FEAT 3 - Advanced FMRI Analysis

Pipeline overview

Advanced preprocessing steps

- Motion artefact correction
- Physiological noise correction

Demeaning EVs

Advanced designs:

- Parametric designs and F-tests
- Factorial designs and interactions
  - Contrast masking
- Correlated EVs
  - Design efficiency
  - F-tests

Pipeline overview

Generic blueprint

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Generic blueprint

Aims:

- Obtain good quality and consistent data
- Optimise SNR

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Keep in mind:

- Consider drop-out and distortions
- What are the most important regions?
- Many trade-offs

Generic blueprint

Aims:

- Reduce noise in data
- Prepare data for analysis
- Prepare data for group comparison

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Keep in mind:

- Requires careful checking
- Can add additional steps if necessary

Generic blueprint

Aims:

- Obtain measure of interest for each subject (often an image)

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Keep in mind:

- Differs considerably between modalities

Generic blueprint

Aims:

- Compare single-subject results across group
- Group mean/ t-test/ correlation

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Keep in mind:

- Can have additional layer to average over sessions
- Account for confounding variables

Generic blueprint

Aims:

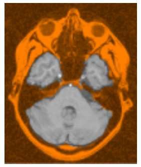
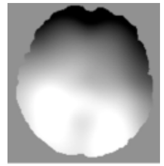
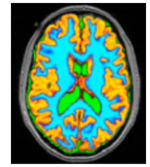
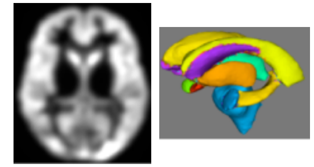
- P-values
- Reliability of results
- Generalise to population

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Keep in mind:

- Need enough subjects to have power
- Cannot interpret null results

What we covered so far

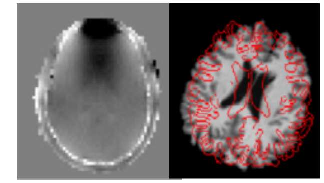
Structural data:

Brain extraction

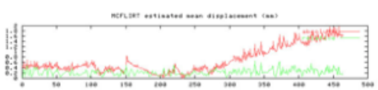
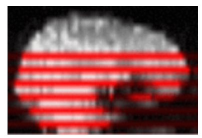
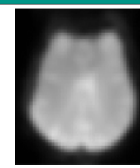
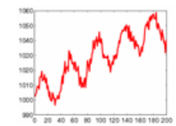
Bias field correction

Segmentation

VBM or vertex analysis



Registration & unwarping

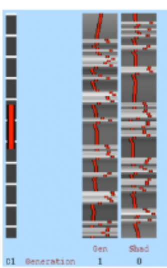
Functional data:

Motion correction

Slice timing correction

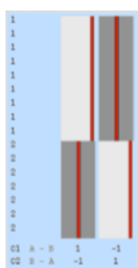
Spatial filtering

Temporal filtering



Regressors & contrasts

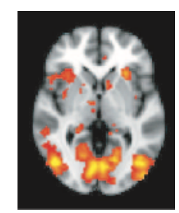
First level GLM



Regressors & contrasts

Group level GLM

Thresholding & correction



What we covered so far

Structural data:

- Brain extraction
- Bias field correction
- Segmentation
- VBM or vertex analysis

- Registration & unwarping

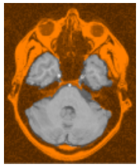
Functional data:

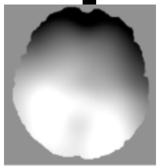
- Motion correction
- Slice timing correction
- Spatial filtering
- Temporal filtering

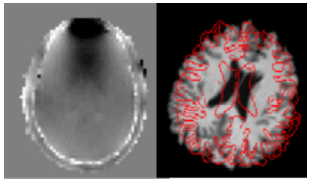
- Regressors & contrasts
- First level GLM

- Regressors & contrasts
- Group level GLM
- Thresholding & correction

Preprocessing







Structural data:

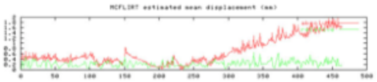
Brain extraction

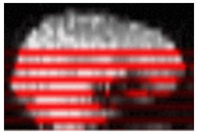
Bias field correction

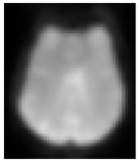
Segmentation

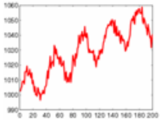
VBM or vertex analysis

Registration & unwarping









Functional data:

Motion correction

Slice timing correction

Spatial filtering

Temporal filtering

Regressors & contrasts

First level GLM

Preprocessing

Regressors & contrasts

Group level GLM

Thresholding & correction

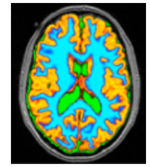
Structural preprocessing summary

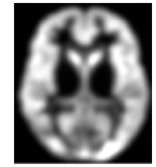
Brain extraction	Remove non-brain tissue to help with registration. Needs to be very precise.
Bias field correction	Corrects for B1 inhomogeneities
Registration	Put images into same space (standard space for group analysis)

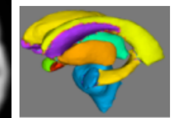
fMRI preprocessing summary

Brain extraction	Remove non-brain tissue to help with registration
Motion Correction	Get consistent anatomical coordinates (always do this)
Slice Timing	Get consistent acquisition timing (use temporal derivative instead)
Spatial Smoothing	Improve SNR & validate GRF
Temporal Filtering	Highpass: Remove *slow* drifts
Registration & unwarping	Unwarping corrects for B0 inhomogeneities. Registration images into same space (standard space for group analysis)

Single-subject analysis







Structural data:

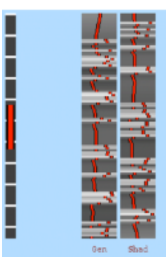
Brain extraction | Bias field correction | Segmentation | VBM / vertex analysis

Registration & unwarping

Preprocessing

Functional data:

Motion correction | Slice timing correction | Spatial filtering | Temporal filtering



Regressors & contrasts | First level GLM

Single-subject analysis

Regressors & contrasts | Group level GLM | Thresholding & correction

Structural single-subject summary

Segmentation	Tissue-type segmentation (FAST) or sub-cortical segmentation (FIRST)
Voxel-based morphometry	To detect differences in local grey matter volume. Jacobian modulation and spatial smoothing.
Vertex analysis	To run shape analysis on subcortical structures. *first_utils* uses bvars output from FIRST to perform vertex analysis (4D output image of all subject meshes)

fMRI single-subject summary

EVs/ regressors	Design matrix: model of predicted responses based on stimuli presented at each time point
GLM	Estimate parameter estimates for each EV so that the linear combination best fits the data
Contrasts (F or t)	Maths on parameter estimates to ask research questions. Result is a COPE image per contrast

Group-level analysis

Structural data:

Brain extraction | Bias field correction | Segmentation | VBM / vertex analysis

Registration & unwarping

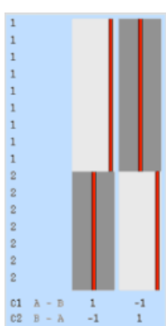
Preprocessing

Functional data:

Motion correction | Slice timing correction | Spatial filtering | Temporal filtering

Regressors & contrasts | First level GLM

Single-subject analysis



Regressors & contrasts | Group level GLM | Thresholding & correction

Group-level analysis

Group-level analysis summary

EVs/ regressors	Design matrix: one entry per subject. Can describe subject groups, confounds etc
GLM	*Structural*: inputs are smoothed, modulated GM volumes (VBM) or single subject subcortical meshes (vertex analysis) *fMRI*: inputs are first-level COPE and VARCOPE images.
Contrasts (F or t)	*Structural*: tests differences in GM density or shape *fMRI*: Each group-level contrast is tested for each of the subject-level contrast

Statistical inference

Structural data:

Brain extraction

Bias field correction

Segmentation

VBM / vertex analysis

Registration & unwarping

Preprocessing

Functional data:

Motion correction

Slice timing correction

Spatial filtering

Temporal filtering

Regressors & contrasts

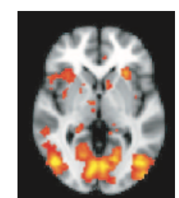
First level GLM

Single-subject analysis

Regressors & contrasts

Group level GLM

Thresholding & correction



Group-level analysis

Statistical inference

Statistical inference summary

Fixed vs mixed effects	Averaging across multiple sessions Generalisation to population
OLS vs FLAME vs Randomise	Quick, doesn't use VARCOPEs Uses COPEs & VARCOPEs Non-parametric
Multiple comparison correction (FWE/ FDR)	Gaussian Random Field (voxel or cluster based) TFCE

What we covered so far

Structural data:

