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

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

Aims:
- Obtain good quality and consistent data
- Optimise SNR

Keep in mind:
- Many trade-offs
- Consider drop-out and distortions
- What are the most important regions?
Generic blueprint

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

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

Keep in mind:
- Requires careful checking
- Can add additional steps if necessary
Generic blueprint

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

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

Keep in mind:
- Differs considerably between modalities
Generic blueprint

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

Keep in mind:
- Can have additional layer to average over sessions
- Account for confounding variables

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Generic blueprint

1. Data acquisition
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Aims:
- P-values
- Reliability of results
- Generalise to population

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
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
- Thresholding & correction
- Regressors & contrasts
- Group level GLM
## Structural preprocessing summary

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain extraction</td>
<td>Remove non-brain tissue to help with registration. Needs to be very precise.</td>
</tr>
<tr>
<td>Bias field correction</td>
<td>Corrects for B1 inhomogeneities</td>
</tr>
<tr>
<td>Registration</td>
<td>Put images into same space (standard space for group analysis)</td>
</tr>
</tbody>
</table>
### fMRI preprocessing summary

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain extraction</td>
<td>Remove non-brain tissue to help with registration</td>
</tr>
<tr>
<td>Motion Correction</td>
<td>Get consistent anatomical coordinates (always do this)</td>
</tr>
<tr>
<td>Slice Timing</td>
<td>Get consistent acquisition timing (use temporal derivative instead)</td>
</tr>
<tr>
<td>Spatial Smoothing</td>
<td>Improve SNR &amp; validate GRF</td>
</tr>
<tr>
<td>Temporal Filtering</td>
<td>Highpass: Remove slow drifts</td>
</tr>
<tr>
<td>Registration &amp; unwarping</td>
<td>Unwarping corrects for B0 inhomogeneities. Registration images into same space (standard space for group analysis)</td>
</tr>
</tbody>
</table>
Single-subject analysis

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
## Structural single-subject summary

<table>
<thead>
<tr>
<th>Segmentation</th>
<th>Tissue-type segmentation (FAST), sub-cortical segmentation (FIRST), white matter hyperintensities (BIANCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxel-based morphometry</td>
<td>To detect differences in local grey matter volume. Jacobian modulation and spatial smoothing.</td>
</tr>
<tr>
<td>Vertex analysis</td>
<td>To run shape analysis on subcortical structures. <code>first_utils</code> uses <code>bvars</code> output from FIRST to perform vertex analysis (4D output image of all subject meshes)</td>
</tr>
</tbody>
</table>
# fMRI single-subject summary

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

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
- Group level GLM
- Thresholding & correction

Regressors & contrasts
## Group-level analysis summary

<table>
<thead>
<tr>
<th>EVs/ regressors</th>
<th>Design matrix: one entry per subject. Can describe subject groups, confounds etc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLM</strong></td>
<td><em>Structural</em>: inputs are smoothed, modulated GM volumes (VBM) or single subject subcortical meshes (vertex analysis)</td>
</tr>
<tr>
<td></td>
<td><em>fMRI</em>: inputs are first-level COPE and VARCOPE images.</td>
</tr>
</tbody>
</table>
| **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 contrasts |
Statistical inference

**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
## Statistical inference summary

<table>
<thead>
<tr>
<th>Fixed effects vs mixed effects</th>
<th>Averaging across multiple sessions Generalisation to population</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLS vs FLAME vs Randomise</td>
<td>Quick, doesn’t use VARCOPEs Uses COPEs &amp; VARCOPEs Non-parametric</td>
</tr>
<tr>
<td>Multiple comparison correction (FWE/ FDR)</td>
<td>Gaussian Random Field (voxel or cluster based) TFCE</td>
</tr>
</tbody>
</table>
What we covered so far

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

Single-subject analysis

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

Group-level analysis

Statistical inference
Looking ahead:
resting state
diffusion
arterial spin labeling
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
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

Consider using multiband
Resting state analysis

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

Consider using multiband

Need to apply extra noise-reduction steps (ICA)
# 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**
   - Group ICA+dual regression/Network analysis (FSLnets)

5. **Statistical inference**
Diffusion analysis

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

Diffusion directions
Blip-up/blip-down
Multi shell
Diffusion analysis

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

Diffusion directions
- Blip-up/blip-down
- Multi shell

Need to correct for eddy currents
Diffusion analysis

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

Diffusion directions
- Blip-up/blip-down
- Multi shell

Need to correct for eddy currents

Fractional anisotropy/ mean diffusivity/ tractography
ASL analysis

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

label and control images
background suppression
calibration image
ASL analysis

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

- label and control images
- background suppression
- calibration image

- label-control subtraction
ASL analysis

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

- label and control images
- background suppression
- calibration image
- label-control subtraction
- Perfusion weighted image
- Absolute perf. measurements
- Partial volume correction
Advanced preprocessing
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%)
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
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)

Bright & Murphy, NeuroImage, 2013
Physiological Measurements

Need to measure cardiac and respiratory cycles.

