Advanced designs

Advanced Analysis: 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?

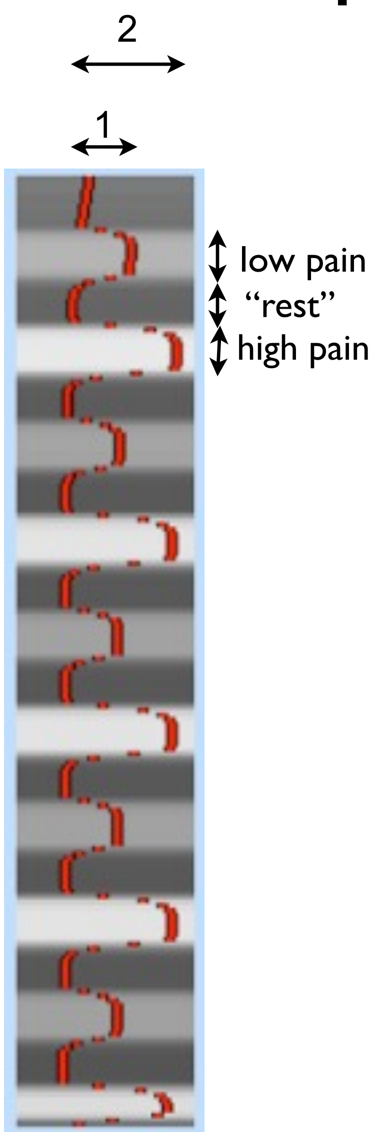
Are there regions with a linear response across multiple levels of stimuli?

Solution:

Multiple regressors

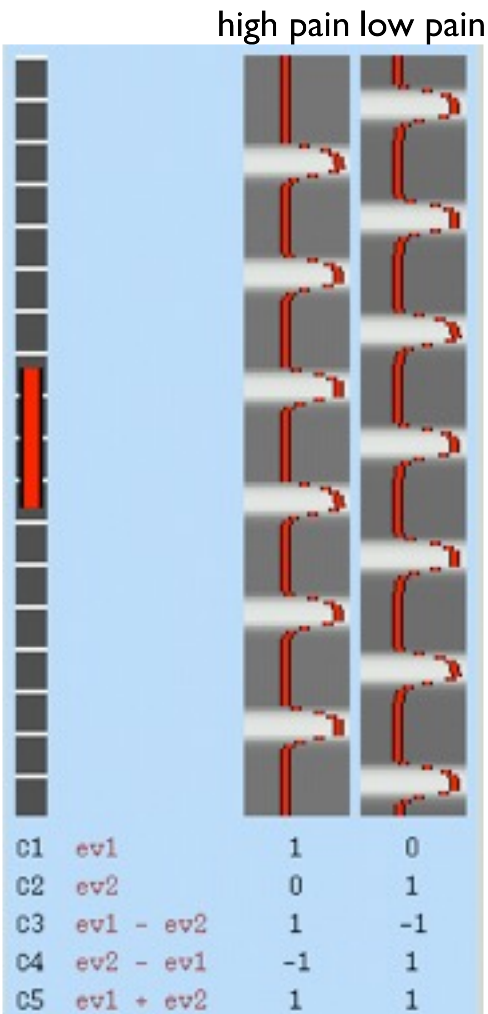
Contrasts and F-tests

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

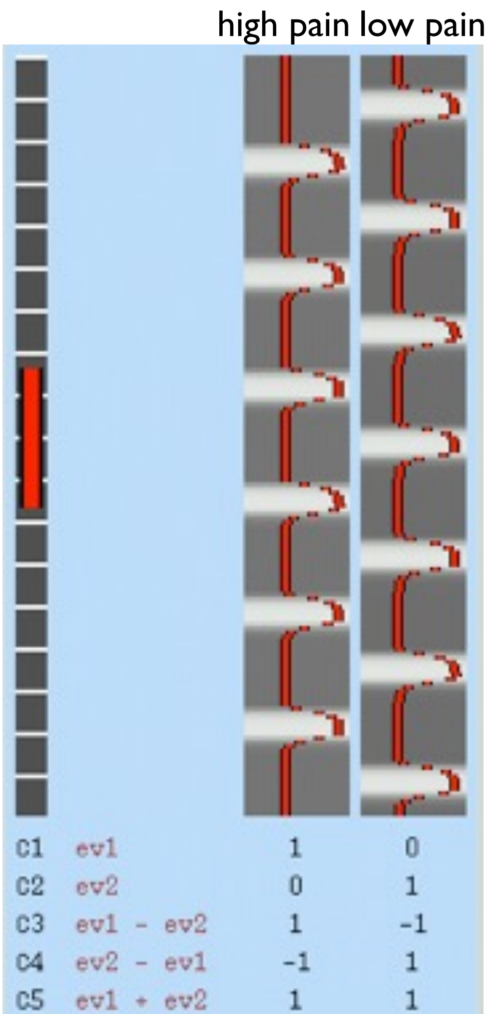


- Better approach: model as if two completely different stimuli
- Now, no pre-supposition about relationship between stimulation strength and response

- Can assess responses to individual stimuli

  - t-contrast [0 1]:" response to low pain"

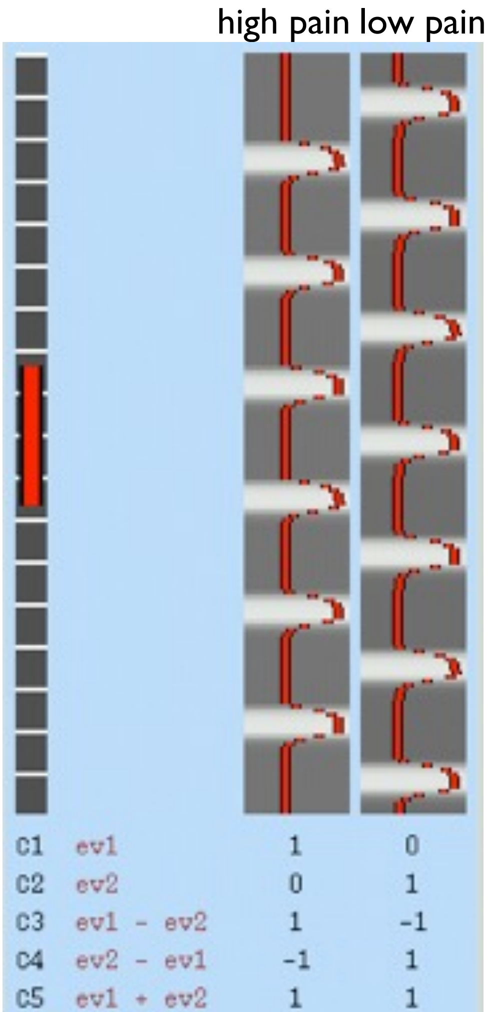
Analysis of responses to multiple levels of painful stimuli: modelling



- 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

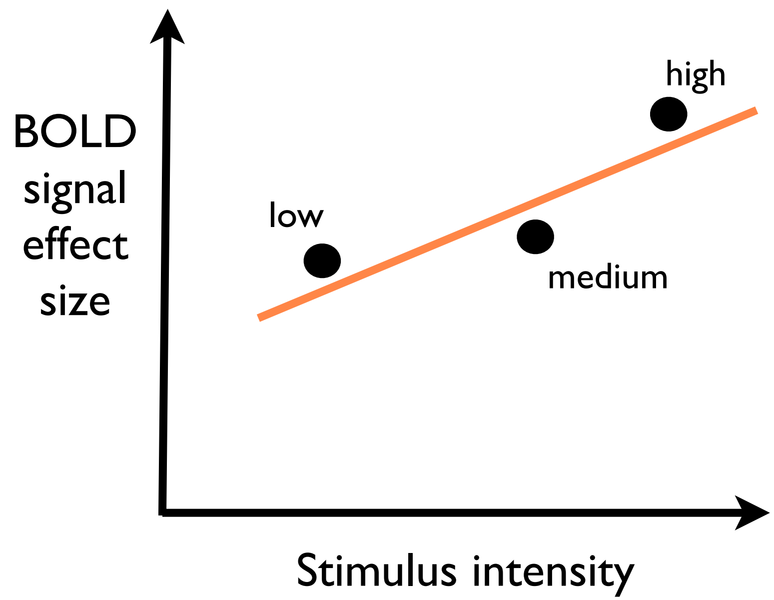
- Average response?
  - t-contrast [1 1] : "is the average response to pain greater than zero?"