Functional data:

istration & warping

s

Group-level analysis

Statistical inference

Looking ahead:

resting state

diffusion

Generic blueprint

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Resting state analysis

1. Data acquisition → Consider using multiband
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Resting state analysis

1. Data acquisition → Consider using multiband
2. Data preprocessing → Need to apply extra noise-reduction steps (ICA)
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Resting state analysis

1. Data acquisition → Consider using multiband
2. Data preprocessing → Need to apply extra noise-reduction steps (ICA)
3. Single-subject analysis → Group ICA+dual regression/ Network analysis (FSLnets)
4. Group-level analysis
5. Statistical inference

Diffusion analysis

1. Data acquisition → Blip-up/blip-down, Multi shell
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Diffusion analysis

1. Data acquisition → Blip-up/blip-down
   Multi shell
2. Data preprocessing → Need to correct for eddy currents
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Diffusion analysis

1. Data acquisition → Blip-up/blip-down
   Multi shell
2. Data preprocessing → Need to correct for eddy currents
3. Single-subject analysis → Fractional anisotropy/ mean diffusivity/ tractography
4. Group-level analysis
5. Statistical inference

The rest of the week

Time	Monday 22 June	Tuesday 23 June	Wednesday 24 June	Thursday 25 June	Friday 26 June
8:00 - 8:30	Course registration				
8:30 - 9:15	Registration (Rach Dawson)	fMRI Preprocessing (Paul McCarthy)	Pipeline overview (Ludovica Griffanti)	Resting state FSLNETS (Rezvan Farahibozorg)	Diffusion MRI (tractography) (Michiel Cottaar)
9:15 - 9:45			Coffee/tea break		
9:45 - 10:30	Unwarping (Rach Dawson)	GLM stats (Paul McCarthy)	Advanced fMRI (Saad Jbabdi)	Resting state FSLNETS (Rezvan Farahibozorg)	Diffusion MRI (tractography) (Michiel Cottaar)
10:30 - 12:15			Practical session		
12:15 - 13:45			Lunch (not provided)		
13:45 - 14:30	Segmentation (Ludovica Griffanti)	Multi-subject stats (Saad Jbabdi)	Resting state ICA (Rezvan Farahibozorg)	Diffusion MRI (DTI) (Michiel Cottaar)	Demos: New and upcoming FSL features and pipelines
14:30 - 15:00			Coffee/tea break		
15:00 - 15:45	Segmentation (Ludovica Griffanti)	Inference (Saad Jbabdi)	Resting state ICA (Rezvan Farahibozorg)	Diffusion MRI (DTI) (Michiel Cottaar)	Final day early close (3pm)
15:45 - 17:30			Practical session		
17:45 - 18:00+	Welcome reception				
19:00 - 20:00+				Dinner at Salon Saint-Emilion	

Advanced preprocessing

- Motion artefact correction
- Physiological noise correction

Case Study: Motion Artefacts

Scenario:

Young/elderly/sick subjects that move a lot during an FMRI study

Problem:

Motion correction does not fully correct for excessive motion

Sudden motion creates massive distortion (>12 DOF)

Smaller, slower motion induces intensity changes due to physics effects (e.g. spin history) and interpolation

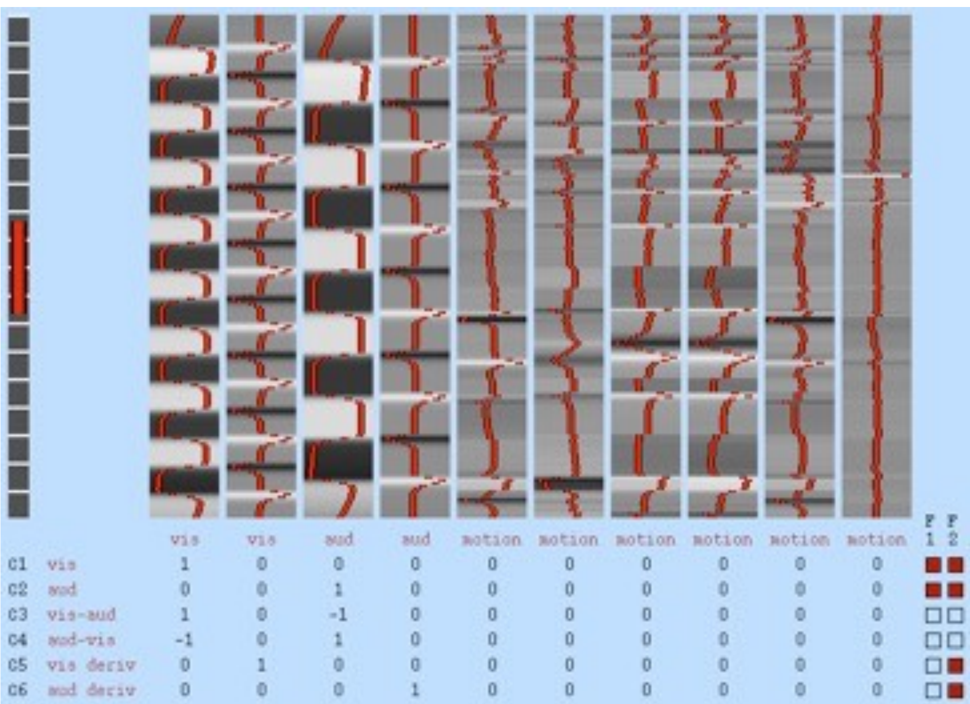
Solution:

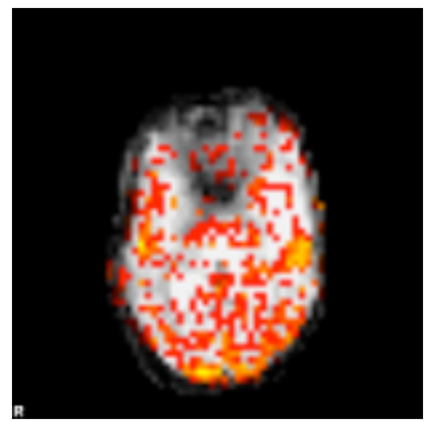
Remove or compensate for motion artefacts

Motion Artefact Correction

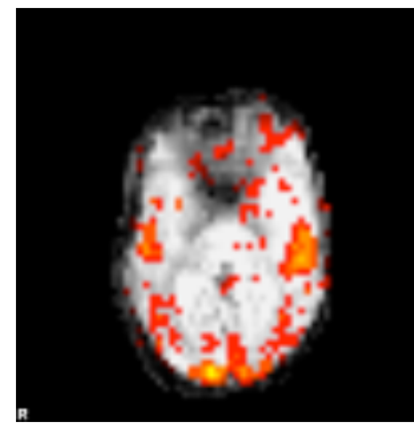
Options for motion artefact correction:

1. Add motion parameters as confound EVs
2. Detect "outlier" timepoints and remove them via confound EVs
3. Use ICA (MELODIC) denoising for cleanup





Without motion parameter EVs

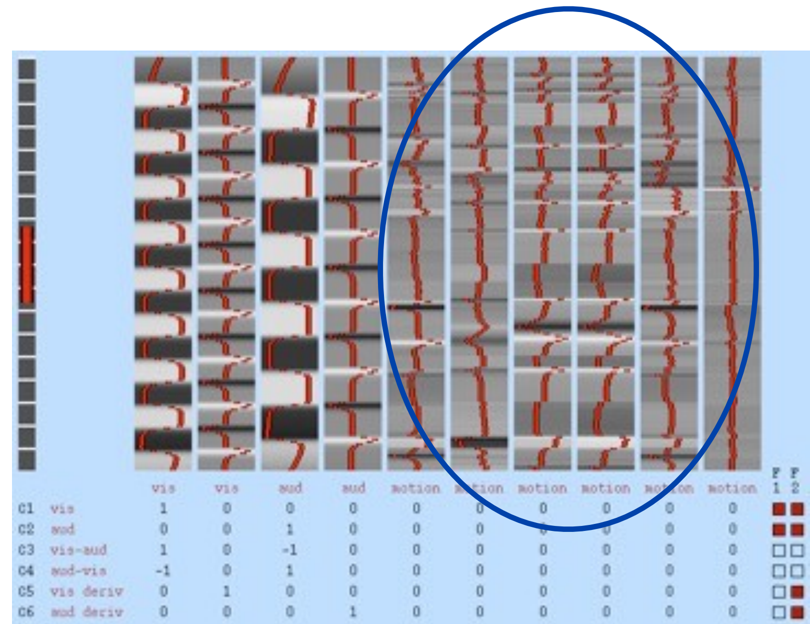


With motion parameter EVs

Motion Parameter Confounds

Add the 6 parameters (rotations and translations) as measured by MCFLIRT to the GLM as *confounds* - simple button in FEAT

