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

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

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

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

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

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
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

**Functional data:**
- Motion correction
- Slice timing correction
- Spatial filtering
- Temporal filtering
- Regressors & contrasts
- First level GLM
- Regressors & contrasts
- Group level GLM
- Thresholding & correction
- Registration & unwarping
fMRI pipeline

**Structural data:**
- Brain extraction

**Functional data:**
- Motion correction
- Slice timing correction
- Spatial filtering
- Temporal filtering

**Preprocessing**
- Registration & unwarping

**Single-subject analysis**
- Regressors & contrasts
- First level GLM

**Group-level analysis**
- Regressors & contrasts
- Group level GLM

**Statistical inference**
- Thresholding & correction
Check all stages!

Structural data:
- Brain extraction

Functional data:
- Registration & unwarping

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

Statistical inference
# Preprocessing summary

<table>
<thead>
<tr>
<th>Process</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>Put images into same space (standard space for group analysis)</td>
</tr>
<tr>
<td>Single-subject analysis summary</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>EVs/ regressors</strong></td>
<td>Design matrix: model of predicted responses based on stimuli presented at each time point</td>
</tr>
<tr>
<td><strong>GLM</strong></td>
<td>Estimate parameter estimates for each EV so that the linear combination best fits the data</td>
</tr>
<tr>
<td><strong>Contrasts (F or t)</strong></td>
<td>Maths on parameter estimates to ask research questions. Result is a COPE image per contrast</td>
</tr>
<tr>
<td>EVs/ regressors</td>
<td>Design matrix: one entry per subject. Can describe subject groups, confounds etc</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>GLM</td>
<td>Inputs are first-level COPE and VARCOPE images.</td>
</tr>
<tr>
<td>Contrasts (F or t)</td>
<td>Each group-level contrast is tested for each of the subject-level contrast</td>
</tr>
</tbody>
</table>
## Statistical inference summary

<table>
<thead>
<tr>
<th></th>
<th>Fixed vs mixed effects</th>
<th>Averaging across multiple sessions</th>
<th>Generalisation to population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLS vs FLAME</strong></td>
<td>Quick, doesn’t use VARCOPEs</td>
<td>Uses COPEs &amp; VARCOPEs</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple comparison correction (FWE/ FDR)</strong></td>
<td>Gaussian Random Field (voxel or cluster based)</td>
<td>TFCE</td>
<td>Randomise</td>
</tr>
</tbody>
</table>
Beyond fMRI:
resting state
diffusion
structural
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
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)
- Group ICA+dual regression/Network analysis (FSLnets)
Diffusion analysis

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

→

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 analysis

1. Data acquisition
   - Blip-up/blip-down
   - Multi shell

2. Data preprocessing
   - Need to correct for eddie currents

3. Single-subject analysis
   - Fractional anisotrophy
   - Mean diffusivity
   - Tractography

4. Group-level analysis

5. Statistical inference
Structural analysis

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

Consider getting $T_2$ or flair for different tissue contrasts
Structural analysis

1. Data acquisition → Consider getting T₂ or flair for different tissue contrasts
2. Data preprocessing → Bias correction
3. Single-subject analysis
   Need very accurate BET
4. Group-level analysis
5. Statistical inference
Structural analysis