Parametric Variation: Linear Trends

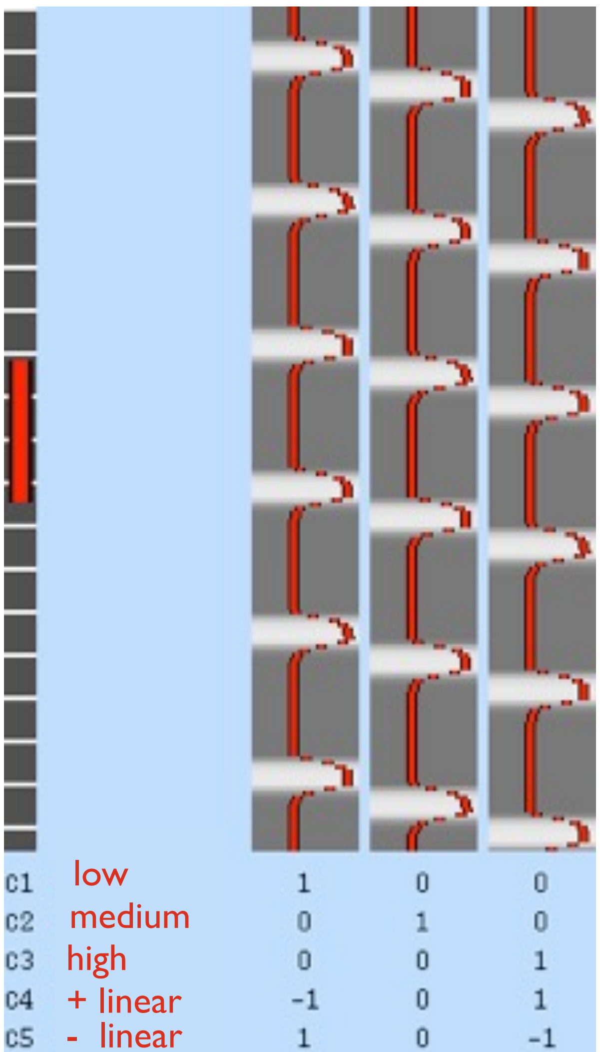
- Is there a linear trend between the BOLD response and stimulus intensity?

Parametric Variation: Linear Trends

- Is there a linear trend between the BOLD response and stimulus intensity?

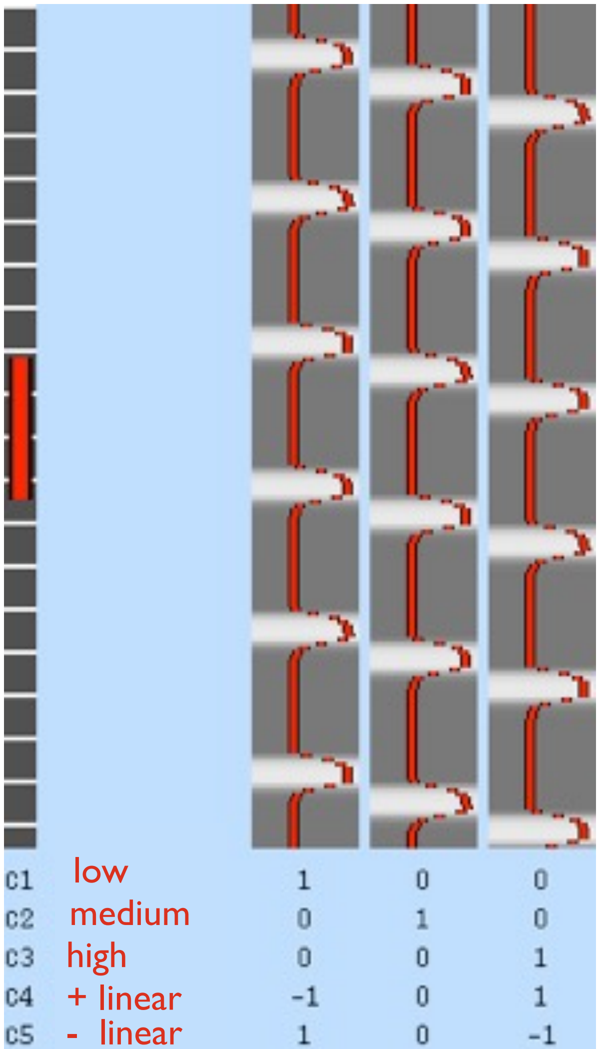


Parametric Variation: Linear Trends

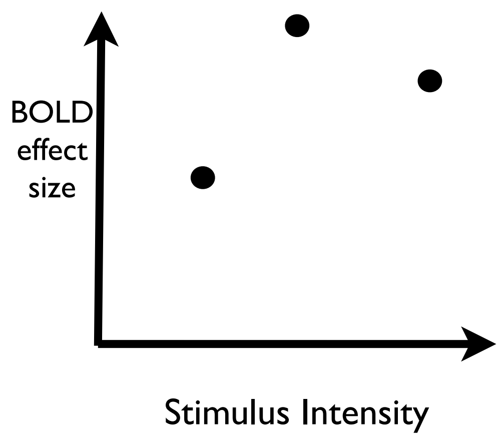


- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- t-contrast [-1 0 1] : Linear trend