Several options available - the easiest are:

- Respiratory Bellows
- Pulse Oximeter

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.
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
Use in FEAT

PNM GUI creates a set of files suitable for use as *Voxelwise Confounds* in FEAT
Results: Pain-punctate arm

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

With PNM  ■  Without PNM  □  Both  ▼
Demeaning EVs
Demeaning at the group level

BOLD Contrast

R (your continuous covariate)

e.g. reaction time

1 r₁
1 r₂
1 r₃
1 r₄
1 r₅
1 r₆
Demeaning

BOLD Contrast

R (your continuous covariate)

e.g. reaction time

mumford.fmripower.org/
mean_centering/
Demeaning

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

\[
\begin{bmatrix}
1 & 0
\end{bmatrix}
\]

BOLD Contrast

R (your continuous covariate)

e.g. reaction time
Demeaning

$\beta_1$ now represents BOLD at group average $R$
**Demeaning**

<table>
<thead>
<tr>
<th>Design matrix</th>
<th>What does the fitted model look like?</th>
<th>Contrast</th>
<th>Does demeaning change the stats?</th>
<th>Demeaning recommended?</th>
</tr>
</thead>
</table>
| \[
\begin{bmatrix}
1 & r_1 \\
1 & r_2 \\
1 & r_3 \\
1 & r_4 \\
1 & r_5 \\
1 & r_6
\end{bmatrix}
\begin{bmatrix}
\beta_1 \\
\beta_r
\end{bmatrix}
\] |
| [1 0] | YES | YES |
| [0 1] | NO  | YES |

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 $EV_2$ (i.e. $r_1$ to $r_6$) **changes** $\beta_1$
Demeaning

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

\[ \begin{bmatrix} 0 & 1 \end{bmatrix} \]

\( \beta_1 \) represents BOLD at \( R=0 \)
$\beta_1$ now represents BOLD at group average R
Does demeaning change the stats?

What does the fitted model look like?

Contrast

Does demeaning change the stats?

Demeaning recommended?

\[
\begin{bmatrix}
1 & r_1 \\
1 & r_2 \\
1 & r_3 \\
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1 & r_5 \\
1 & r_6 \\
\end{bmatrix}
\begin{bmatrix}
\beta_1 \\
\beta_r \\
\end{bmatrix}
\]

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 \( EV_2 \) (i.e. \( r_1 \) to \( r_6 \)) \textbf{changes} \( \beta_1 \)
Advanced designs
Case Study: Parametric Designs

Scenario:
Interested in specific responses to multiple levels of a painful stimulus

Specific questions:
Are there regions showing significant responses to painful stimuli?
Are there regions where higher intensity stimuli produce larger responses?
Are there regions with a linear response across multiple levels of stimuli?

Solution:
Multiple regressors
Contrasts and F-tests
Analysis of responses to multiple levels of painful stimuli: modelling

• Possible approach: model a specific hypothesis - high produces twice the response as low

• Pre-supposes relationship between stimulation strength and response

• Can only ask the question about the pre-supposed relationship
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Can assess responses to individual stimuli
  - t-contrast [0 1]: “response to low pain”
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Can compare the size of the fits of the two regressors -
  - $t$-contrast $[1\ -1]$: "is the response to high pain greater than that to low pain?"
  - $t$-contrast $[-1\ 1]$: "is the response to low pain greater than that to high pain?"
Analysis of responses to multiple levels of painful stimuli: modelling

- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Average response?
  - \( t\)-contrast \([1 -1]\) : "is the average response to pain greater than zero?"
Parametric Variation - Linear Trends

- Is there a linear trend between the BOLD response and the painful stimulus intensity?
A three-strength experiment

Is there a linear trend between the BOLD response and some task variable?

t-contrast [-1 0 1] : Linear trend
- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- $t$-contrast $[-1 \ 0 \ 1]$ : Linear trend
• A three-strength experiment

• Is there a linear trend between the BOLD response and some task variable?

• t-contrast [-1 0 1]: Linear trend
### Parametric Variation - Linear Trends

- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- \( t \)-contrast \([-1 \ 0 \ 1] \): Linear trend
Parametric Variation - Linear Trends

- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- \( t \)-contrast \([-1 0 1] \): Linear trend

Slope \((\beta_3 - \beta_1)\) is the same for both...
Parametric Variation - Linear Trends

- A four-strength experiment
- t-contrast [-3 -1 1 3] : Positive linear trend
Parametric Variation - Linear Trends

- A four-strength experiment
- \( t \)-contrast \([-3 -1 1 3]\) :
  Positive linear trend

<table>
<thead>
<tr>
<th></th>
<th>strength 1</th>
<th>strength 2</th>
<th>strength 3</th>
<th>strength 4</th>
<th>pos trend</th>
<th>neg trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-3</td>
<td>3</td>
</tr>
<tr>
<td>C2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>C3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>-3</td>
</tr>
<tr>
<td>C5</td>
<td>pos trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>neg trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
But what if it isn’t that predictable?