- Removes any correlated signals (since they are confounds)
- Assumes a linear relationship between motion parameters and intensity of motion artefact
- Assumes that MCFLIRT estimation is accurate
- Problematic if motion parameters and EVs of interest are highly correlated (stimulus-correlated motion)
  - can result in loss of activation
  - orthogonalising EVs does not change result
- Also possible to include non-linear (e.g. squared) parameters

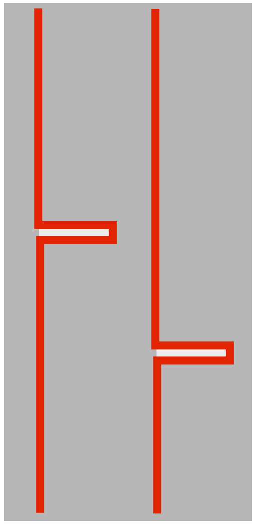


Outlier Timepoint Detection

Use *fsl_motion_outliers* to detect timepoints that display large intensity differences to the reference timepoint (after motion correction)

- Removes ***all*** influence of the timepoints declared as outliers but does not introduce any bias (unlike "deleting" timepoints from data)
- Uses one extra confound regressor per outlier timepoint
  - the regressor is zero at all timepoints except the outlier
- Implemented via confound matrix in the GLM
  - another simple button in FEAT
- Does not assume that MCFLIRT is accurate or that the effect is linear
- Can cope with very extreme motion effects but leaves other timepoints uncorrected
- Can be combined with other correction methods

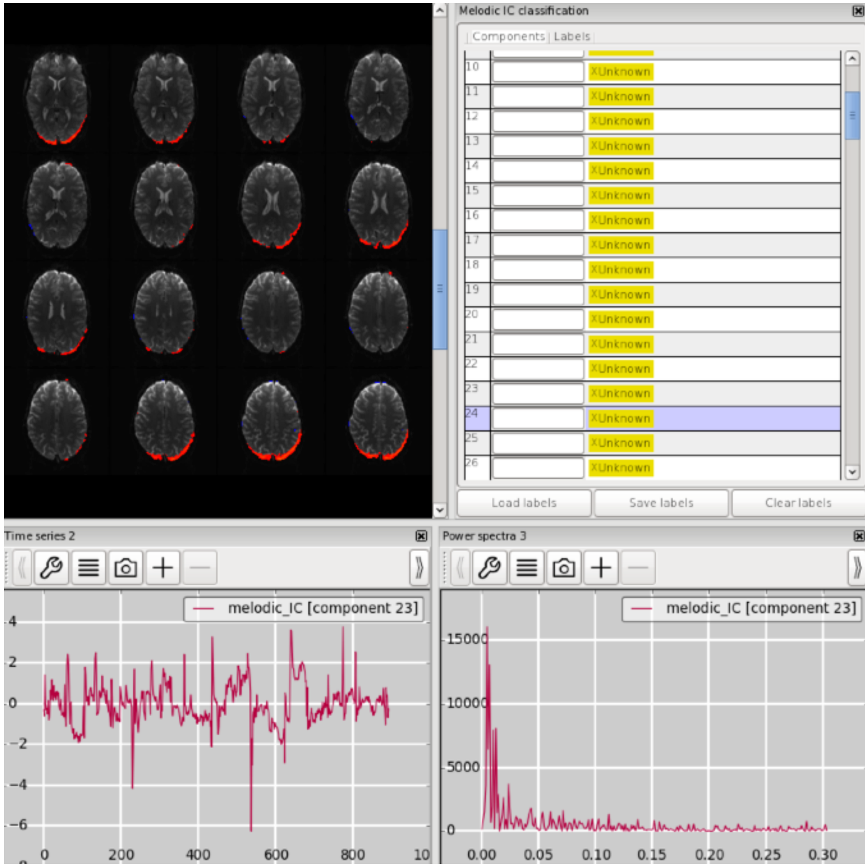
Confound matrix with 2 outlier timepoints



ICA denoising

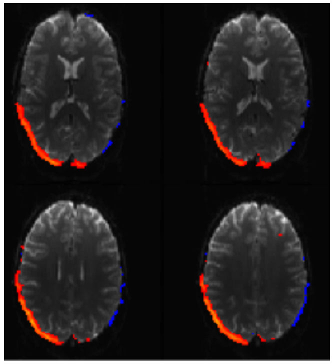
Use ICA (MELODIC) on individual runs to identify components related to motion artefacts and remove these from the 4D data

- Requires identification of components
  - manual classification
  - (semi-) automated classification (FIX/ AROMA)
- Can also be combined with other cleanup techniques
  - ICA denoising should be done first
- Can also be used to identify and remove structured noise that is not related to motion

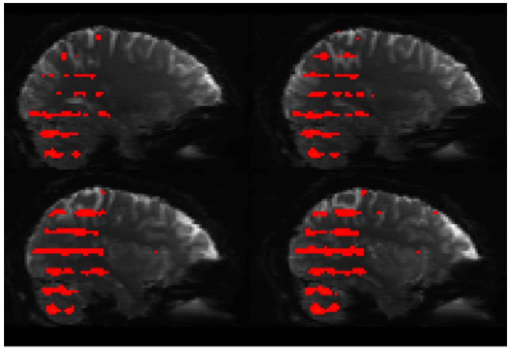


ICA denoising

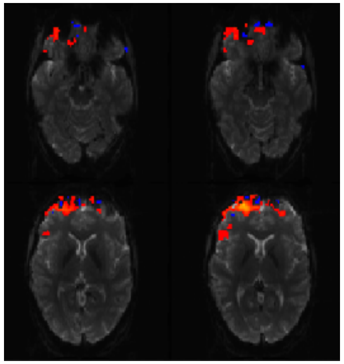
- Typical motion components display ringing around brain edge
- Can also note sharp effects in timecourses
- There are typically a large number of noise components (70-90%)



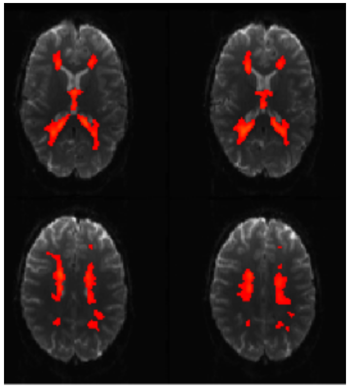
Classic motion



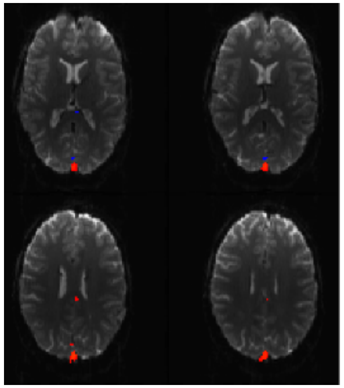
Multiband motion



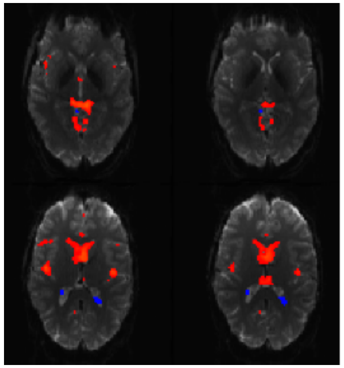
Susceptibility motion



White matter

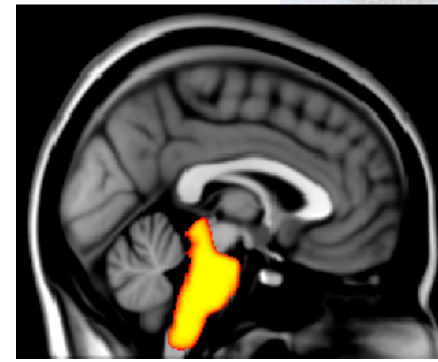


Sagittal sinus



Cardiac/CSF

Case Study: Physiological Noise Correction



Scenario:

FMRI study of the brainstem

Problem:

High levels of pulsatility and respiratory effects in the brainstem and in other inferior areas

Solution:

Use Physiological Noise Model (PNM) to correct for physiological noise

Requires independent physiological measurements

Physiological Measurements

Need to measure cardiac and respiratory cycles.

Several options available - the easiest are:

Pulse Oximeter

Respiratory Bellows

Also ***record scanner triggers*** from the scanner console

Triggers are essential for accurate timing over the course of the experiment. Beware of standard scanner recordings and timing drift or rescalings.