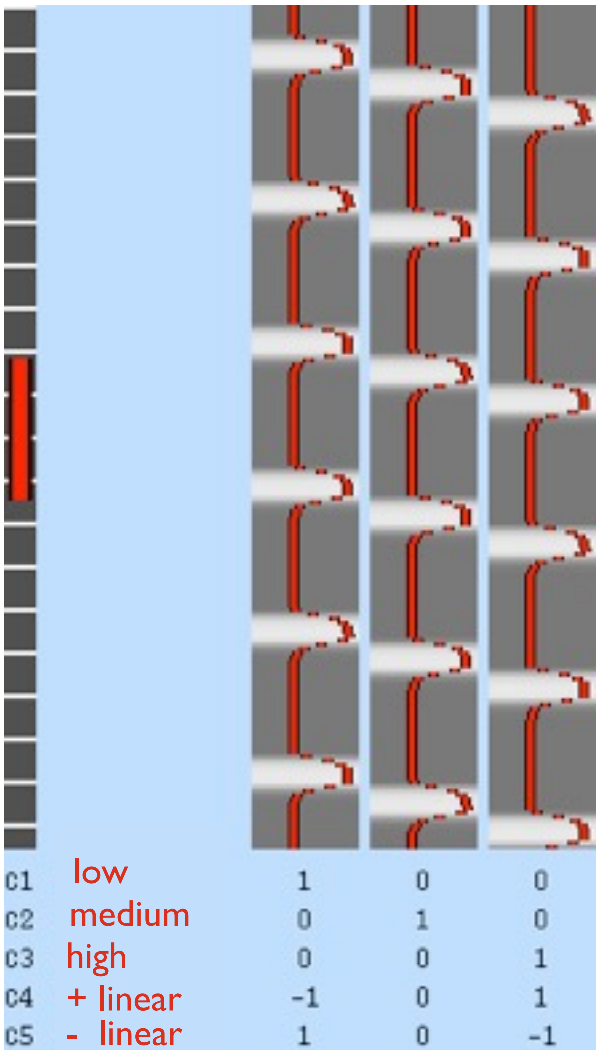
Parametric Variation: Linear Trends



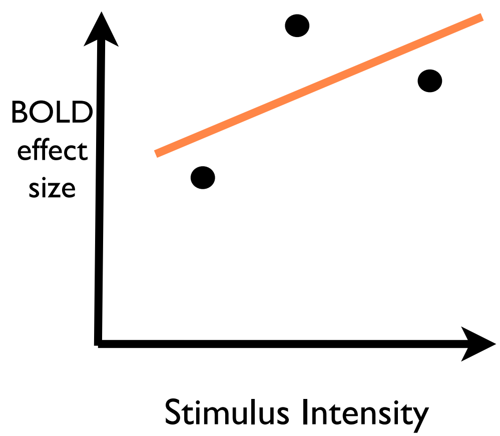
- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- t-contrast [-1 0 1] : Linear trend



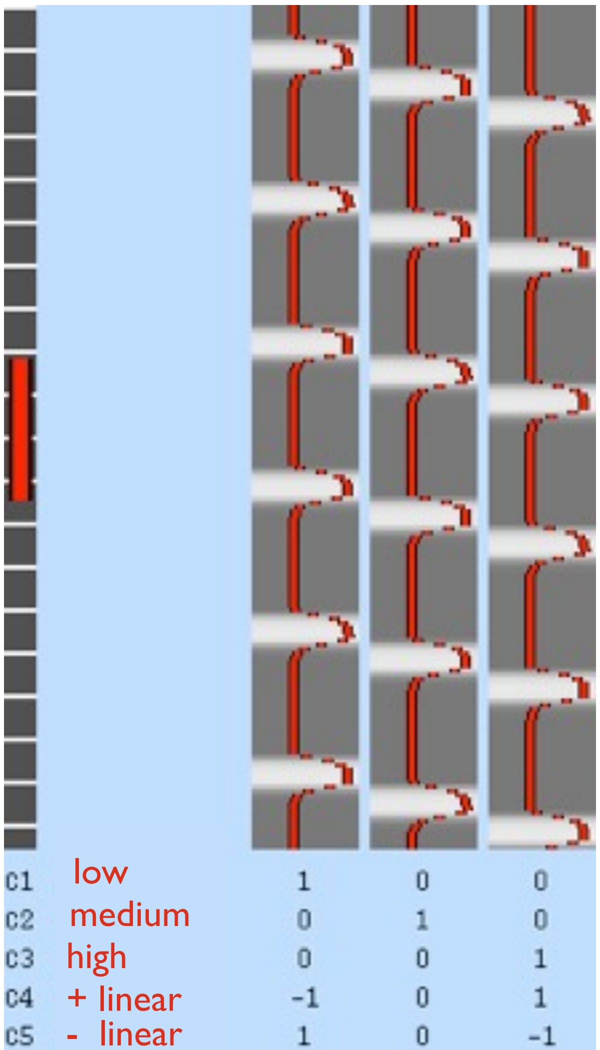
Parametric Variation: Linear Trends



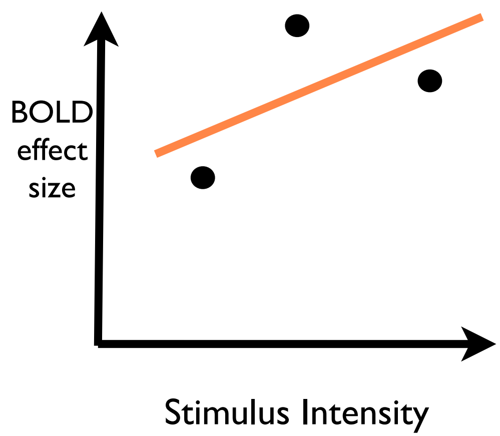
- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- t-contrast [-1 0 1] : Linear trend

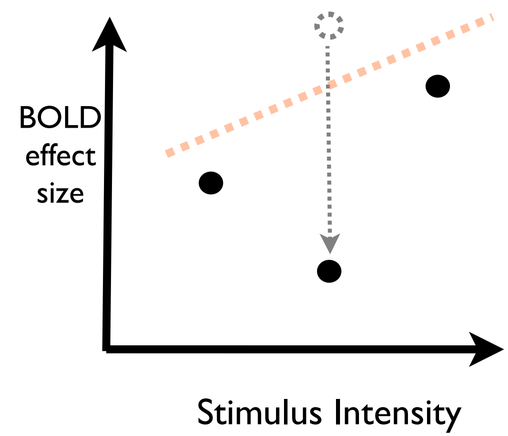


Parametric Variation: Linear Trends

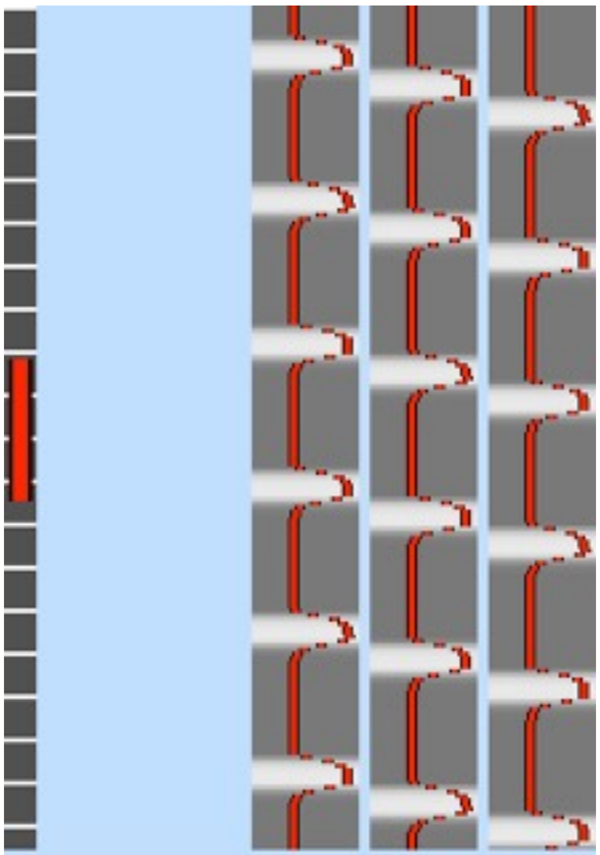


- A three-strength experiment
- Is there a linear trend between the BOLD response and some task variable?
- t-contrast [-1 0 1] : Linear trend



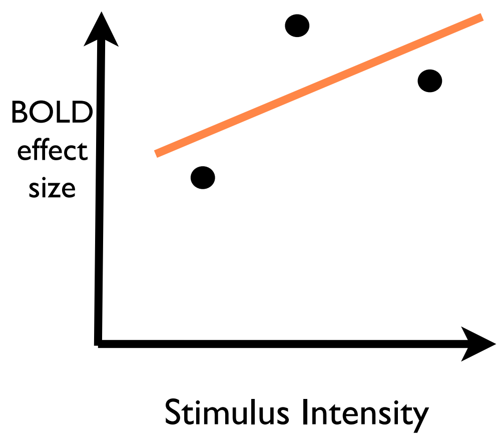


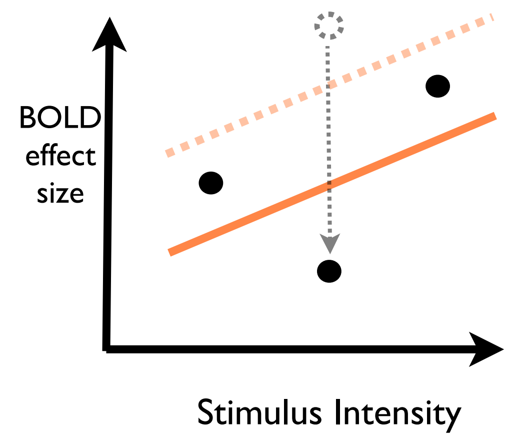
Parametric Variation: Linear Trends



c1	low	1	0	0
c2	medium	0	1	0
c3	high	0	0	1
c4	+ linear	-1	0	1
c5	- linear	1	0	-1

- 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 (β_3-β_1) is the same for both