Auditory word presentation at different rates

True story

Vernicke
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

More activation to 500 than to 100 WPM?

But no...
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

Activation proportional to WPM?

Still no...
But what if it isn’t that predictable?

Given this design what would be “reasonable” questions to ask?

Inversely proportional to WPM squared?

Vernicke

But seriously... would you have asked that question?

Yaay!

True story
But what if it isn’t that predictable?

There is a (very real) risk of missing interesting but unpredicted responses

What can we do about that?
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

An F-contrast is a series of questions (t-contrasts) with an OR between them
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

Let’s start with “Greater activation to 200 than 100 WPM”
F-contrasts to the rescue

We can define an F-contrast that spans "the range of possible responses"

OR

300 WPM > 200 WPM

True story
F-contrasts to the rescue

We can define an F-contrast that spans “the range of possible responses”

OR

400WPM > 300WPM
F-contrasts to the rescue

OR

500 WPM > 400 WPM

N.B.

True story
F-contrasts to the rescue

But ... that doesn’t span all possible response, what about for example 300>100?
F-contrasts to the rescue

But ... that doesn’t span all possible response, what about for example 300>100?

300>100 implies 200>100 AND/OR 300>200 which we have covered
F-contrasts to the rescue

But ... what about for example 100>200, you haven’t covered that?

This $t$-contrast asks “where is 200>100?”

F-contrasts are bi-directional
F-contrasts to the rescue

But this F-contrast asks “where is 200 ≠ 100?”

F-contrasts are bi-directional

But ... what about for example 100 > 200, you haven’t covered that?
Case Study: Factorial Designs and Interactions

Scenario:
Investigating in multi-sensory regions

Specific questions:
What regions show responses to vision, touch
What regions respond significantly to both?
Are responses additive where there is both visual and touch stimulation, or is there an interaction?

Solution:
Specific regressors
Contrast masking
Multisensory study

- EV1 models vision on/off
- EV2 models touch on/off

- Can generate simple contrasts for:
  - vision activation/deactivation $[1 \ 0]\]
  - touch activation/deactivation $[0 \ 1]\]
  - differences in responses $[1 \ -1]\]

- Regions showing both visual and tactile response??
- Not $[1 \ 1]$: this only assesses the average
Contrast Masking

- Often it is of interest to identify regions showing significant effects in multiple contrasts (e.g. responds to visual AND tactile stimulations)
- This can be achieved by masking a thresholded z image for a chosen contrast using the thresholded z image from one or more other contrasts.

![Contrast Masking Image](image-url)
Contrast Masking

- Often it is of interest to identify regions showing significant effects in multiple contrasts (e.g. responds to visual AND tactile stimulations)
- This can be achieved by masking a thresholded z image for a chosen contrast using the thresholded z image from one or more other contrasts.

For example, say we had two t contrasts C1 (1 0) and C2 (0 1). We may be interested in only those voxels which are significantly "active" for both contrasts.
Contrast Masking

• Rather than masking with voxels which survive thresholding, it may be desirable to mask using positive z statistic voxels instead.

For example, say that we have two t contrasts C3 (1 -1) and C1 (1 0). It may be desirable to see those voxels for which EV1 is bigger than EV2, only when EV1 is positive.
Factorial design

- Allows you to characterise interactions between component processes
  - i.e. effect that one component has on another

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
No Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Bar chart showing no interaction effect between vision and touch]
No Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Bar chart showing Vision, Touch, and Vision+Touch](image)

- Vision: Red
- Touch: Green
- Vision+Touch: Red and Green
No Interaction Effect

<table>
<thead>
<tr>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
</tr>
</tbody>
</table>

No interaction - effects add linearly
## Positive Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Graph showing the comparison of Vision, Touch, and Vision+Touch.*
Positive Interaction Effect

<table>
<thead>
<tr>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
</tr>
</tbody>
</table>

Positive interaction - “superadditive”
Negative Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Bar chart showing Vision, Touch, and Vision+Touch]
## Negative Interaction Effect

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Negative interaction - “subadditive”
Modelling Interactions Between EVs

- EV1 models vision on/off
- EV2 models touch on/off
Modelling Interactions Between EVs

- EV1 models vision on/off
- EV2 models touch on/off
- EV3 Models interaction

<table>
<thead>
<tr>
<th></th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 01 vision  | 1 | 0 | 0 |
| 02 touch   | 0 | 1 | 0 |
| 03 Pos interaction | 0 | 0 | 1 |
| 04 Neg interaction | 0 | 0 | -1 |
Correlation of EVs
Correlation of EVs

- Correlated EVs are relatively common, but **strong correlation is a problem** in either first-level or group-level designs.

- When EVs are correlated, it is the **unique contribution** from each EV that determines the model’s fit to the data and the statistics.