Location of Effects

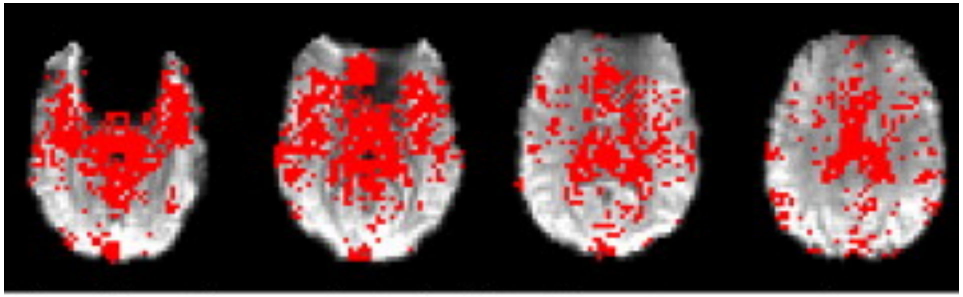
Cardiac effects typically occur:

- near vessels and areas of CSF pulsatility (e.g. brainstem, ventricles)

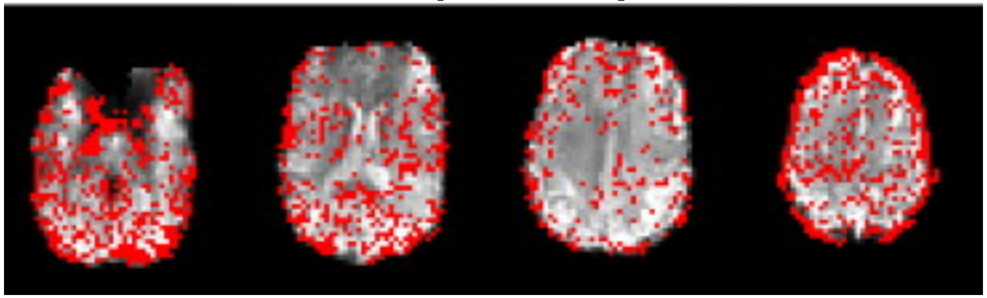
Respiratory effects typically occur:

- in inferior areas (where the induced B0 field changes due to lung volume changes are highest)
- near image edges (due to geometric shifts/distortion by B0 causing large intensity changes)
- throughout the grey matter (due to oxygenation changes)

Cardiac



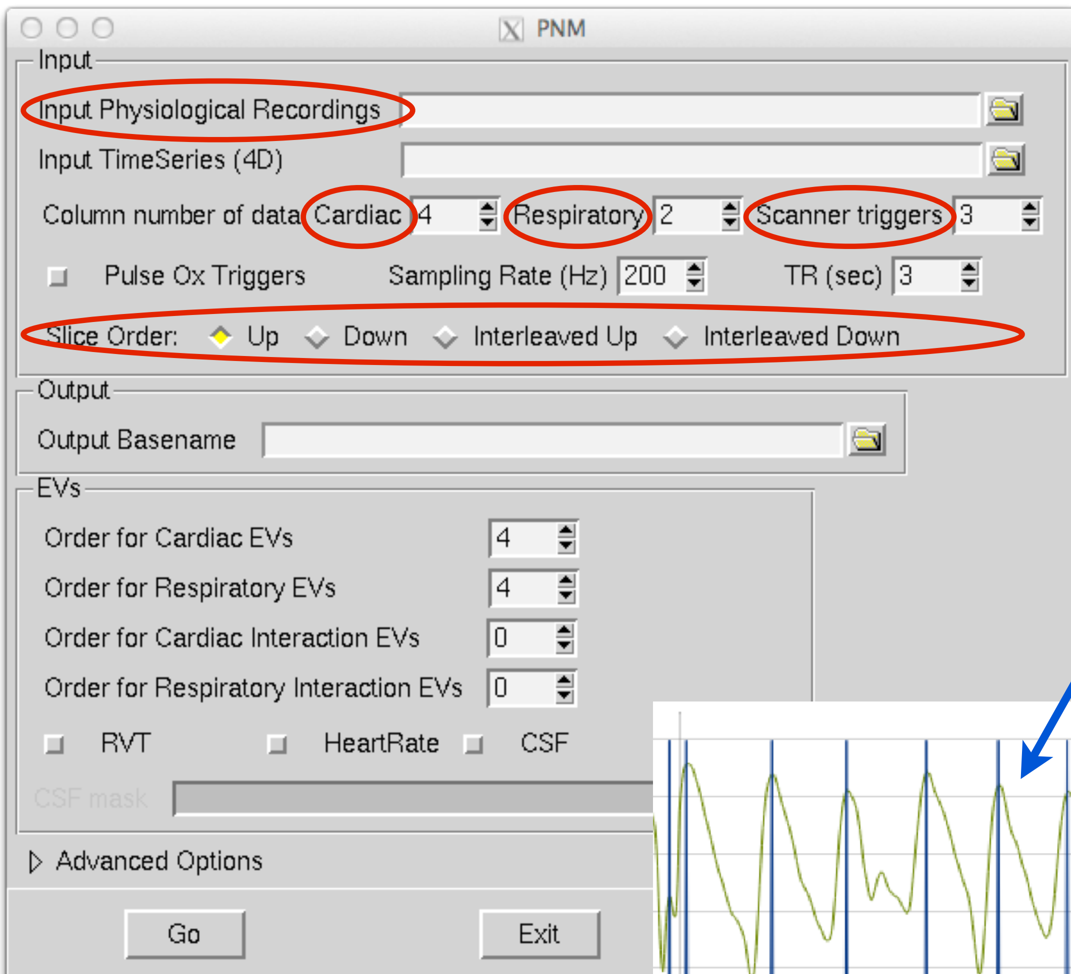
Respiratory



Bright & Murphy, NeuroImage, 2013

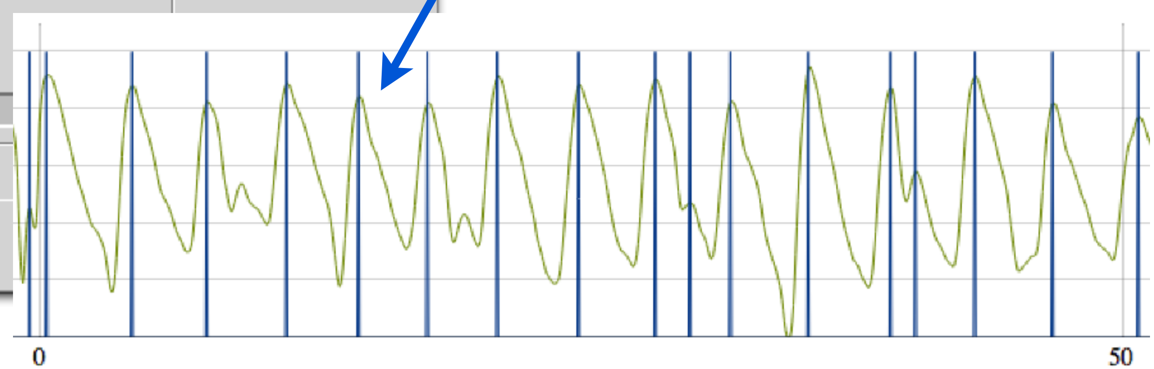
PNM

Physiological Noise Model (GUI)



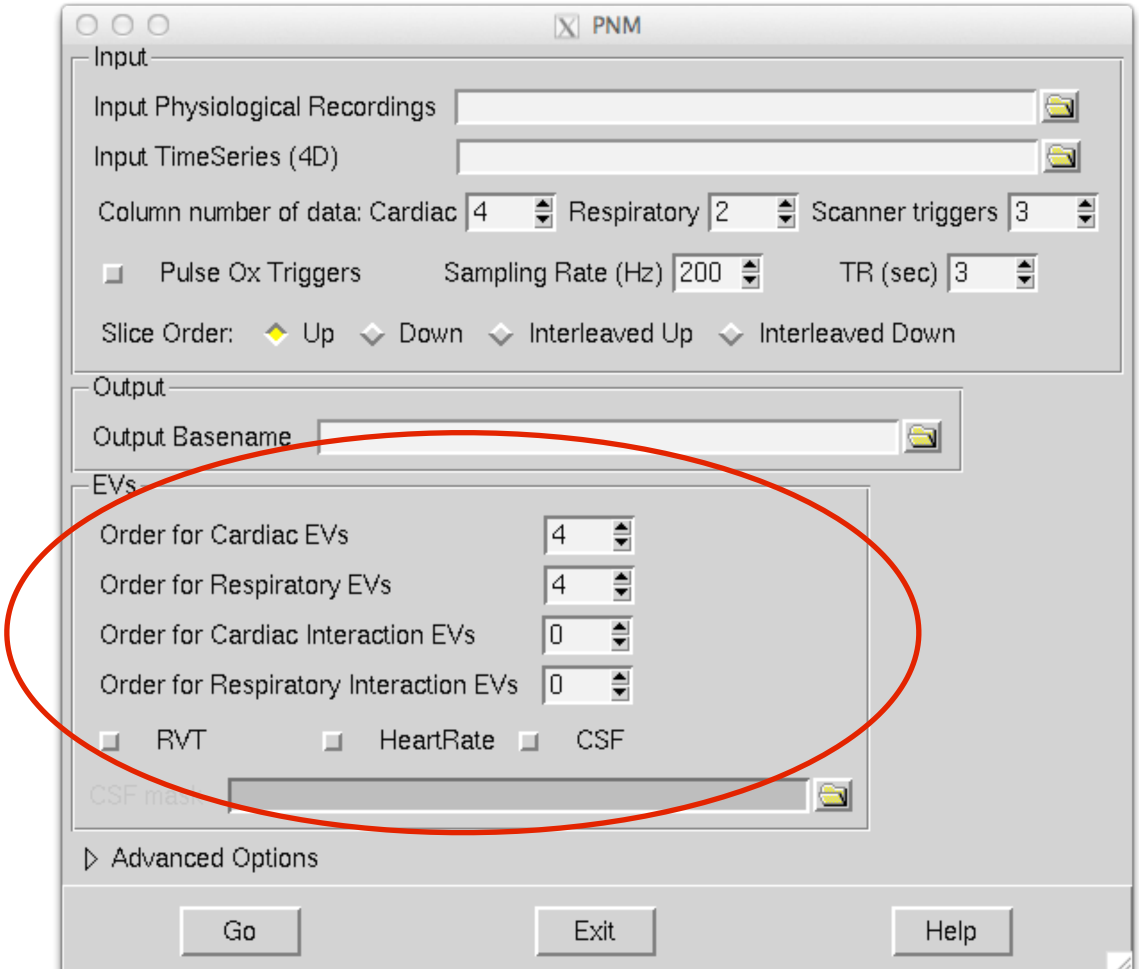
Requires text file with physiological recordings (cardiac, respiratory, triggers)