Parametric Variation: Linear Trends

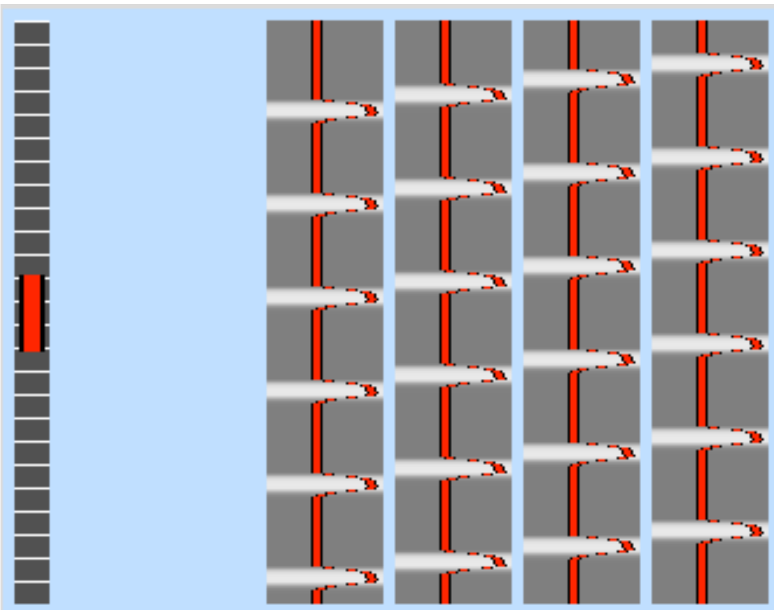
- What about c = [1,2,3] ??

[1,2,3] = [2,2,2] + [-1,0,1]

mean? or trend?

Need to "orthogonalise" contrast wrt mean

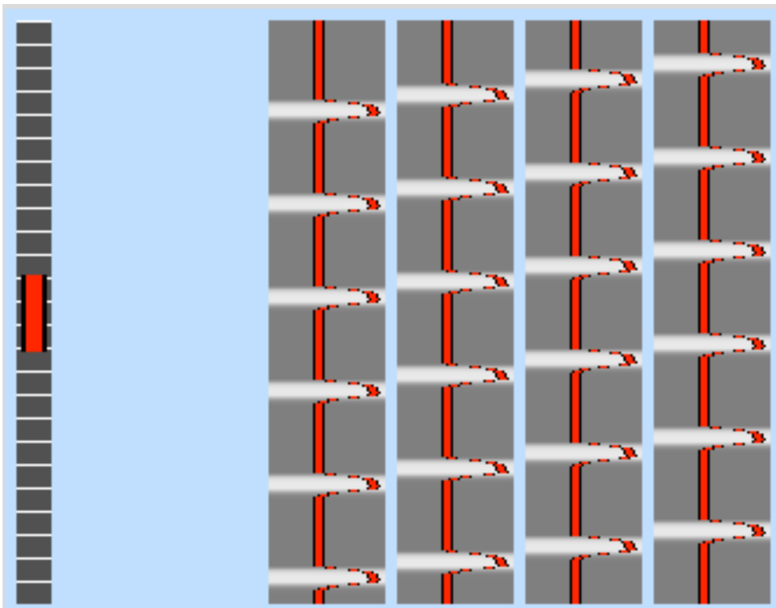
Parametric Variation: Linear Trends



C1	strength 1	1	0	0	0
C2	strength 2	0	1	0	0
C3	strength 3	0	0	1	0
C4	strength 4	0	0	0	1
C5	pos trend	-3	-1	1	3
C6	neg trend	3	1	-1	-3

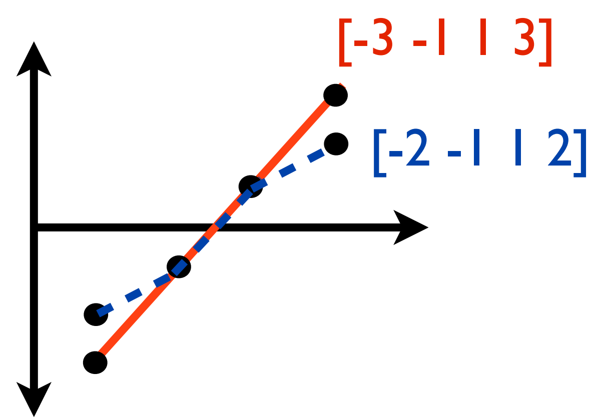
- A four-strength experiment
- t-contrast [-3 -1 1 3] : Positive linear trend

Parametric Variation: Linear Trends

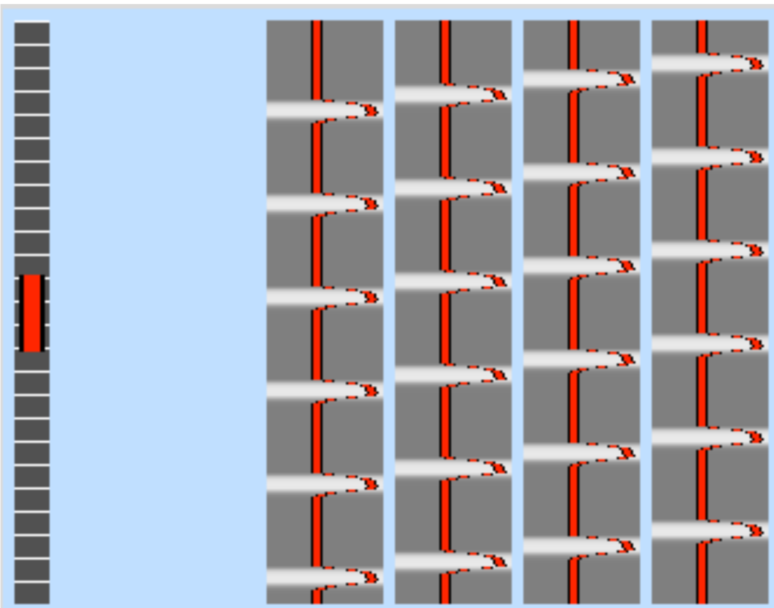


C1	strength 1	1	0	0	0
C2	strength 2	0	1	0	0
C3	strength 3	0	0	1	0
C4	strength 4	0	0	0	1
C5	pos trend	-3	-1	1	3
C6	neg trend	3	1	-1	-3

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



Parametric Variation: Linear Trends



C1	strength 1	1	0	0	0
C2	strength 2	0	1	0	0
C3	strength 3	0	0	1	0
C4	strength 4	0	0	0	1
C5	pos trend	-3	-1	1	3
C6	neg trend	3	1	-1	-3

- Or another way to see it:

[1 2 3 4] --> demeaned

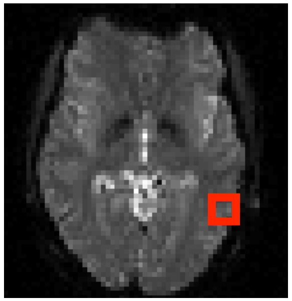
= [1 2 3 4] - 2.5*[1,1,1,1]