- Start by looking at first-level examples:
  - correlation and rank deficiency
  - design efficiency tool
Correlation of EVs: First-level designs
Design Matrix Rank Deficiency

- A design matrix is rank deficient when a linear combination of EVs is exactly zero
- Model can fit exactly the same signal in multiple ways!
- e.g. visual and tactile stimulation occurs at very similar times, so it is not possible to separate the responses!
Design Matrix Rank Deficiency

- A design matrix is rank deficient when a linear combination of EVs is exactly zero
- Model can fit exactly the same signal in multiple ways!
- e.g. visual and tactile stimulations are exactly opposed (so no baseline)
Design Matrix Rank Deficiency

- A design matrix is rank deficient when a linear combination of EVs is exactly zero
- Model can fit exactly the same signal in multiple ways!
- e.g. modelling visual, tactile, and rest (the last one is effectively baseline and shouldn’t be modelled in FSL)
Close to Rank Deficient
Design Matrices

- **Good News:** The statistics always take care of being close to rank deficient
Good News: The statistics always take care of being close to rank deficient

Bad News: the ignorant experimenter may have found no significant effect, because:
   a) Effect size was too small.
   b) Being close to rank deficient meant finding an effect would have required a HUGE effect size
      e.g. may need a lot of data to determine how two EVs with very similar timings best combine to explain the data.
When do we have a problem?

- Depends on SNR, and **crucially** the contrasts we are interested in:
  - \([1 \ -1]\) e.g. vis-tact??
  - \([1 \ 1]\) e.g. average response??
  - \([1 \ 0]\) or \([0 \ 1]\) ?? e.g. visual? or tactile?
When do we have a problem?

- Depends on SNR, and **crucially** the contrasts we are interested in:

  - \([1\ -1]\) e.g. vis-tact??
    - no chance:
  - \([1\ 1]\) e.g. average response??
    - no problems:
  - \([1\ 0]\) or \([0\ 1]\) ?? e.g. visual? or tactile?
    - no chance:
Design Efficiency

Desired P-Value

Design Matrix, X
Contrast, c
Noise level
Temporal autocorrelation

Design Efficiency

Required percent change
Design Efficiency

Settings for design efficiency calculations

Correlation matrix

Eigenvalues

% change required for each contrast to pass specified z-threshold

These are the most useful!
When do we have a problem?

- Depends on SNR, and **crucially** the contrasts we are interested in:
  - $[1 \ -1]$ e.g. vis-tact??  
    - no chance: 5.3%
  - $[1 \ 1]$ e.g. average response??  
    - no problems: 0.84%
  - $[1 \ 0]$ or $[0 \ 1]$ ?? e.g. visual? or tactile?  
    - no chance: 5.3%
Case Study: Correlated EVs

Scenario:
Investigating whether there is a relationship between a patient’s disease/behavioural scores and their BOLD responses

Problem:
Different scores are likely to be strongly correlated. Which regions’ responses correlate with disease scores but not age?

Solutions:
Combination of F-tests and t-tests
• Consider a case example:
  ‣ Disease Duration (DD) + age (demeaned)
    ‣ where we want to ‘correct’ for age
• Consider a case example:
  ‣ Disease Duration (DD) + age (demeaned)
    ‣ where we want to ‘correct’ for age
  ‣ If there is correlation between DD and age then it becomes tricky
  ‣ One option is orthogonalisation of DD and age …
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
    - where we want to ‘correct’ for age
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
  - where we want to ‘correct’ for age

A t-test for a single EV is determined only by variability in BOLD signal that cannot be accounted for by other EVs.

This is a conservative result: only when DD can uniquely explain the measurements will there be a significant result.
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
  - where we want to ‘correct’ for age

\[
\begin{bmatrix}
0 & 1 & 0 \\
0 & 1 & 0 \\
1 & 0 & 0 \\
\end{bmatrix}
\]

- t-test

- F-test

\[
\begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1 \\
\end{bmatrix}
\]
A better alternative to orthogonalisation

- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
  - where we want to ‘correct’ for age

An F-test finds regions where signal can be explained by *any combination* of EVs.

Will show significant results where either DD or age or both can explain the measurements.
A better alternative to orthogonalisation

Results (a fairly typical example with strong correlation):

Not significant (t-test)  Significant (F-test)

Interpretation: Significant correlation with both DD and age, but cannot separate the effects as they are too highly correlated and the response to unique portions (if any) are too weak.

Follow on: one way to (potentially) separate the effects would be to recruit new subjects such that DD and age were less correlated (need more data to go beyond the above interpretation).
That's All Folks
Appendix

Case Studies:

- HRF Variability
- Perfusion FMRI
- Orthogonalisation & more on demeaning
Case Study

Scenario:
- Patient vs Control study
- Patients on a drug treatment
- FMRI cognitive task

Problem:
- Drugs affect cerebral vascularity
- Haemodynamic Response Function (HRF) is altered
- Want to separate changes in HRF & neuronal activity
  - otherwise poor HRF model leads to bias in activation strength and increased residual noise

Solution:
- Basis functions to model HRF variability
Dealing with Variations in Haemodynamics

• The haemodynamic responses vary between subjects and areas of the brain
• How do we allow haemodynamics to be flexible but remain plausible?

