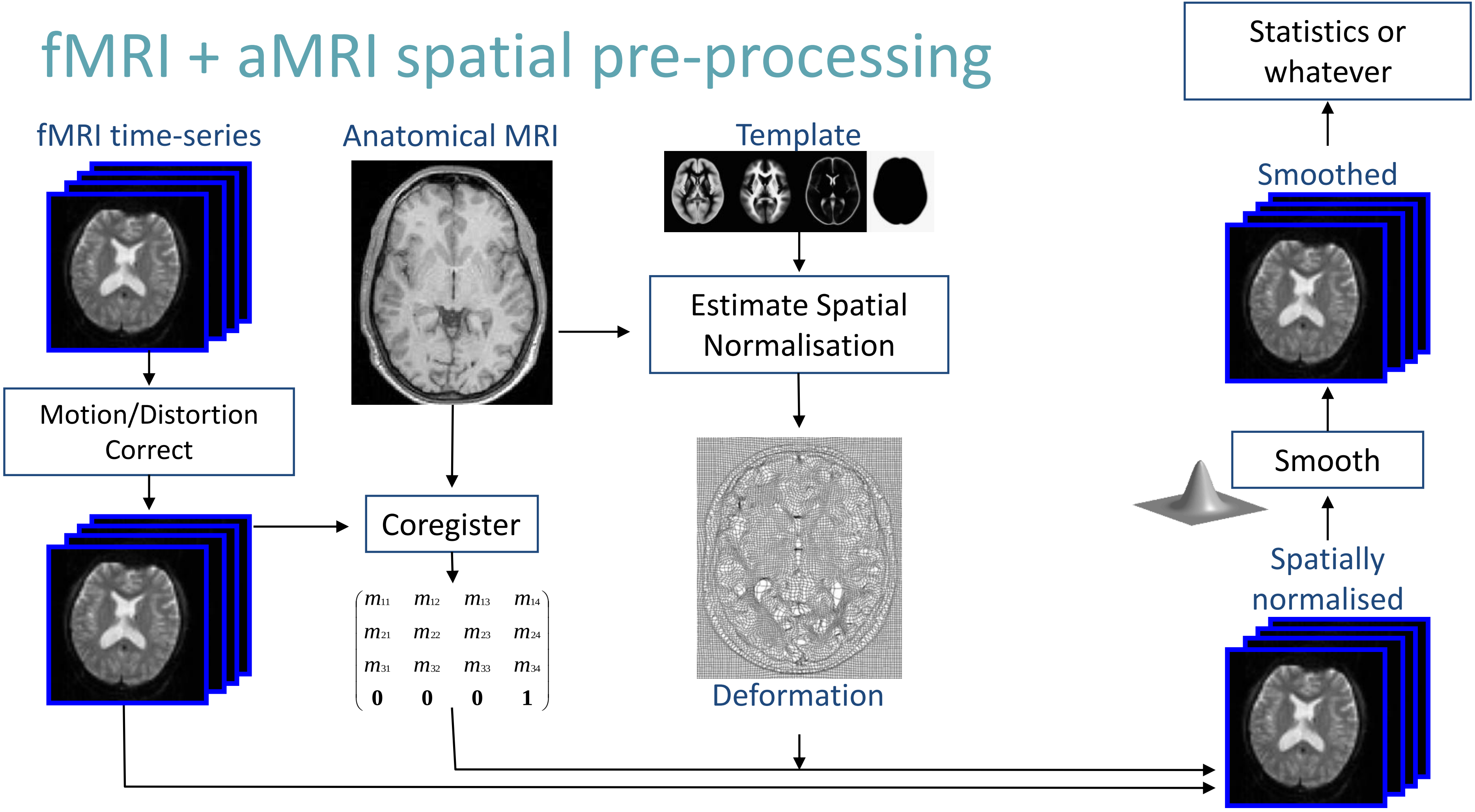
Spatial processing: within-subject

- Head movement during ~12 minutes of fMRI acquisition
  ➔ "realignment"
- Match anatomical and (mean) functional MRI
  ➔ "coregistration"
- Bring all subjects brain image into same reference space
  ➔ "spatial normalization", aka. "warping"
- Variance reduction
  ➔ "smoothing"