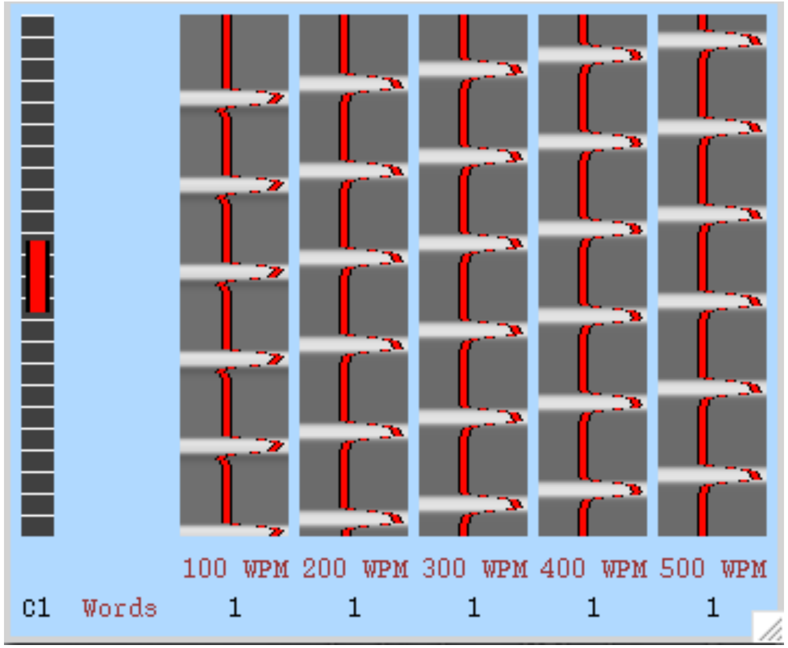
= [-1.5 -0.5 0.5 1.5]

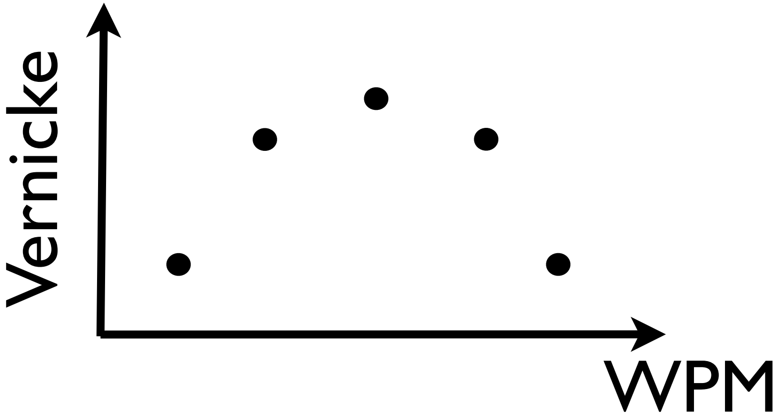
(but [-3 -1 1 3] is prettier)

But what if it isn't that predictable?

Auditory word presentation at different rates



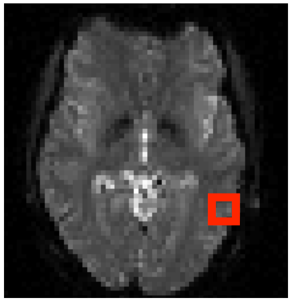


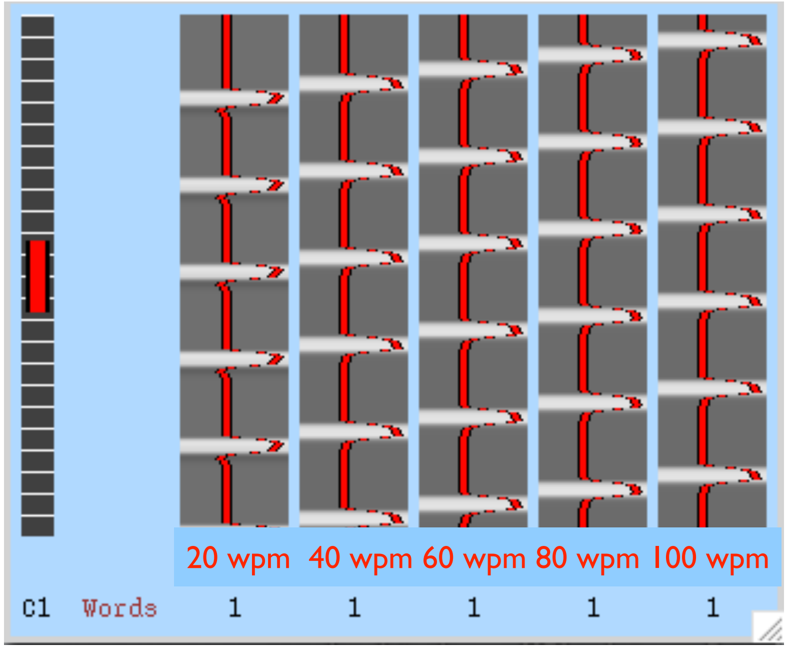


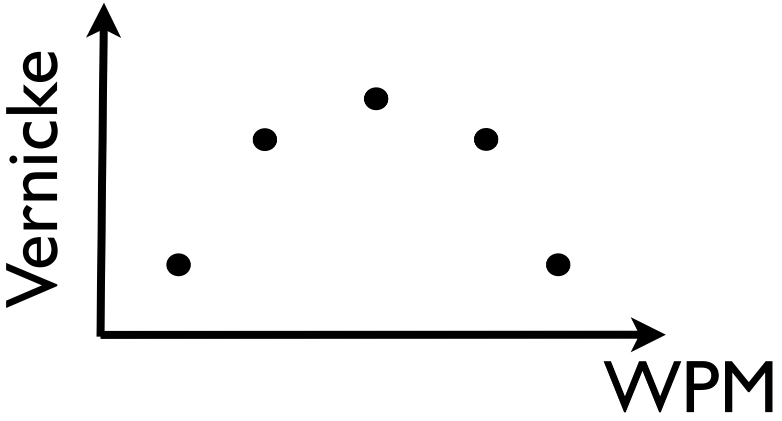
True story

But what if it isn't that predictable?

Auditory word presentation
at different rates





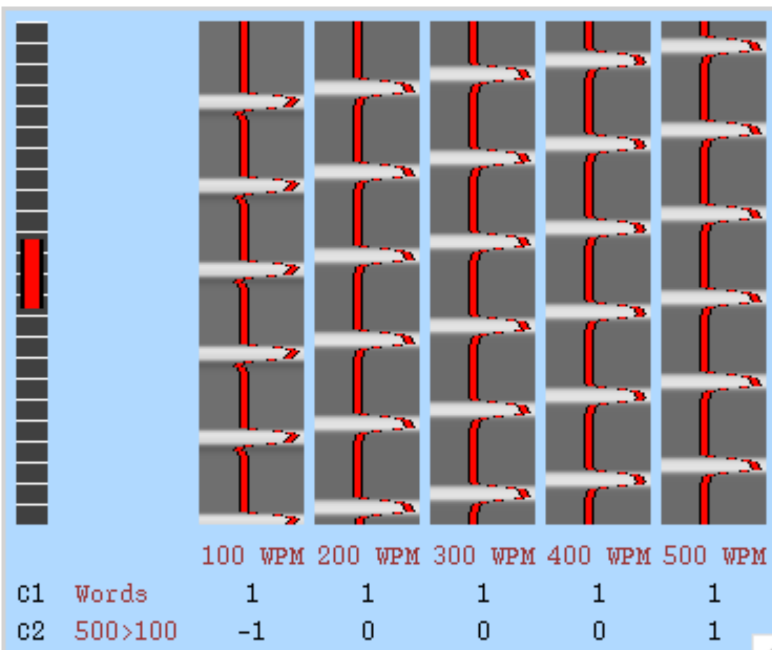


Bonkers!