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

Consider getting T$_2$ or flair for different tissue contrasts

Bias correction
Need very accurate BET

Voxel-Based Morphometry
Shape analysis
# The rest of the week

<table>
<thead>
<tr>
<th>Start time</th>
<th>Monday 19 June</th>
<th>Tuesday 20 June</th>
<th>Wednesday 21 June</th>
<th>Thursday 22 June</th>
<th>Friday 23 June</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>Course Registration (coffee provided)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:30</td>
<td>Registration <em>MJ</em></td>
<td>Multi-subject stats <em>MJ</em></td>
<td>Resting state ICA <em>JB</em></td>
<td>DTI <em>JA</em></td>
<td>Segmentation <em>MJ</em></td>
</tr>
<tr>
<td>9:15</td>
<td>Coffee break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:45</td>
<td>Unwarping <em>MJ</em></td>
<td>Permutation testing <em>JA</em></td>
<td>Resting state ICA <em>JB</em></td>
<td>DTI <em>JA</em></td>
<td>Segmentation <em>MJ</em></td>
</tr>
<tr>
<td>10:30</td>
<td>Practical session</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12:00</td>
<td>Lunch (not provided, attendees must make their own arrangements)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13:30</td>
<td>fMRI Preprocessing <em>MJ</em></td>
<td>Pipeline overview <em>JB</em></td>
<td>Resting state FSLnets <em>SS</em></td>
<td>Tractography <em>MB</em></td>
<td>Human Connectome Project/ Future work <em>DvE/MJ</em></td>
</tr>
<tr>
<td>14:15</td>
<td>Coffee break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14:45</td>
<td>GLM stats <em>JA</em></td>
<td>Advanced fMRI <em>MJ</em></td>
<td>Resting state FSLnets <em>SS</em></td>
<td>Tractography <em>MB</em></td>
<td></td>
</tr>
<tr>
<td>15:30</td>
<td>Practical session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17:00-18:00</td>
<td>Evening physics lecture <em>MC</em></td>
<td>Extra practical catch-up time</td>
<td>Evening physics lecture <em>MC</em></td>
<td>Thursday night social (17:30-19:30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evening reception (18:00-22:00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
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
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
Physiological Measurements

Need to measure cardiac and respiratory cycles.

Several options available - the easiest are:

- **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)
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
Demeaning EVs
Demeaning at the group level

BOLD Contrast

R (your continuous covariate)

e.g. reaction time

mumford.fmripower.org/mean_centering/
Demeaning

BOLD Contrast

R (your continuous covariate)

e.g. reaction time

mumford.fmripower.org/mean_centering/
Demeaning

\[ R \text{ (your continuous covariate)} \]

\[ \beta_1, \beta_r \]

\[ \text{e.g. reaction time} \]

Demeaning contrasts.

mumford.fmripower.org/
mean_centering/
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{pmatrix}
1 & r_1 \\
1 & r_2 \\
1 & r_3 \\
1 & r_4 \\
1 & r_5 \\
1 & r_6
\end{pmatrix}
\begin{pmatrix}
\beta_1 \\
\beta_r
\end{pmatrix}
| ![Graph showing BOLD Contrast vs. r](image.jpg) | \[
\begin{bmatrix}
1 & 0
\end{bmatrix}
\] | YES | YES |
| | | \[
\begin{bmatrix}
0 & 1
\end{bmatrix}
\] | 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

$\beta_1$ represents BOLD at $R=0$
Demeaning

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

**Design matrix**

| 1  | r₁  | β₁    |
| 1  | r₂  |       |
| 1  | r₃  |       |
| 1  | r₄  |       |
| 1  | r₅  |       |
| 1  | r₆  |       |

**What does the fitted model look like?**

- **Contrast**
  - \([ 1 \ 0 ]\)
  - Does demeaning change the stats? **YES**
  - **YES**
  - **YES**

**Mean centred value**

\[
\text{Mean centred value} = r₁ - \bar{r}
\]

where \(\bar{r}\) is the mean of \(r₁\) to \(r₆\)

**Adding or subtracting a mean from**

\(EV₂\) (i.e. \(r₁\) to \(r₆\)) **changes** \(β₁\)
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?

![Graph showing linear trend between BOLD signal effect size and pain stimulus intensity.](image)
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
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
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>1</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>strength 1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>strength 2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C3</td>
<td>strength 3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>strength 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C5</td>
<td>pos trend</td>
<td>-3</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>C6</td>
<td>neg trend</td>
<td>3</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>
But what if it isn’t that predictable?

Auditory word presentation at different rates

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?

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

Yaay!
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?
An F-contrast is a series of questions (t-contrasts) with an OR between them.