Other possible steps:

slice time correction, fMRI artefact correction, diffeomorphic warping,…

fMRI + aMRI spatial pre-processing



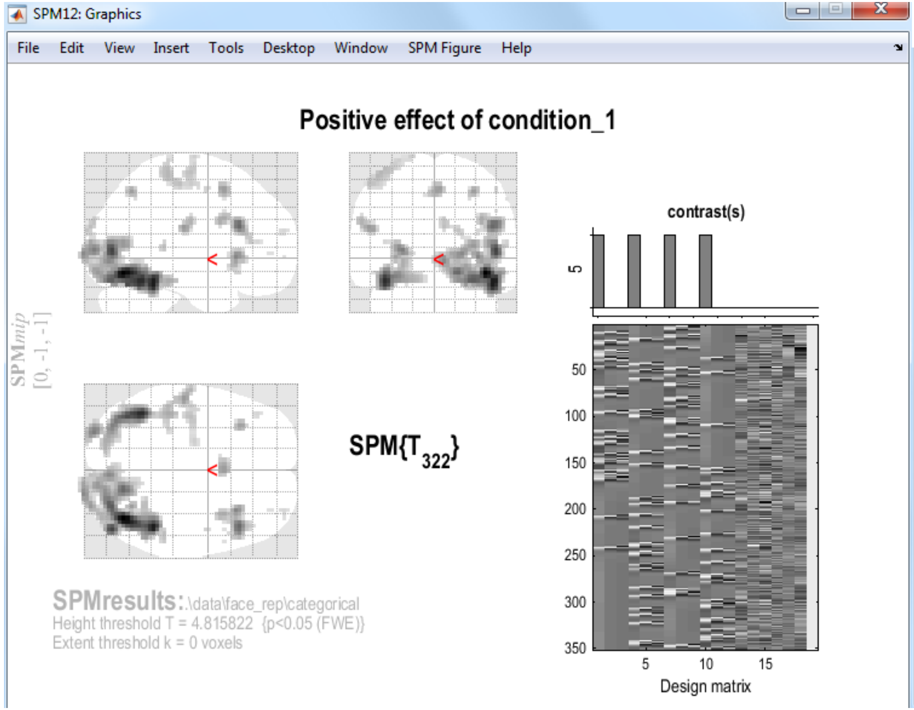
Statistical analysis: within-subject, i.e. FFX

- Experimental design through “General Linear Model”, i.e. model the 4 “conditions” (N1, N2, F1, F2) + movement parameters
- Contrast definition to test effect of interest at subject level

Single subject's activation

Contrast: *Faces > Baseline*

i.e. "which part of the brain lights up when I see a face?"



Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_\equiv)$	p_{uncorr}			
0.000	18	0.000	0.000	1171	0.000	0.000	0.000	14.76	Inf	0.000	39	-70	-13
						0.000	0.000	13.35	Inf	0.000	45	-46	-19
						0.000	0.000	11.60	Inf	0.000	48	-79	5
		0.000	0.000	380	0.000	0.000	0.000	12.65	Inf	0.000	-42	-55	-19
						0.000	0.000	11.17	Inf	0.000	-39	-67	-22
						0.000	0.000	7.14	6.88	0.000	-42	-34	-19
		0.000	0.000	144	0.000	0.000	0.000	9.97	Inf	0.000	45	23	23
						0.000	0.000	7.08	6.82	0.000	36	11	29
		0.000	0.000	79	0.000	0.000	0.000	9.00	Inf	0.000	-27	-94	5
		0.000	0.000	96	0.000	0.000	0.000	8.72	Inf	0.000	33	20	-1
						0.001	0.028	5.68	5.54	0.000	54	17	2
						0.003	0.069	5.47	5.34	0.000	51	20	-13
		0.000	0.000	51	0.000	0.000	0.000	7.86	7.51	0.000	-54	-22	23
						0.000	0.000	6.72	6.50	0.000	-60	-16	26
		0.000	0.000	44	0.000	0.000	0.000	7.71	7.38	0.000	0	11	50
		0.000	0.001	21	0.001	0.000	0.000	7.60	7.28	0.000	30	-64	50
		0.000	0.000	27	0.000	0.000	0.000	7.45	7.15	0.000	-33	23	-1
		0.000	0.000	148	0.000	0.000	0.000	6.59	6.38	0.000	-45	-34	65
						0.000	0.002	6.26	6.07	0.000	-39	-16	65
						0.000	0.002	6.21	6.03	0.000	-54	-25	56
		0.000	0.004	15	0.002	0.000	0.002	6.27	6.08	0.000	51	-37	8
		0.006	0.162	3	0.126	0.003	0.079	5.44	5.31	0.000	48	-4	53
		0.002	0.056	6	0.037	0.006	0.139	5.30	5.19	0.000	33	59	20