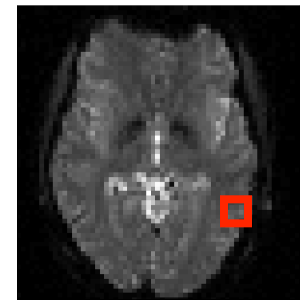
True story

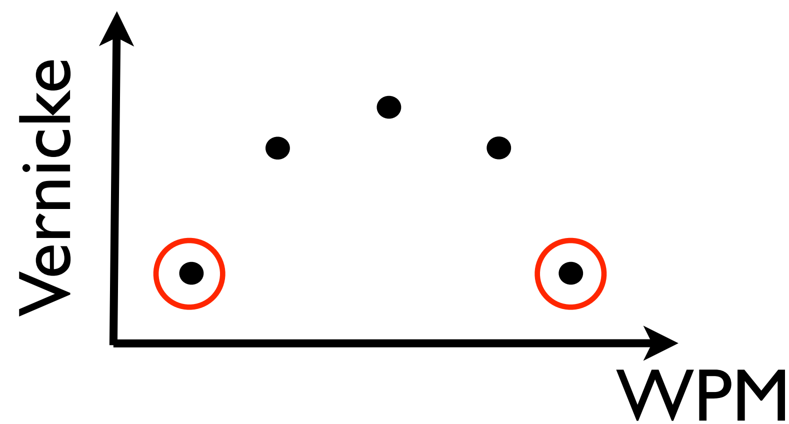
But what if it isn't that predictable?

Given this design what would be "reasonable" questions to ask?



More activation to 500 than to 100 WPM?



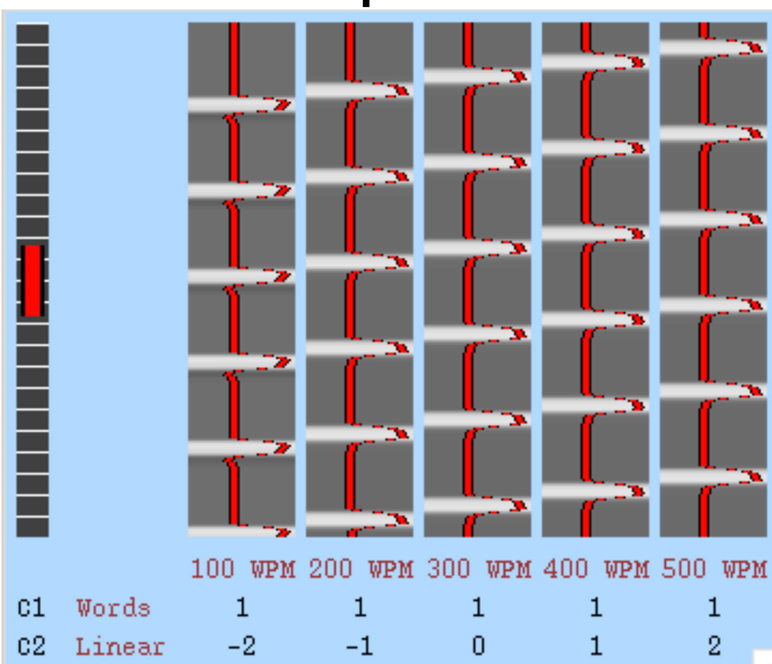


But no...

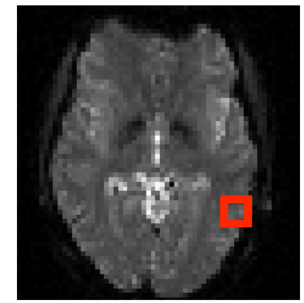
True story

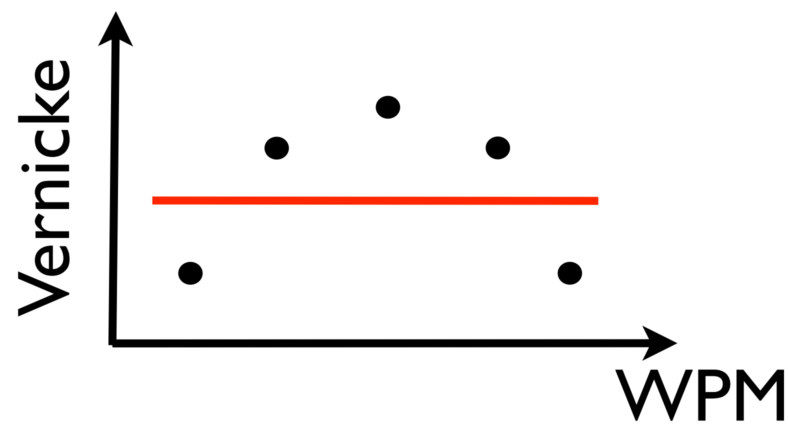
But what if it isn't that predictable?

Given this design what would be "reasonable" questions to ask?



Activation proportional to WPM?



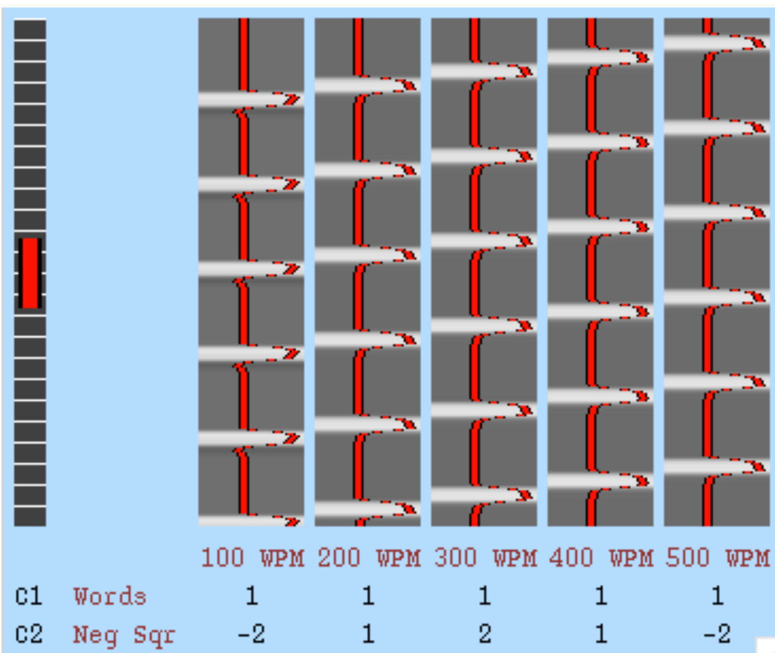


Still no...

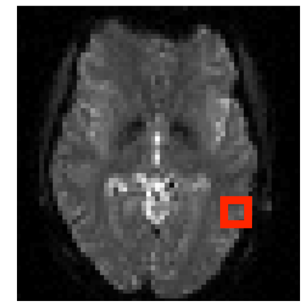
True story

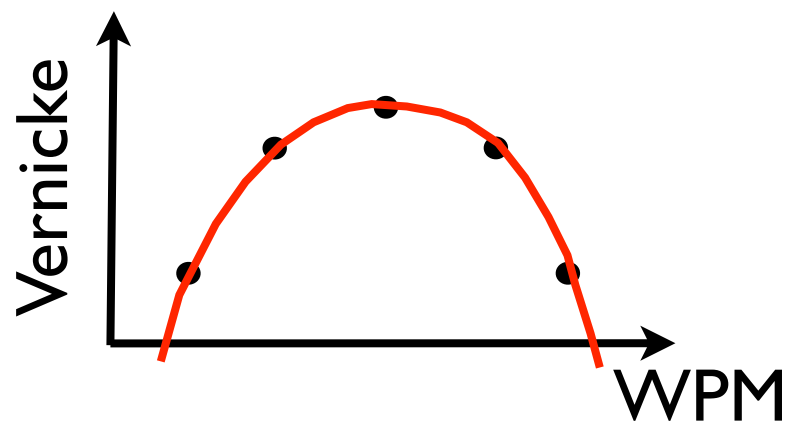
But what if it isn't that predictable?