Reminder: the haemodynamic response function (HRF) describes the BOLD response to a short burst of neural activity
Using Parameterised HRFs

- We need to allow flexibility in the shape of the fitted HRF

Ideally, parameterise HRF shape and fit shape parameters to the data

Needs nonlinear fitting - HARD
Using Basis Sets

- We need to allow flexibility in the shape of the fitted HRF

Ideally, parameterise HRF shape and fit shape parameters to the data.

Or, we can use **linear basis sets** to span the space of expected HRF shapes.

Needs nonlinear fitting - HARD

Linear fitting (use GLM) - EASY
Temporal Derivatives

- Can model some HRF variability using the temporal derivative
- The temporal derivative of an EV allows for a small shift in time of that EV (it is a small basis set)
- Based upon 1st-order Taylor series expansion:
  \[ f(t+a) \approx f(t) + a.f'(t) \]
How do HRF Basis Sets Work?

Temporal derivative is a simple example of a basis function - need more basis functions to allow for shape changes

Different linear combinations of several basis functions can be used to create different HRF shapes

\[
\begin{align*}
\text{basis fn 1} & \quad 1.0^* \\
+ \quad \text{basis fn 2} & \quad 0.3^* \\
+ \quad \text{basis fn 3} & \quad -0.1^* \\
= & \quad \text{HRF}
\end{align*}
\]
How do HRF Basis Sets Work?

Temporal derivative is a simple example of a basis function - need more basis functions to allow for shape changes.

Different linear combinations of several basis functions can be used to create different HRF shapes.

\[
\begin{align*}
\text{basis fn 1} & \quad + \quad 0.3^* & \quad + \quad -0.1^* \\
1.0^* & \quad + \quad 0.3^* & \quad + \quad -0.1^* \\
0.7^* & \quad + \quad -0.2^* & \quad + \quad 0.5^* \\
\end{align*}
\]

But how do we choose the basis functions?
FMRIB’s Linear Optimal Basis Set (FLOBS)

Using FLOBS we can:

• Specify a priori expectations of parameterised HRF shapes

• Generate an appropriate basis set (from a large set of samples)
FMRIB’s Linear Optimal Basis Set (FLOBS)

Select the main modes of variation as the optimal basis set

- Canonical HRF
- Dispersion derivative
- Temporal derivative
HRF Basis Functions in FEAT

The FEAT GUI allows a range of different basis functions to choose from.
The FEAT GUI allows a range of different basis functions to choose from:

- **Stimulus/Neural Activity**
- **HRF Basis functions**

Convolution options include:
- **Phase of**
- **File name**

Additional options:
- Orthogonalize basis functions with each other
- Apply temporal filtering
The FEAT GUI allows a range of different basis functions to choose from.
Recall that F-tests allow us to test if there is significant amounts of power explained by linear combinations of contrasts.
How do we Test for Significance?

Recall that F-tests allow us to test if there is significant amounts of power explained by linear combinations of contrasts

\[
\begin{pmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{pmatrix}
\]

But note: the F-test cannot distinguish between a positive or negative activation
HRF Basis Functions in FEAT

In FEAT the GUI allows contrasts to be setup on “Original EVs” or “Real EVs”

“Original EVs” represent the underlying experimental conditions
In FEAT the GUI allows contrasts to be setup on “Original EVs” or “Real EVs”.

“Original EVs” represent the underlying experimental conditions.

“Real EVs” represent the actual basis function EVs in the design matrix.
How do we Test for Significant Differences (at first level)?

We want to test for a significant difference between two underlying experimental conditions (e.g. two cognitive tasks)
How do we Test for Significant Differences (at first level)?

We want to test for a significant difference between two underlying experimental conditions (e.g. two cognitive tasks)

<table>
<thead>
<tr>
<th>EVs</th>
<th>Contrasts &amp; F-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setup contrasts &amp; F-tests for</td>
<td>Original EVs</td>
</tr>
<tr>
<td>Contrasts</td>
<td>F-tests</td>
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<tr>
<td>3</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>Paste</th>
<th>Title</th>
<th>EV1</th>
<th>EV2</th>
</tr>
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<tbody>
<tr>
<td>OC1</td>
<td>condition 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>OC2</td>
<td>condition 2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>OC3</td>
<td>cond1-cond2</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>
How do we Test for Significant Differences (at first level)?