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.82, p = 0.000 (0.050)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 1.337
Expected number of clusters, <c> = 0.05
FWEp: 4.816, FDRp: 5.581, FWEc: 1, FDRc: 15

Degrees of freedom = [1.0, 322.0]
FWHM = 10.7 10.7 10.3 mm mm mm; 3.6 3.6 3.4 {voxels}
Volume: 1612683 = 59729 voxels = 1229.6 resels
Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 43.44 voxels)
Page 1

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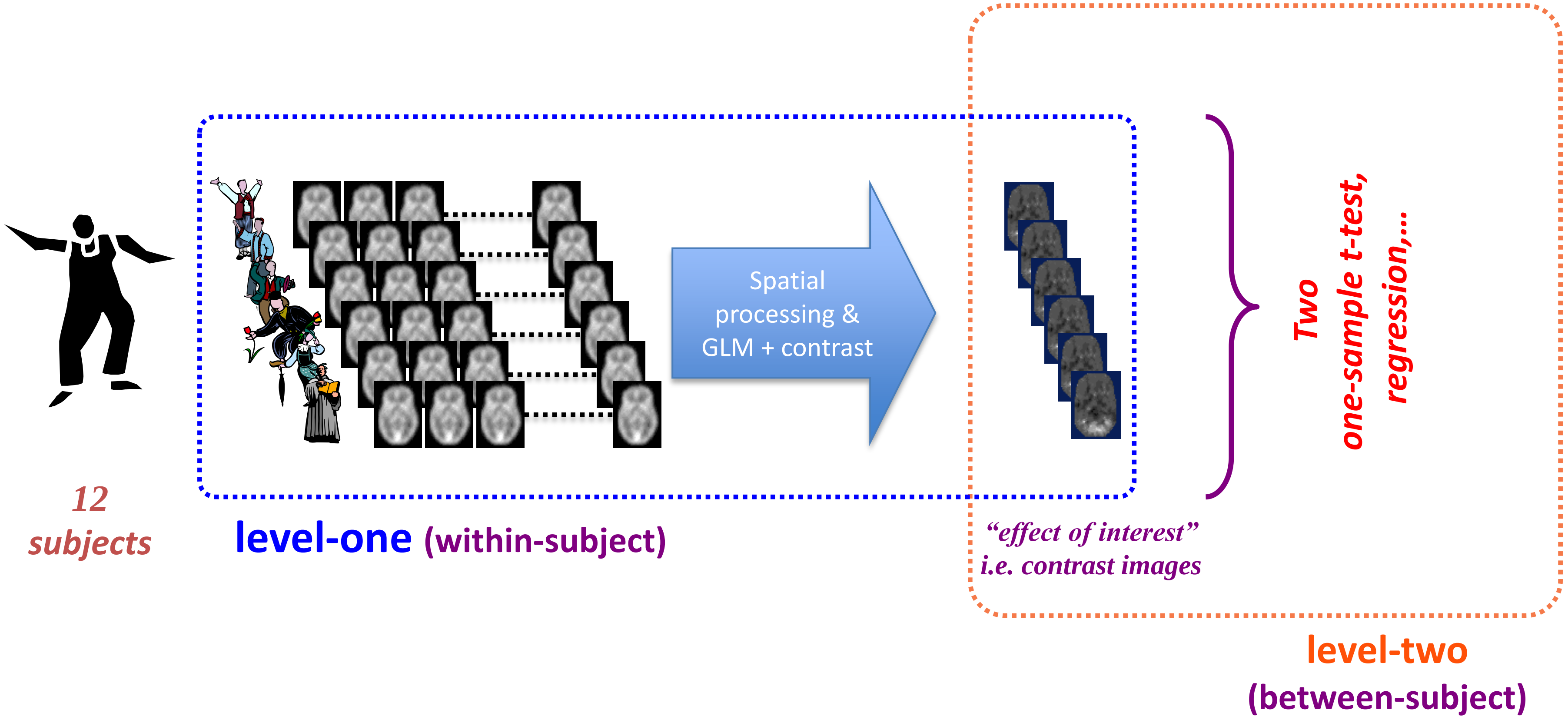
Statistical analysis: between-subject, i.e. RFX