Peak detection in physiological trace needs manual checking via webpage



PNM

Physiological Noise Model (GUI)



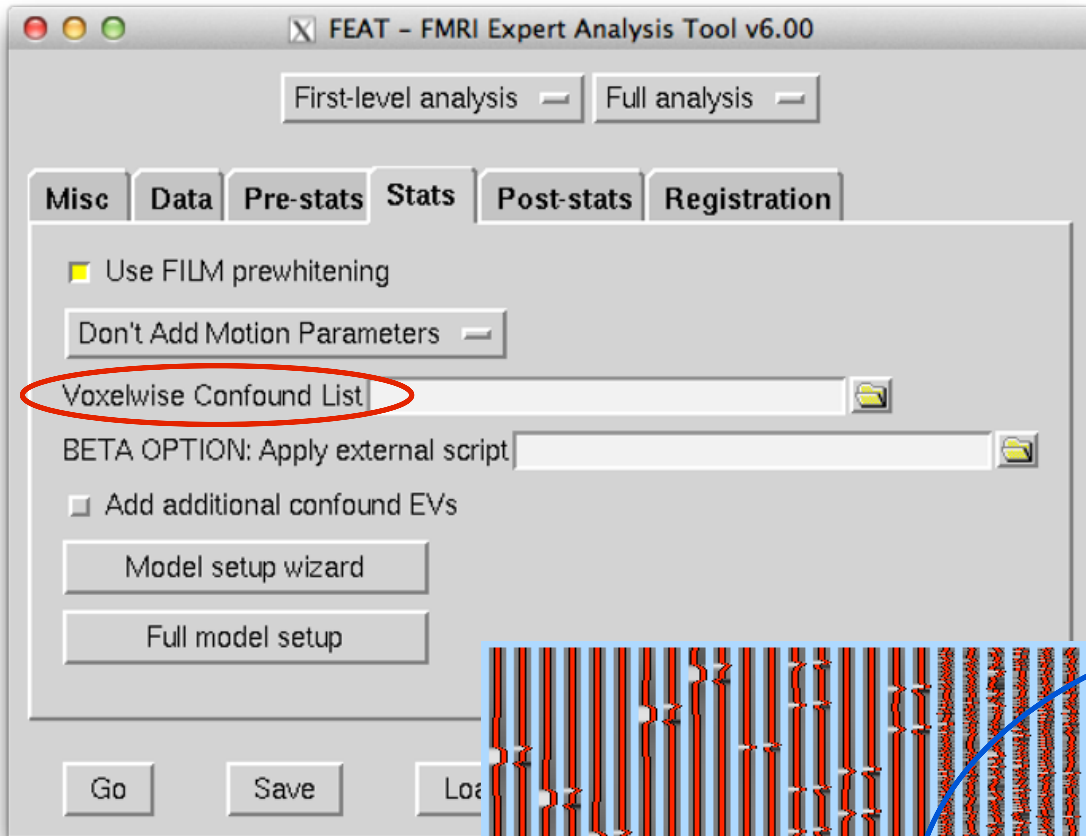
Need to specify what type of corrections:

- Fourier series
  (harmonics / shape)
- Interactions
  (resp x cardiac)

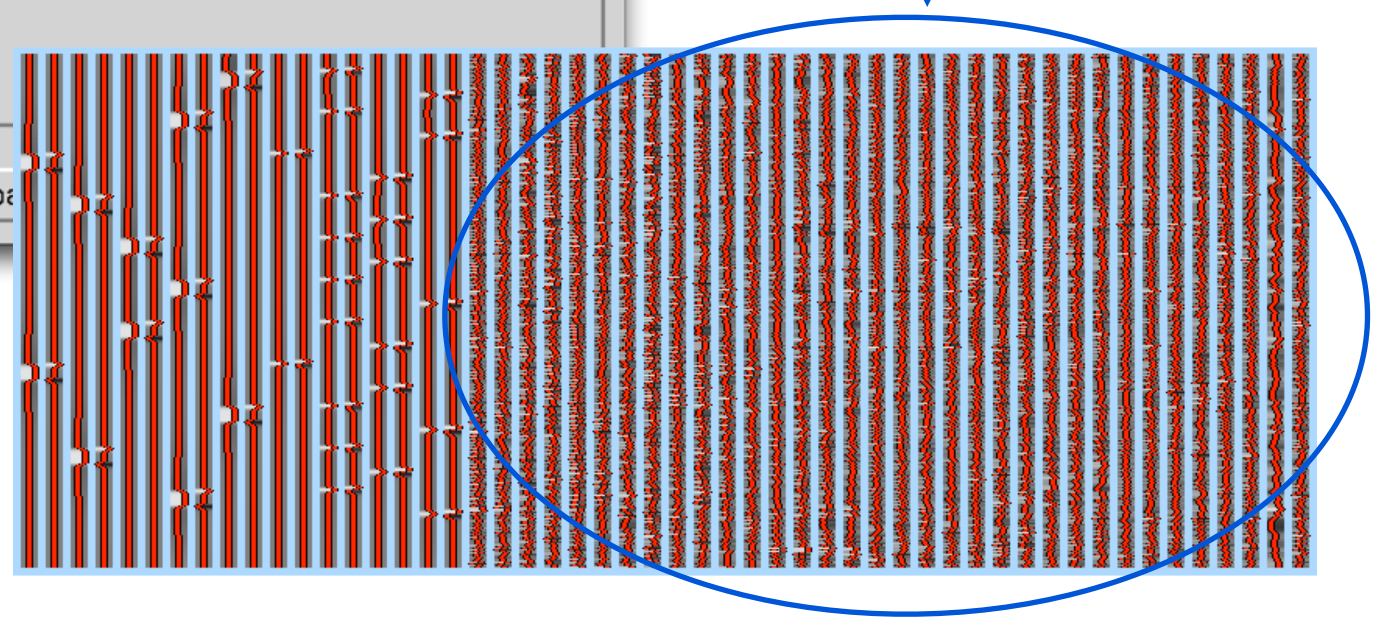
NB: higher orders = better fit to shape, but many more EVs and so less DOF