Given this design what would be "reasonable" questions to ask?



Inversely proportional to WPM squared?



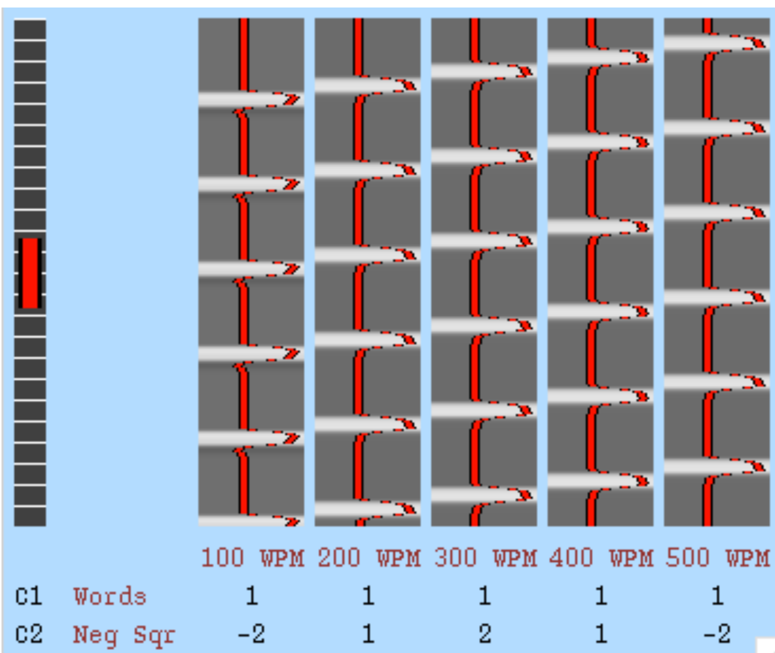


Yaay!

True story

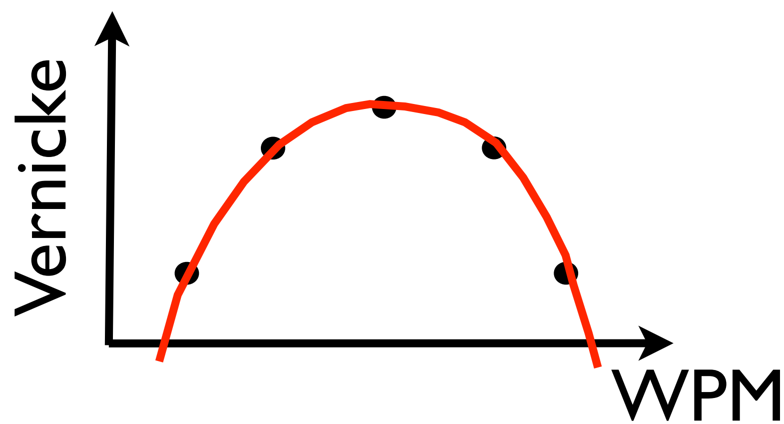
But what if it isn't that predictable?

Given this design what would be "reasonable" questions to ask?



Inversely proportional to WPM squared?

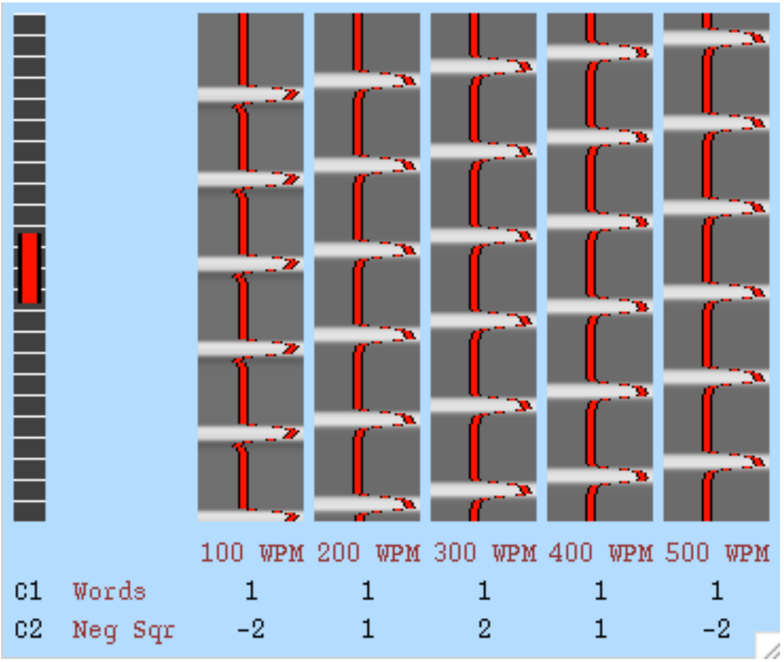
But seriously … would you have asked that question?



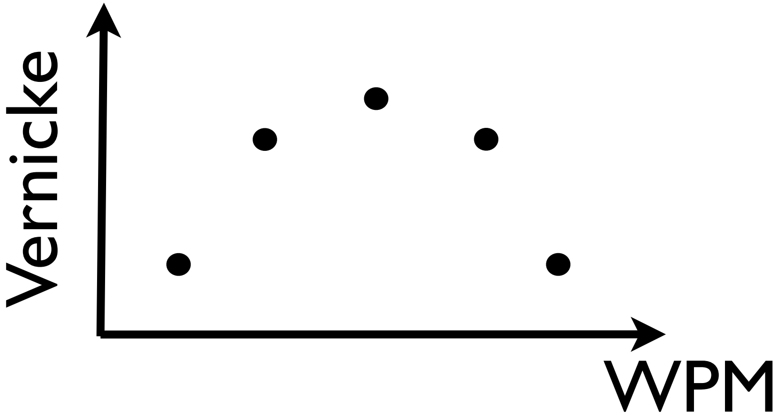
Yaay!

True story

But what if it isn't that predictable?



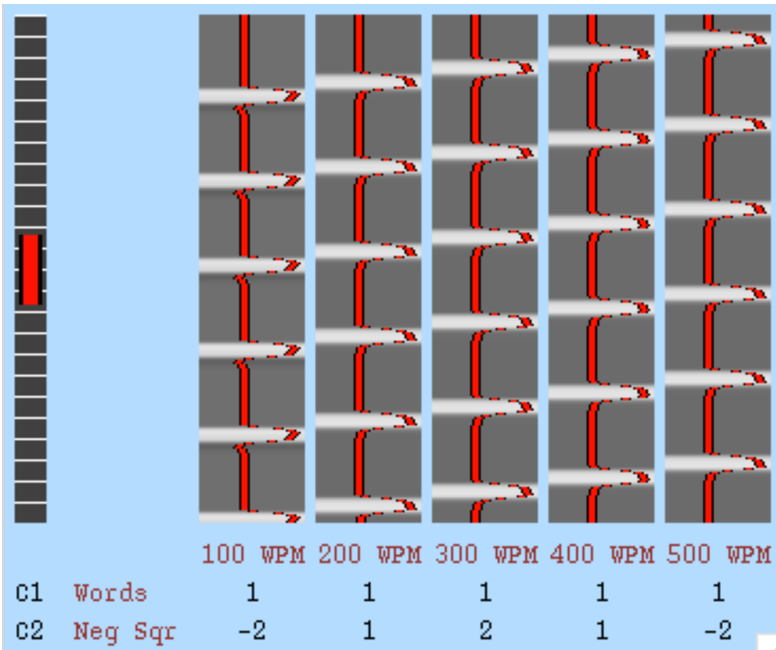
There is a (very real) risk of missing interesting but unpredicted responses