We want to test for a significant difference between two underlying experimental conditions (e.g. two cognitive tasks).
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</tr>
</thead>
<tbody>
<tr>
<td>Setup contrasts &amp; F-tests for Original EVs</td>
<td></td>
</tr>
<tr>
<td>Contrasts 3 F-tests 0</td>
<td></td>
</tr>
<tr>
<td>Paste</td>
<td>Title</td>
</tr>
<tr>
<td>OC1</td>
<td>condition 1</td>
</tr>
<tr>
<td>OC2</td>
<td>condition 2</td>
</tr>
<tr>
<td>OC3</td>
<td>cond1-cond2</td>
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</table>

<table>
<thead>
<tr>
<th>Basis fn EVs for condition 1</th>
<th>Basis fn EVs for condition 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>c1 condition 1 (1)</td>
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<tr>
<td>c2 condition 1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>c3 condition 1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>c4 condition 2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>c5 condition 2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>c6 condition 2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>c7 cond1-cond2 (1)</td>
<td>1</td>
</tr>
<tr>
<td>c8 cond1-cond2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>c9 cond1-cond2 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>
How do we Test for Significant Differences (at first level)?

We want to test for a significant difference between two underlying experimental conditions (e.g. two cognitive tasks).

- F-test combines [1 -1] t-contrasts for corresponding basis fn EVs
- this will find significance if there are **size** or **shape** differences
How do we Test for Significant Differences (at higher levels)?

- Using basis fns and F-tests is problematic when it comes to doing inference on groups of subjects.
- This is because we are typically interested in only size (not shape) at the group level.

Controls

Patients

Between group differences in size and shape.

At the group level look at size differences.
How do we Test for Significant Differences (at higher levels)?

- Using basis fns and F-tests is problematic when it comes to doing inference on groups of subjects
- This is because we are typically interested in only size (not shape) at the group level

Options:

1) Only use the “canonical HRF” EV PE in the group inference
   - e.g. when EVs with temporal derivatives, only use the main EV’s PE in the group inference
How do we Test for Significant Differences (at higher levels)?

• Using basis fns and F-tests is problematic when it comes to doing inference on groups of subjects
• This is because we are typically interested in only size (not shape) at the group level

• Options:

  1) Only use the “canonical HRF” EV PE in the group inference
     - e.g. when EVs with temporal derivatives, only use the main EV’s PE in the group inference

  2) Calculate a “size” statistic from the basis function EVs PEs and use in the group inference
     - must use randomise for this, not standard FEAT/FLAME
Case Study

Scenario:
Pain study of tonic, ongoing pain and involving infusion of drugs during scanning
(or any other slow-acting physiological stimuli e.g. thirst)

Problem:
Very slow changes in BOLD activity (> several minutes)
- slow drifts in noise cannot be separated from neuronally-induced BOLD activity by normal temporal filtering

Solution:
Alternative to BOLD = Arterial Spin Labelling (ASL)
Perfusion FMRI using Arterial Spin Labelling (ASL)

- Alternative to BOLD
- Noisier than BOLD for high frequency designs
- Potentially less noisy than BOLD for low frequency designs
- More quantitative
- Only a few slices
Perfusion FMRI using Arterial Spin Labelling (ASL)

- Blood is **tagged** in the arteries (e.g. in the neck) using an RF pulse
- After a delay to allow tagged blood to flow into the imaging region, the image is read out
- A **control** image is also collected without the tag. The subtraction of the two images gives a **perfusion-weighted image**
Perfusion FMRI Modelling

- Timeseries alternates between "control" (up) and "tag" (down)
- Activation seen as modulation of control-tag difference
- There are two GLM approaches available in FEAT:
Perfusion FMRI Modelling

• Timeseries alternates between "control" (up) and "tag" (down)
• Activation seen as modulation of control-tag difference
• There are two GLM approaches available in FEAT:

1) Pre-subtract data (using sinc interpolation)
Perfusion FMRI Modelling

- Timeseries alternates between "control" (up) and "tag" (down)
- Activation seen as modulation of control-tag difference
- There are two GLM approaches available in FEAT:
  1) Pre-subtract data (using sinc interpolation)
  2) Use full model of unsubtracted data
Simultaneous BOLD and Perfusion
FMRI Modelling

• Dual-echo sequences commonly used to extract BOLD and perfusion changes simultaneously
• Traditionally, separate analysis of low TE (for perfusion) and high TE (for BOLD) results in biased results
Simultaneous BOLD and Perfusion FMRI Modelling

- Dual-echo sequences commonly used to extract BOLD and perfusion changes simultaneously
- Traditionally, separate analysis of low TE (for perfusion) and high TE (for BOLD) results in biased results

- **FABBER** uses nonlinear simultaneous modelling of both TEs to give uncontaminated, more sensitive information
Orthogonalisation - A cautionary tale

• You are running a study to see what parts of the brain are less active when performing a task in patients with the neurodegenerative disease “Syndrome X”

• In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)

So you set up a design where you model the activation as a linear function of DoD (and a mean)
Orthogonalisation - A cautionary tale