- RVT
  (resp volume per time)
- HeartRate
- CSF mean signal

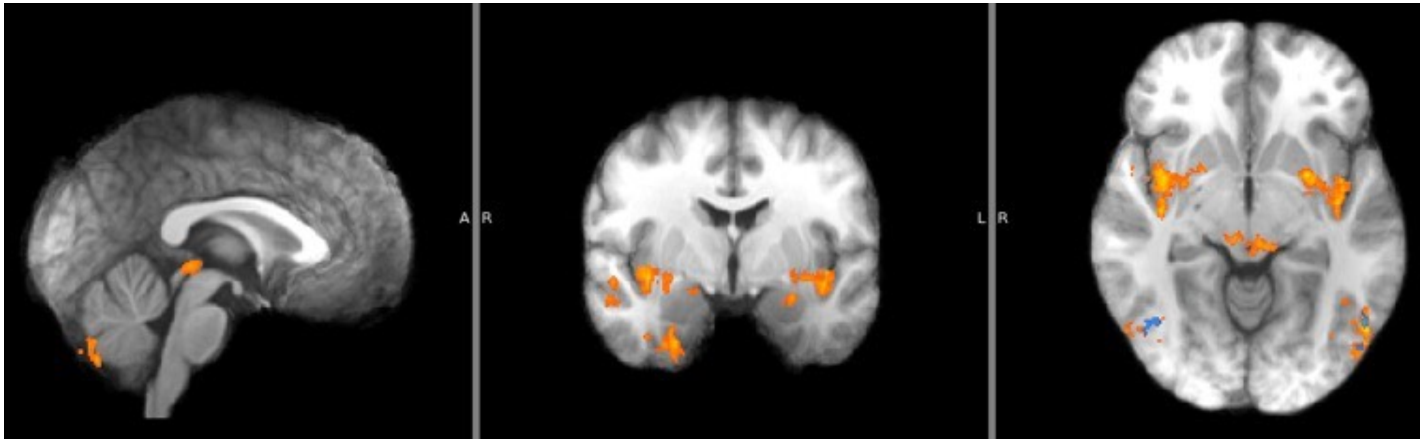
Use in FEAT



PNM GUI creates a set of files suitable for use as ***Voxelwise Confounds*** in FEAT

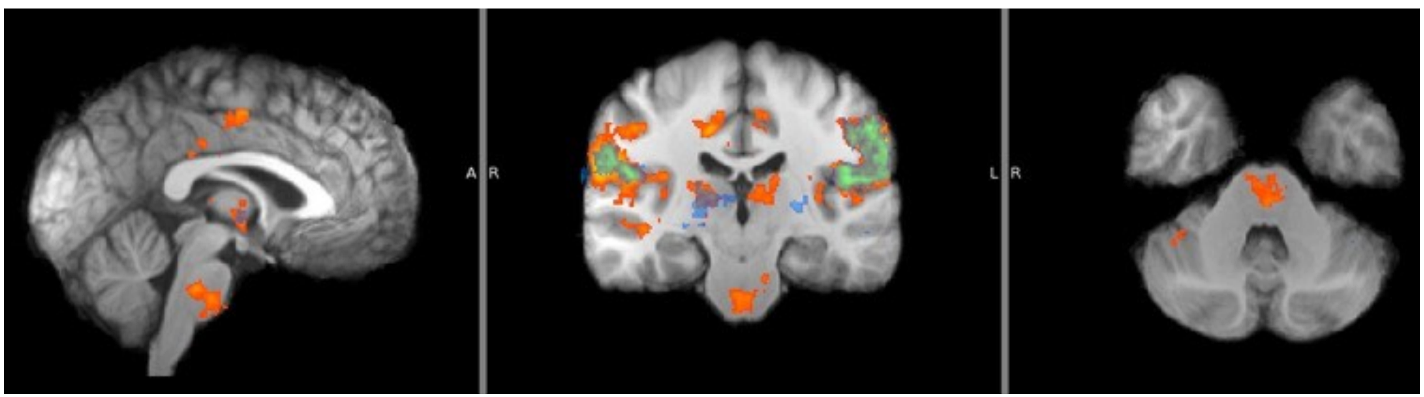


Results: Pain-punctate arm



AXIAL

N=6, Group mean (Fixed effects), Z=1.8 $p<0.05$



CORONAL

With PNM ■ Without PNM ■ Both ■

Advanced preprocessing summary

Options for **motion artefact correction**:

1. Add motion parameters as confound EVs
2. Detect outliers (fsl_motion outliers) and remove them via confound EVs
3. ICA-based cleanup

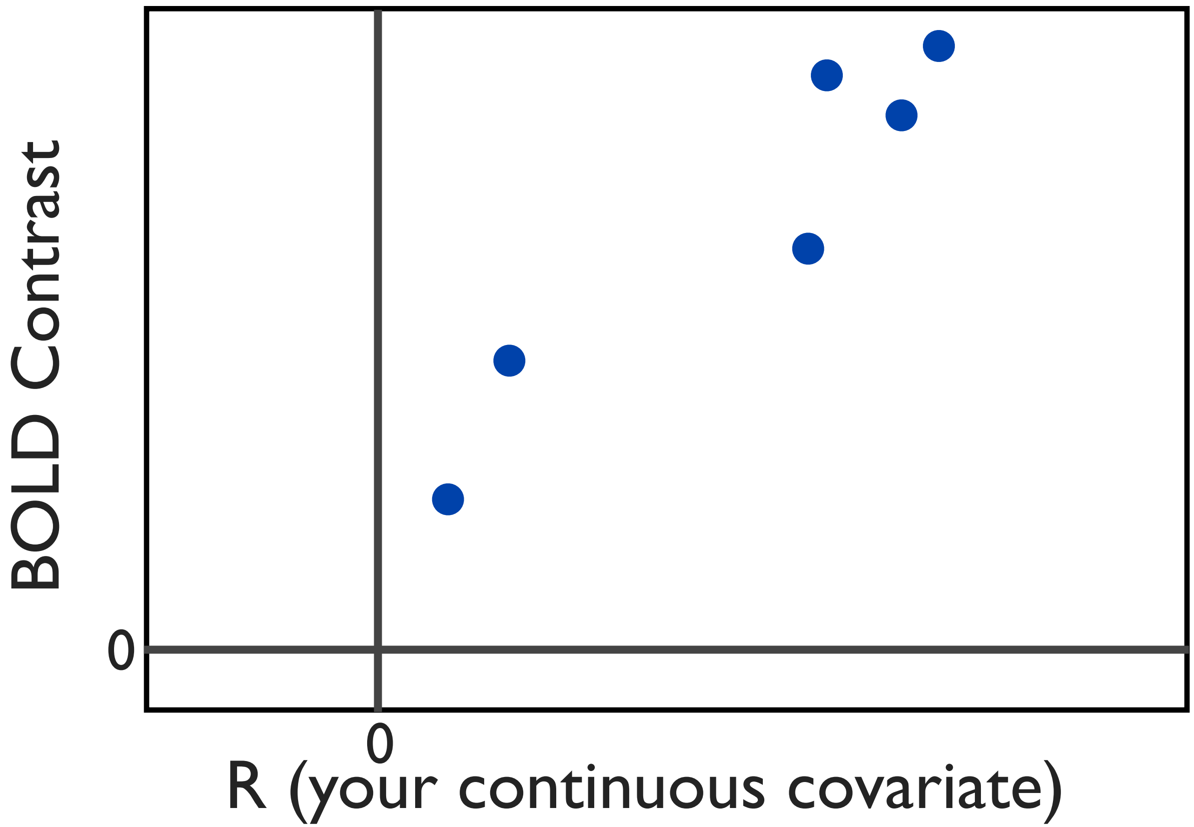
Options for **physiological noise correction**:

1. ICA-based cleanup
2. Physiological recordings + PNM + voxelwise confound EVs

Demeaning EVs

Demeaning at the group level

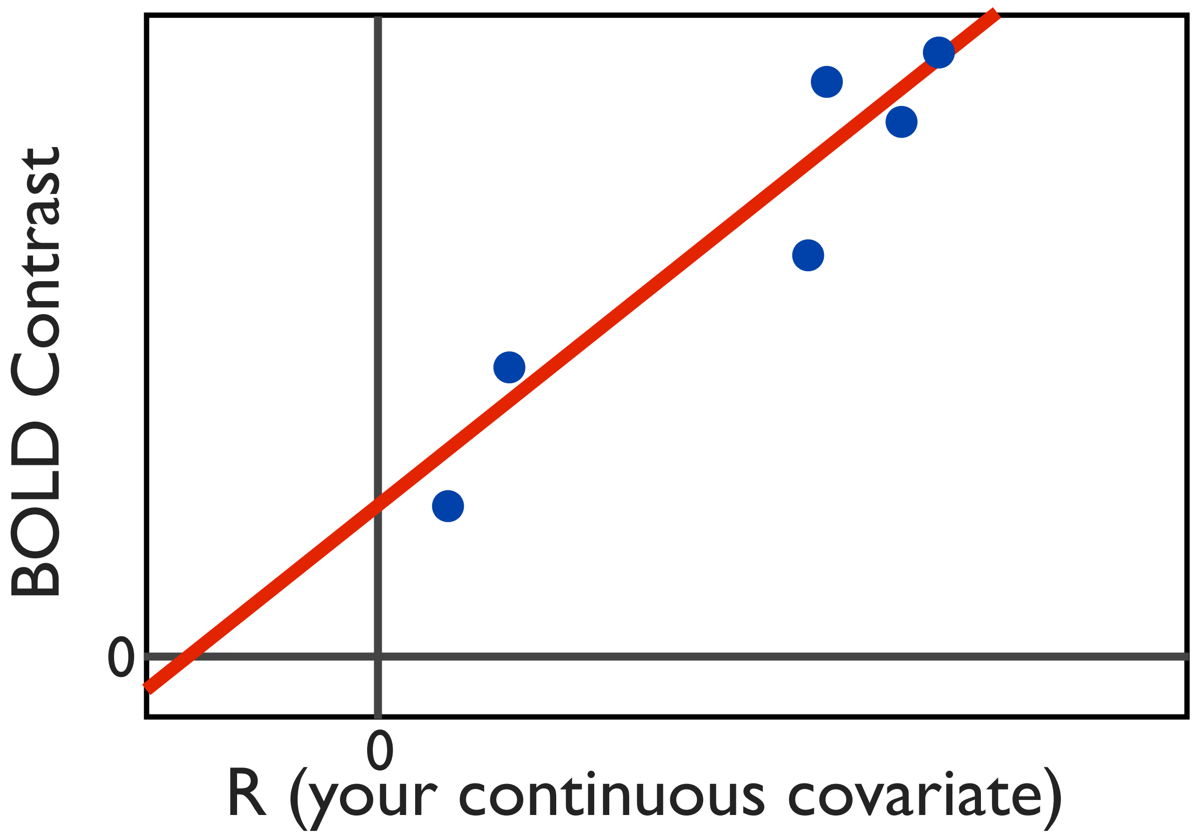
$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix}$$