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

300WPM > 200WPM
F-contrasts to the rescue

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

OR

400 WPM > 300 WPM
F-contrasts to the rescue

OR

500 WPM > 400 WPM

N.B.
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

FSL
F-contrasts to the rescue

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

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

F-contrasts are bi-directional

True story
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

- 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>No Touch</th>
<th>No Vision</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td></td>
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</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](image)

- Vision
- 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 categories]
No Interaction Effect

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

![Bar chart showing Vision, Touch, and Vision+Touch interaction effects]
Positive Interaction
Effect

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

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

Negative interaction - "subadditive"
Modelling Interactions Between EVs

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

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

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
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<td>C3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>
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)
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
Close to Rank Deficient Design Matrices

- **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

Required percent change
Design Efficiency

Settings for design efficiency calculations

Correlation matrix

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

Eigenvalues

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?? **Effect size required**
    - 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
Correlations, Covariates & Corrections

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

- 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

 t-test

F-test

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

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

\[
f(t+a) \approx f(t) + a.f'(t)
\]

- Temporal derivative
- Shifting EV
- EV
- Model fit without derivative
- Model fit with derivative
- Data
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.
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

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.

Stimulus/Neural Activity

convolved with

HRF Basis functions

View design  Efficiency  Done
HRF Basis Functions in FEAT

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

- Stimulus/Neural Activity
- convolved with
- HRF Basis functions
- Basis function stimulus responses
The FEAT GUI allows a range of different basis functions to choose from.
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.
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.

But note: the F-test cannot distinguish between a positive or negative activation.
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)
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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)

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

\[t = -6.33\]

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

use as x-value

use as y-value
Orthogonalisation - A cautionary tale

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

![Graph showing BOLD signal vs. Subject #]

A different way of looking at your data

![Graph showing BOLD signal vs. Duration of Disease]

use as y-value

BOLD signal

use as x-value

0.808

-0.005

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?
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?

\[ t = -2.84 \]

No, not all of it. So what happened?
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

The regressor we want to test

“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”
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.

By fitting them to the data

“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”?

- 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” (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 for unexplained and unique to age aspects.](image)
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

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

\[ t = -7.08 \]

The regressor we want to test

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

$$t = -7.08$$

Or viewed in the other way

The regressor we want to test

Fitted to the unexplained part
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

<table>
<thead>
<tr>
<th>mean</th>
<th>DoD</th>
<th>ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
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</table>

<table>
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<th>DoD</th>
<th>ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

F-tests:

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

**t-test**

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

**F-tests**

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

**Results:**

Not significant

**Both 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

- 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”
- 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**

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

**What does the fitted model look like?**

- Same slope in both groups

**Contrast**

- $[1 \ -1 \ 0]$  
- $[0 \ 0 \ 1]$  
- $[1 \ 0 \ 0]$  
- $[0 \ 1 \ 0]$  

**Does demeaning change the stats?**

- NO
- NO
- YES
- YES

**Demeaning recommended?**

- NO
- YES
- YES
- YES
### 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>
| \[
\begin{pmatrix}
1 & 0 & r_1 & 0 \\
1 & 0 & r_2 & 0 \\
1 & 0 & r_3 & 0 \\
0 & 1 & 0 & r_4 \\
0 & 1 & 0 & r_5 \\
0 & 1 & 0 & r_6
\end{pmatrix}
\] |

| \( \begin{pmatrix}
\beta_{G_1} \\
\beta_{G_2} \\
\beta_{r_1} \\
\beta_{r_2}
\end{pmatrix} \) |

*Different slopes in the two groups*

*Do not demean* within groups

*Demean all values and then split into groups*

- \([1 -1 0 0]\)
  - YES
  - YES*
- \([1 0 0 0]\)
  - YES
  - YES*
- \([0 1 0 0]\)
  - YES
- \([0 0 1 -1]\)
  - NO
  - YES
- \([0 0 1 0]\)
  - YES*
- \([0 0 0 1]\)
  - YES*

*YES* = it is probably better to do it, although these contrasts are VERY hard to interpret either way