- You are running a study to see what parts of the brain are less active when performing a task in patients with the neurodegenerative disease “Syndrome X”

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)

And in one voxel the data happens to look like this
Orthogonalisation - A cautionary tale

- You are running a study to see what parts of the brain are less active when performing a task in patients with the neurodegenerative disease “Syndrome X”
- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)

![Graph showing BOLD signal and subject number]

\[
\begin{bmatrix}
0.808 \\
-0.005
\end{bmatrix}
\]

\[t = -6.33\]

And this is the model fit to the data. You are very pleased with yourself.
Orthogonalisation - A cautionary tale

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)

\[
\begin{bmatrix}
0.808 \\
-0.005
\end{bmatrix}
\]

A different way of looking at your data
Orthogonalisation - A cautionary tale

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)

\[
\text{mean DoD} = 0.808, 0.005
\]

A different way of looking at your data

slope = -0.005

And at your model fit
Orthogonalisation - A cautionary tale

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)
- Then someone points out that we all suffer from a neurodegenerative disease called “life”

So you complement your design with an (uninteresting) age regressor

And the model fit still looks good
(maybe even a little better)
Orthogonalisation - A cautionary tale

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)
- Then someone points out that we all suffer from a neurodegenerative disease called “life”

\[
\begin{bmatrix}
0 & 1 & 0
\end{bmatrix}
\]

And you test your DoD for significance

What on earth just happened?

\[ t = 0.11 \]
Orthogonalisation - A cautionary tale

- In particular you want to know in what areas the activity is proportional to the duration of the disease (DoD)
- Then someone points out that we all suffer from a neurodegenerative disease called “life”

\[
\begin{bmatrix}
0 & 0 & 1
\end{bmatrix}
\]

Is it that age explains everything?

No, not all of it. So what happened?

\[ t = -2.84 \]
Orthogonalisation - A cautionary tale

- Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

- But what does that really mean?

\[
\begin{bmatrix}
0 & 1 & 0
\end{bmatrix}
\]

Full model  \[\text{DoD} \quad \text{ag}\]  \text{The regressor we want to test}  \[\text{DoD}\]  \text{“The other regressors”}
Orthogonalisation - A cautionary tale

- Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

- So, let’s use “the other regressors” to explain these data

“The other regressors”

```
subject # | signal
---------|-------
1         | 0.35  
2         | 0.65  
3         | 0.90  
4         | 0.40  
5         | 0.70  
6         | 0.10  
7         | 0.80  
8         | 0.50  
9         | 0.20  
10        | 0.60  
11        | 0.90  
12        | 0.40  
13        | 0.70  
14        | 0.10  
15        | 0.80  
16        | 0.50  
17        | 0.20  
18        | 0.60  
19        | 0.90  
20        | 0.40  
21        | 0.70  
22        | 0.10  
23        | 0.80  
24        | 0.50  
25        | 0.20  
26        | 0.60  
27        | 0.90  
28        | 0.40  
29        | 0.70  
30        | 0.10  
31        | 0.80  
32        | 0.50  
33        | 0.20  
34        | 0.60  
35        | 0.90  
36        | 0.40  
37        | 0.70  
38        | 0.10  
39        | 0.80  
40        | 0.50  
41        | 0.20  
42        | 0.60  
43        | 0.90  
44        | 0.40  
45        | 0.70  
```

BOLD signal vs Subject # graph
Orthogonalisation - A cautionary tale

• Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

• So, let’s use “the other regressors” to explain these data

“The other regressors”

By fitting them to the data
Orthogonalisation - A cautionary tale

- Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

- And what is left is the “unexplained” part
Orthogonalisation - A cautionary tale

• Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

• And what is left is the “unexplained” part

Original and “Explanation”

“Unexplained”
(not well represented by DoD)
Orthogonalisation - A cautionary tale

- Remember how we have been saying “GLM tests for a regressor after it has explained as much as it possibly can using the other regressors”?

- And the reason for all of this is that Age and DoD are correlated

- GLM says “I cannot be sure if this explanatory power belongs to you or to you. So neither can have it.”

- Much like a parent would.
Orthogonalisation - A cautionary tale

- So what about orthogonalisation then. What does that do?
- To orthogonalise A with B is to say to B “You, B, can have all the explanatory power. A doesn’t get any”.
- Let us see how we would orthogonalise Age w.r.t. DoD

![Graph showing Age and DoD with annotations](image)
• So what about orthogonalisation then. What does that do?

• To orthogonalise A with B is to say to B “You, B, can have all the explanatory power. A doesn’t get any”.

• And this “unique” part is “Age orthogonalised w.r.t. DoD”
Orthogonalisation - A cautionary tale

• So what about orthogonalisation then. What does that do?

• To orthogonalise A with B is to say to B “You, B, can have all the explanatory power. A doesn’t get any”.