e.g. age, reaction time, …

$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix}$$

Demeaning



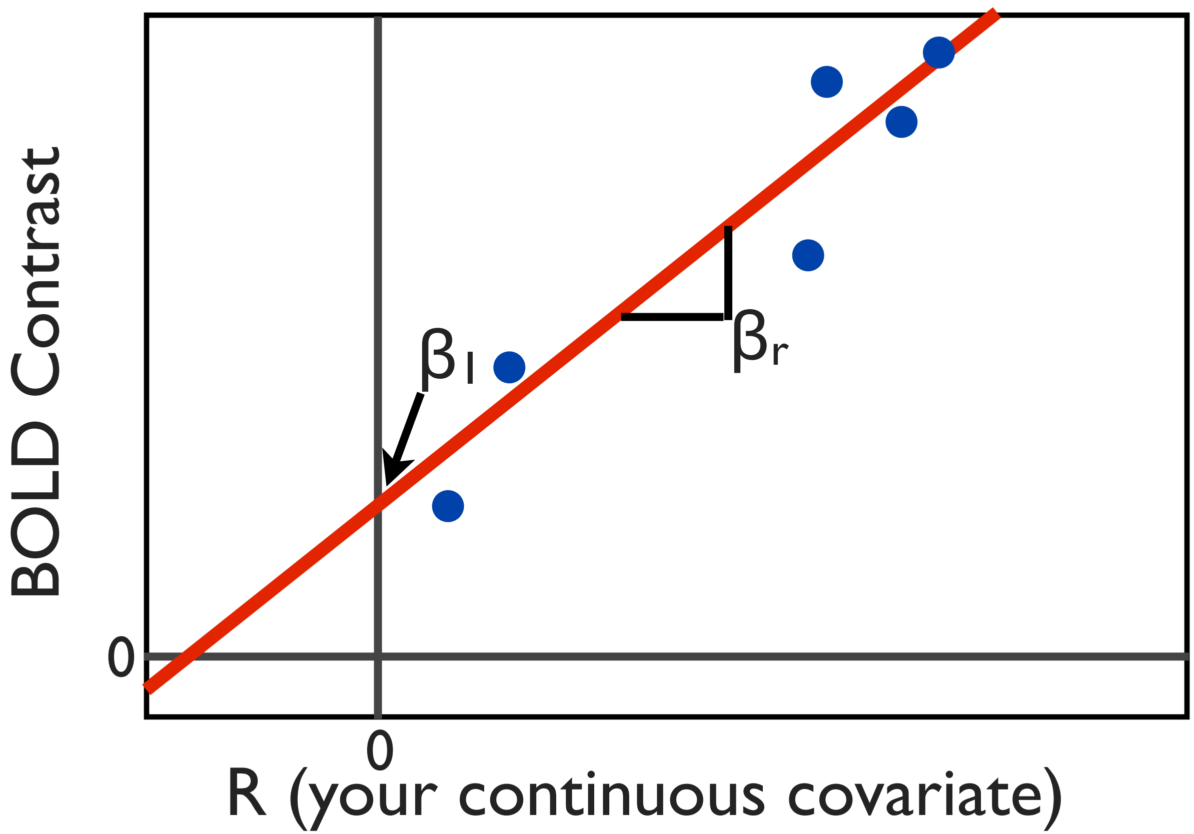
e.g. age, reaction time, …

$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$$

[1 0]

Demeaning

β_1 represents BOLD at R=0



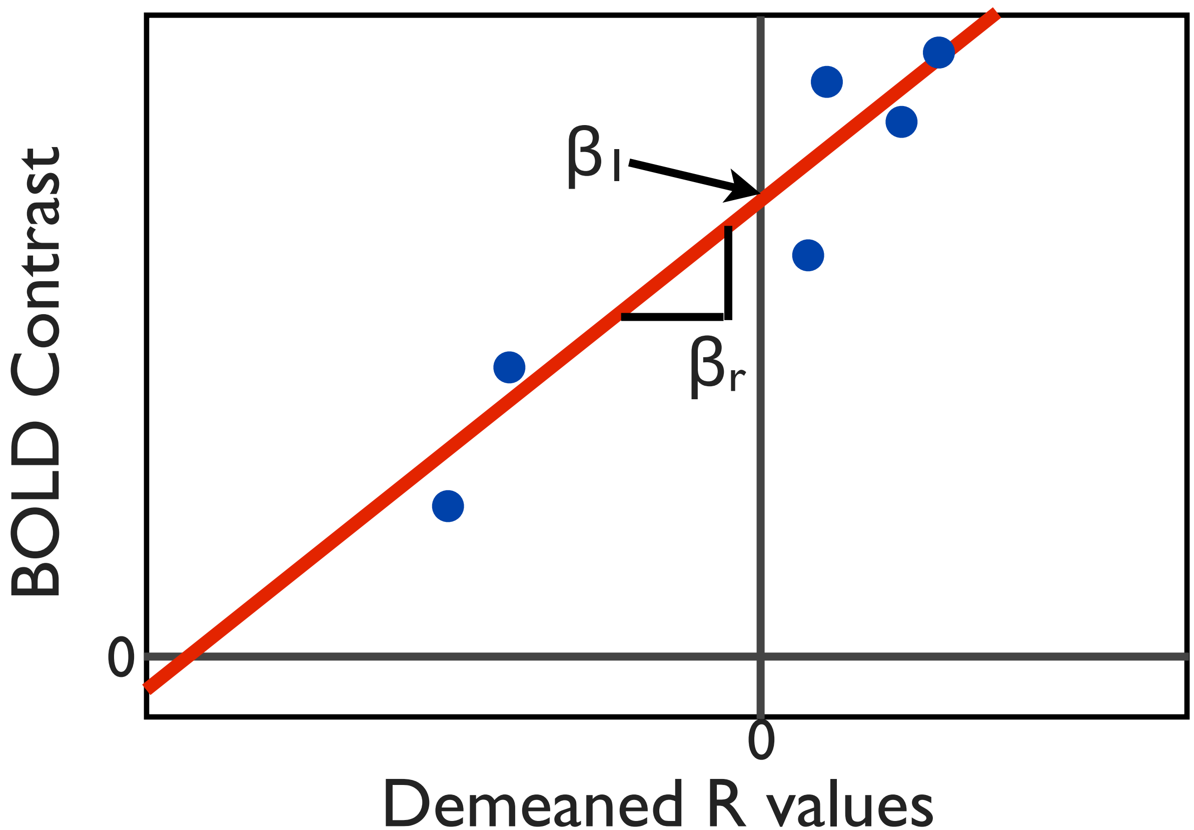
e.g. age, reaction time, …

Demeaning

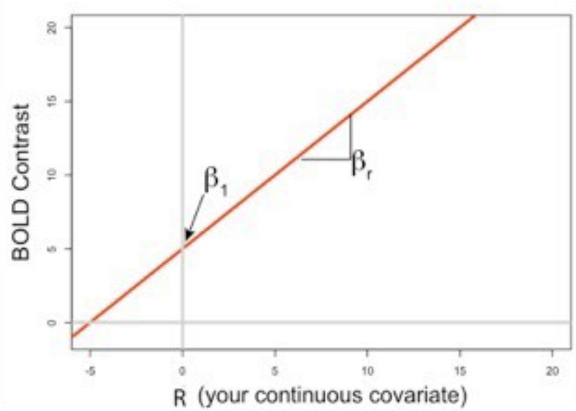
$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$$