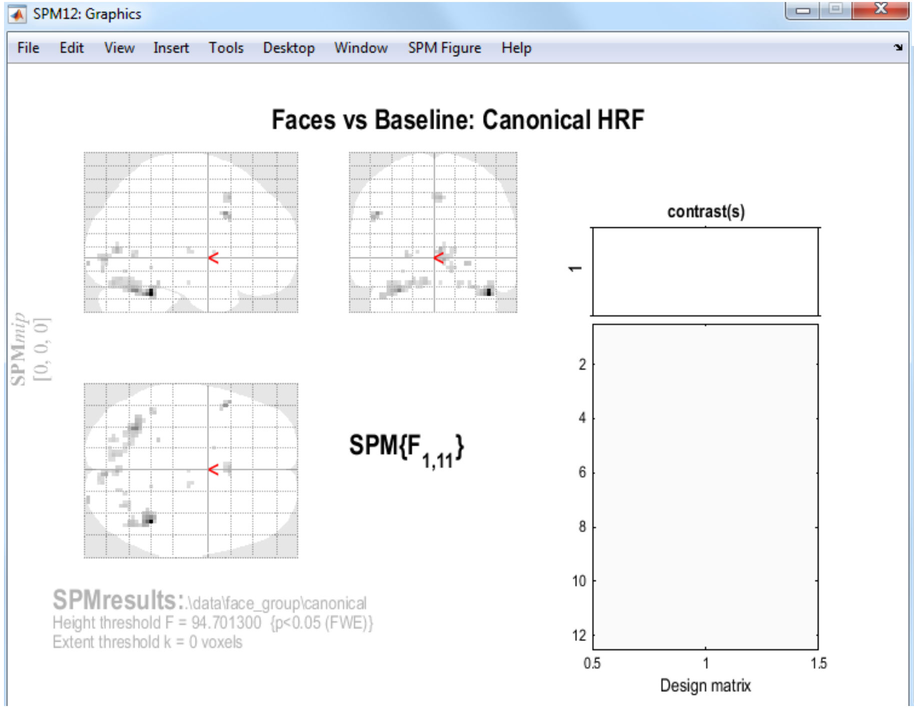
- Experimental design through "General Linear Model", i.e. model the 4 "conditions" (N1, N2, F1, F2) + movement parameters
- Contrast definition to test effect of interest at subject level
- Group-level analysis, i.e. "Random Effect" analysis
  - Summarize effect of interest at subject level, i.e. contrast of interest
  - Group-level 1-sample t-test
- Classical inference with t-/F-test
- Correction for "multiple comparison problem"

Group-level analysis, i.e. RFX



Group-level activation

- 12 subjects, with “*Faces* > *Baseline*” contrast
- 1-sample t-test model, no regressor



Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm	mm	mm
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	F	$(Z_{\equiv})$	p_{uncorr}			
0.000	17	0.000	0.000	45	0.000	0.000	0.036	547.52	6.36	0.000	42	-48	-30
						0.003	0.497	160.81	5.28	0.000	45	-63	-24
		0.000	0.000	72	0.000	0.000	0.246	277.52	5.78	0.000	-30	-60	-27
						0.006	0.535	144.80	5.18	0.000	-9	-78	-21
						0.011	0.575	127.99	5.06	0.000	-18	-66	-21
		0.000	0.000	8	0.000	0.000	0.246	251.67	5.69	0.000	-48	12	33
		0.000	0.000	31	0.000	0.001	0.381	192.97	5.45	0.000	6	-84	-3
						0.002	0.381	187.35	5.42	0.000	3	-75	6
						0.014	0.610	122.01	5.01	0.000	12	-87	-12
		0.000	0.000	14	0.000	0.003	0.497	166.76	5.31	0.000	3	15	45
		0.003	0.028	2	0.021	0.004	0.535	152.29	5.22	0.000	24	-99	-6
		0.003	0.028	2	0.021	0.007	0.535	140.56	5.15	0.000	-21	-42	-21
		0.000	0.000	7	0.000	0.007	0.535	139.89	5.14	0.000	-45	-48	-33
		0.000	0.001	5	0.001	0.008	0.535	137.04	5.12	0.000	-24	-63	0
		0.000	0.000	7	0.000	0.008	0.535	135.44	5.11	0.000	30	-69	-24
		0.000	0.001	5	0.001	0.014	0.610	121.89	5.01	0.000	-21	-78	-24
		0.012	0.088	1	0.088	0.021	0.766	112.16	4.93	0.000	15	-48	-9
		0.000	0.001	5	0.001	0.022	0.766	111.11	4.92	0.000	18	-75	-21
		0.012	0.088	1	0.088	0.027	0.777	106.85	4.88	0.000	-15	3	3
		0.000	0.001	5	0.001	0.029	0.777	105.26	4.87	0.000	15	-18	6
		0.012	0.088	1	0.088	0.044	0.950	97.35	4.79	0.000	-27	-69	-12
		0.012	0.088	1	0.088	0.047	0.955	95.96	4.77	0.000	3	-18	-21

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 94.70, p = 0.000 (0.050)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 0.352
Expected number of clusters, <c> = 0.14
FWEp: 94.701, FDRp: 547.516, FWEc: 1, FDRc: 2

Degrees of freedom = [1.0, 11.0]
FWHM = 13.1 13.2 13.8 mm mm mm; 4.4 4.4 4.6 {voxels}
Volume: 1392120 = 51560 voxels = 521.2 resels
Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 88.07 voxels)

Program

- MRI “flavours”
- MRI data processing
  - Within-/between-subject processing
  - Subject-/reference-space
  - Statistical inference
- “Vanilla fMRI protocol” example
- Take home message

“MRI data processing” take home message

- MRI = very flexible technique
- Multiple “flavours” of MRIs can be acquired in 1 session
- …but not all, as scanning time is limited (subject’s comfort!)
- …so must chose what is relevant for the project!

- Data curation (safe storage, clear filenaming & organization) required
- **Complicated data to process** :
  - multiple steps/tools
  - different steps/tools for different MRI flavours
- Computer intensive data processing, i.e. need scripting!

"MRI data processing" take home message

Use existing tools to process and analyse your data!

- SPM & many extensions, https://www.fil.ion.ucl.ac.uk/spm/
- FSL, https://fsl.fmrib.ox.ac.uk/fsl/
- AFNI, https://afni.nimh.nih.gov/
- fMRIprep, https://fmriprep.org/en/stable/
- MRtrix3, https://www.mrtrix.org/
- ANTs, https://stnava.github.io/ANTs/
- …

Favour open-source and well-established tools !

LIÈGE université
GIGA
CRC Human Imaging

Thank you for your attention!