• And this “unique” part is “Age orthogonalised w.r.t. DoD”
Orthogonalisation - A cautionary tale

- So what about orthogonalisation then. What does that do?
- To orthogonalise A with B is to say to B “You, B, can have all the explanatory power. A doesn’t get any”.
- And then fit DoD to the unexplained part

The regressor we want to test

$\mathbf{t} = -7.08$

Fitted to the unexplained part
Orthogonalisation - A cautionary tale

• So what about orthogonalisation then. What does that do?

• To orthogonalise A with B is to say to B “You, B, can have all the explanatory power. A doesn’t get any”.

• And then fit DoD to the unexplained part

Or viewed in the other way

The regressor we want to test

Fitted to the unexplained part

\[ t = -7.08 \]
A better alternative to orthogonalisation

- Look at the results of F-tests on the combined effects:
  - mean + DoD + age
  - DoD + age (as DoD and age are demeaned)
  - Plus the t-test on the desired effect: DoD
A better alternative to orthogonalisation

Results:
Not significant

Interpretation: Significant correlation with both DoD and age, but cannot separate the effects as they are too highly correlated and the response to unique portions (if any) are too weak.

Follow on: to separate effects could potentially recruit new subjects such that DoD and age were less correlated.
Orthogonalisation - A cautionary tale

• So what has orthogonalisation done for us?

• When we orthogonalised DoD with Age we took all the explanatory power that was shared/common to Age and DoD and put all of it with DoD.

• This gave a highly significant effect of DoD

• But was this a good thing to do?

• No! There is nothing in our data that allows us to say if the effect came from Age or Disease Duration. We have just made an arbitrary decision to attribute it to Disease Duration.

• GLM did the right thing by saying: “I don’t know who this belongs to, so I can’t give it to either”
Orthogonalisation - A cautionary tale

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• And in fact I simulated these data, so I happen to know that the causality was:
When to orthogonalise?

• **ESSENTIALLY NEVER:** The GLM automatically deals with correlations between regressors in a conservative manner.

  • We generally cannot be certain which of two correlated regressors contributes to BOLD signal effects. e.g. head motion or task?

• Orthogonalisation may make sense in certain models where causality is unambiguous.

  • I challenge someone to give me an unambiguous example.

  • However, it is usually still clearer to conduct the appropriate F-tests and t-tests and interpret these results since all the information is there. It generally isn’t necessary or safe to arbitrarily force explanatory power
Demeaning

Design matrix

What does the fitted model look like?

Contrast

Does demeaning change the stats?

Demeaning recommended?

\[ \begin{pmatrix}
1 & 0 & r_1 \\
1 & 0 & r_2 \\
1 & 0 & r_3 \\
0 & 1 & r_4 \\
0 & 1 & r_5 \\
0 & 1 & r_6 \\
\end{pmatrix} \begin{pmatrix}
\beta_{G1} \\
\beta_{G2} \\
\beta_r \\
\end{pmatrix} \]

Same slope in both groups

\[
\begin{bmatrix}
1 & -1 & 0 \\
0 & 0 & 1 \\
1 & 0 & 0 \\
0 & 1 & 0 \\
\end{bmatrix}
\]

NO

YES

NO

YES

YES

YES

mumford.fmripower.org/mean_centering/
<table>
<thead>
<tr>
<th>Design matrix</th>
<th>What does the fitted model look like?</th>
<th>Contrast</th>
<th>Does demeaning change the stats?</th>
<th>Demeaning recommended?</th>
</tr>
</thead>
</table>
| \[
\begin{pmatrix}
1 & 0 & r_1 & 0 \\
1 & 0 & r_2 & 0 \\
1 & 0 & r_3 & 0 \\
0 & 1 & 0 & r_4 \\
0 & 1 & 0 & r_5 \\
0 & 1 & 0 & r_6 \\
\end{pmatrix}
\] | Different slopes in the two groups | \[
\begin{bmatrix}
1 & -1 & 0 & 0 \\
\end{bmatrix}
\] | YES | YES* |
| \[
\begin{pmatrix}
\beta_{G1} \\
\beta_{G2} \\
\beta_{r1} \\
\beta_{r2} \\
\end{pmatrix}
\] | Do not demean \textit{within} groups | \[
\begin{bmatrix}
1 & 0 & 0 & 0 \\
\end{bmatrix}
\] or \[
\begin{bmatrix}
0 & 1 & 0 & 0 \\
\end{bmatrix}
\] | YES | YES* |
| \[
\begin{bmatrix}
0 & 0 & 1 & -1 \\
\end{bmatrix}
\] or \[
\begin{bmatrix}
0 & 0 & 1 & 0 \\
\end{bmatrix}
\] or \[
\begin{bmatrix}
0 & 0 & 0 & 1 \\
\end{bmatrix}
\] | Demean all values \textit{and then} split into groups | YES* = it is probably better to do it, although these contrasts are \textit{VERY} hard to interpret either way | YES |

\textit{YES*} = it is probably better to do it, although these contrasts are \textit{VERY} hard to interpret either way.