[1 0]

β_1 now represents BOLD at group average R



Demeaning

Design matrix	What does the fitted model look like?	Contrast	Does demeaning change the stats?	Demeaning recommended?
$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$		[1 0]	YES	YES
		[0 1]		

Mean centred value = $r_1 - \bar{r}$

where $\bar{r}$ is the mean of r_1 to r_6

Adding or subtracting a mean from EV2 (i.e. r_1 to r_6) **changes β_1**

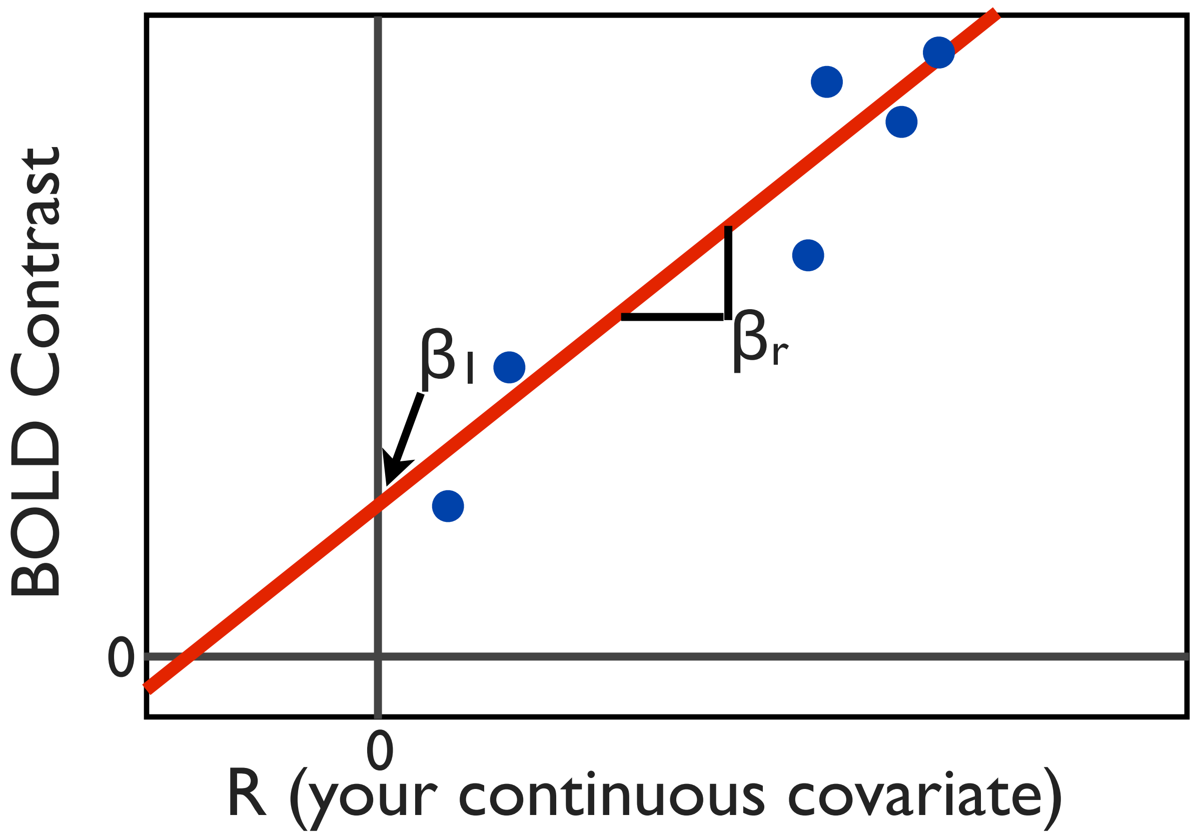
https://jeanettemumford.org/assets/files/mean_centering_regressors_mumford.pdf

Demeaning

$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$$

$[\,0 \;\; 1\,]$

β_r is the slope of the fitting line



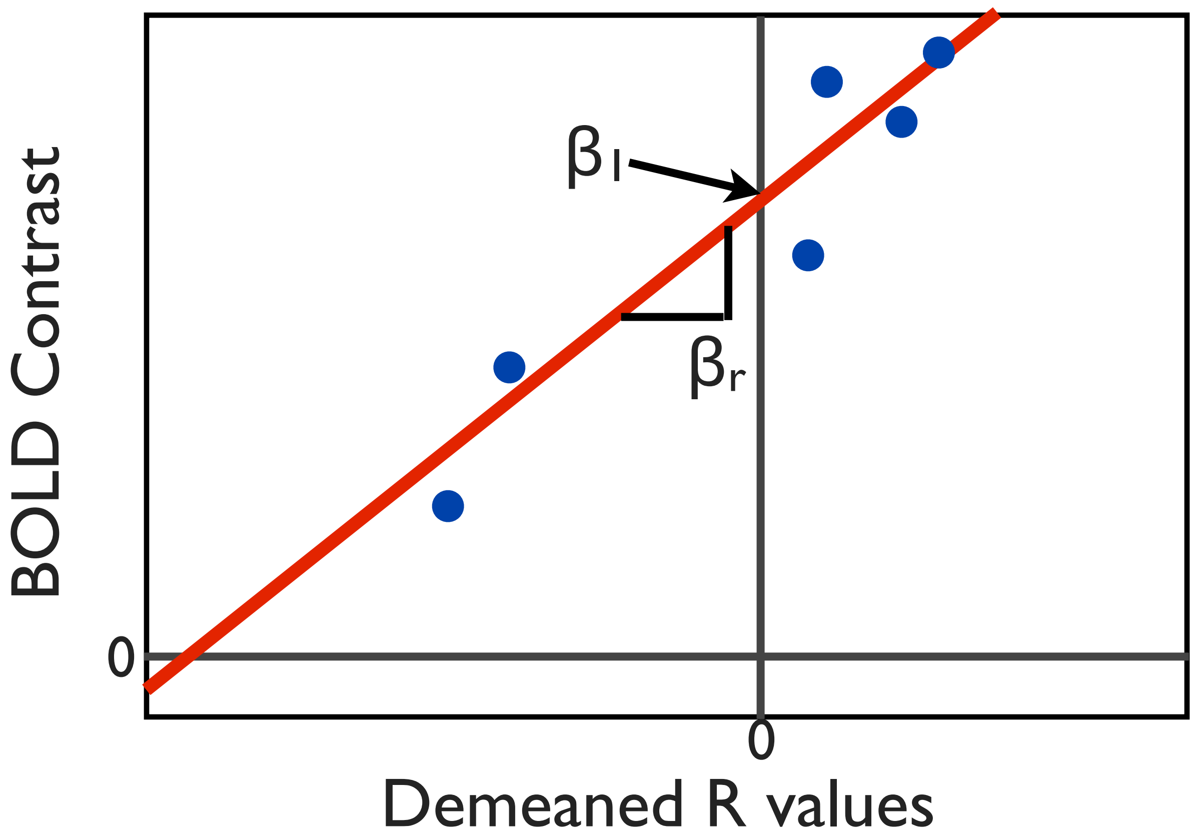
e.g. age, reaction time, …

Demeaning

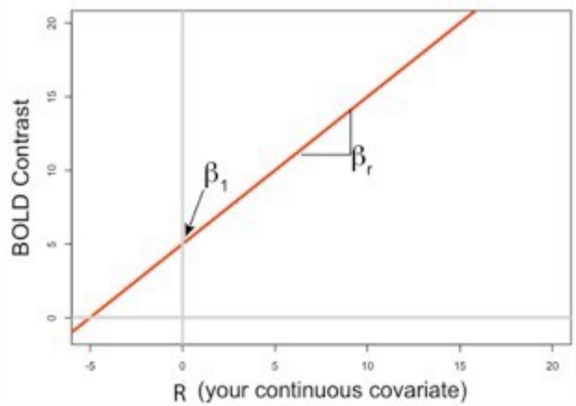
$$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$$

[0 1]

β_r is the slope of the fitting line



Demeaning

Design matrix	What does the fitted model look like?	Contrast	Does demeaning change the stats?	Demeaning recommended?
$\begin{pmatrix} 1 & r_1 \\ 1 & r_2 \\ 1 & r_3 \\ 1 & r_4 \\ 1 & r_5 \\ 1 & r_6 \end{pmatrix} \begin{bmatrix} \beta_1 \\ \beta_r \end{bmatrix}$		[1 0]	YES	YES
		[0 1]	NO	YES

Adding or subtracting a mean from EV_2
(i.e. r_1 to r_6) **does not changes β_r**

https://jeanettemumford.org/assets/files/mean_centering_regressors_mumford.pdf

Demeaning summary

- We can control for confound variables at the group level adding EVs
- Demeaning EVs can change the interpretation of the statistics
- Demeaning EVs generally recommended (also for binary variables)