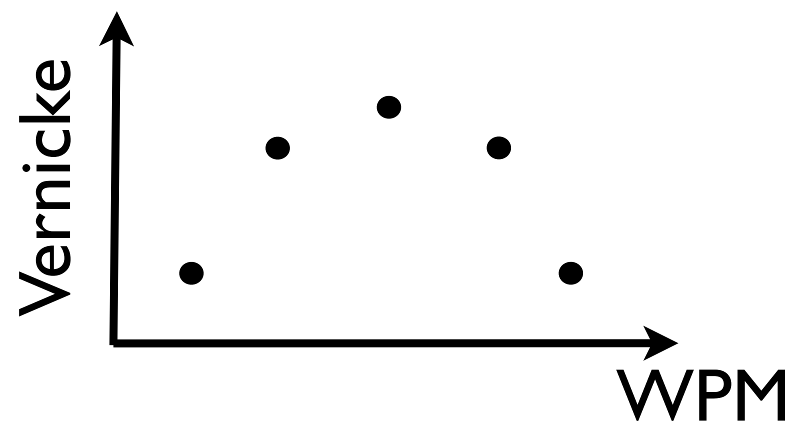
What can we do about that?

True story

F-contrasts to the rescue



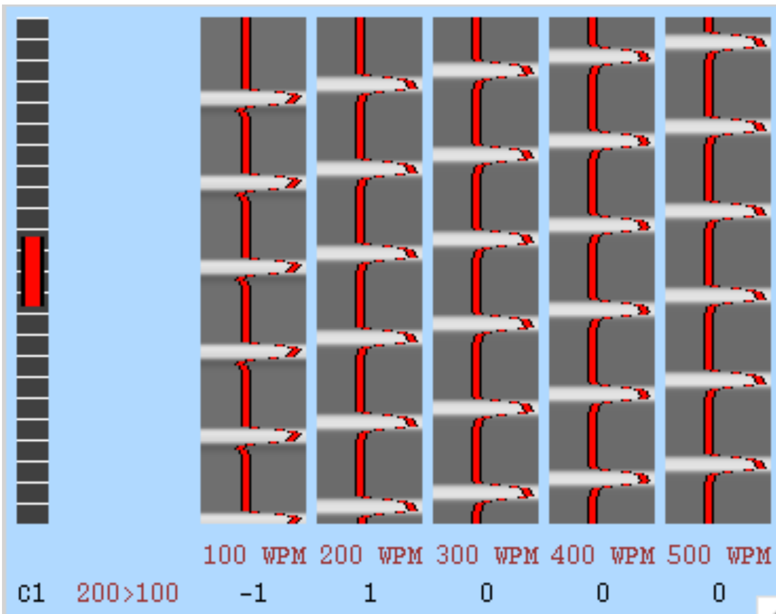
We can define an F-contrast that spans "the range of possible responses"



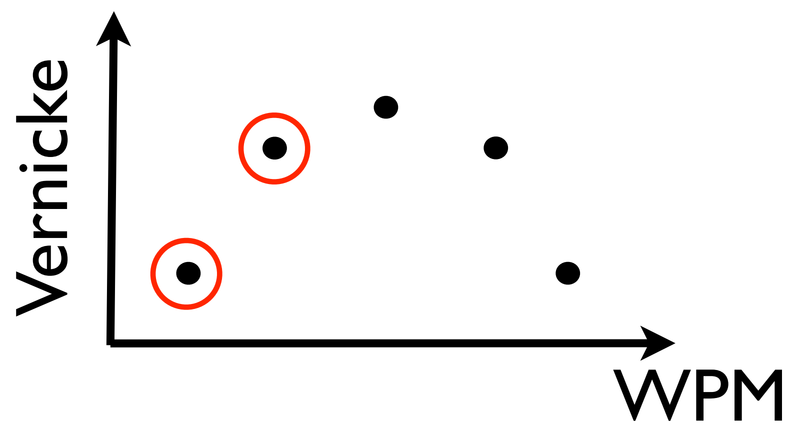
An F-contrast is a series of questions (*t*-contrasts) with an OR between them

True story

F-contrasts to the rescue



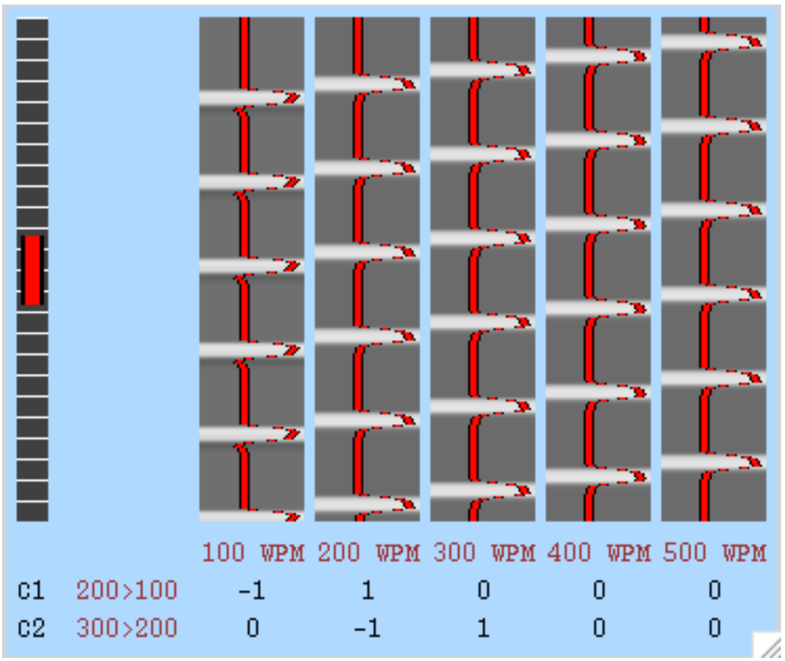
We can define an F-contrast that spans "the range of possible responses"



Let's start with "Greater activation to 200 than 100 WPM

True story

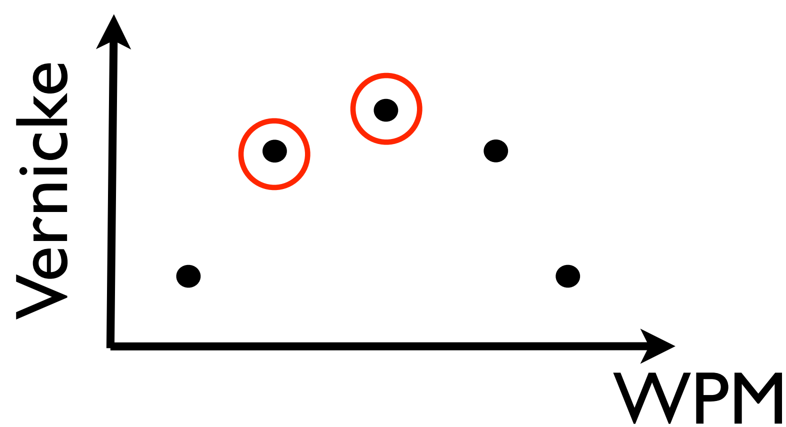
F-contrasts to the rescue



OR

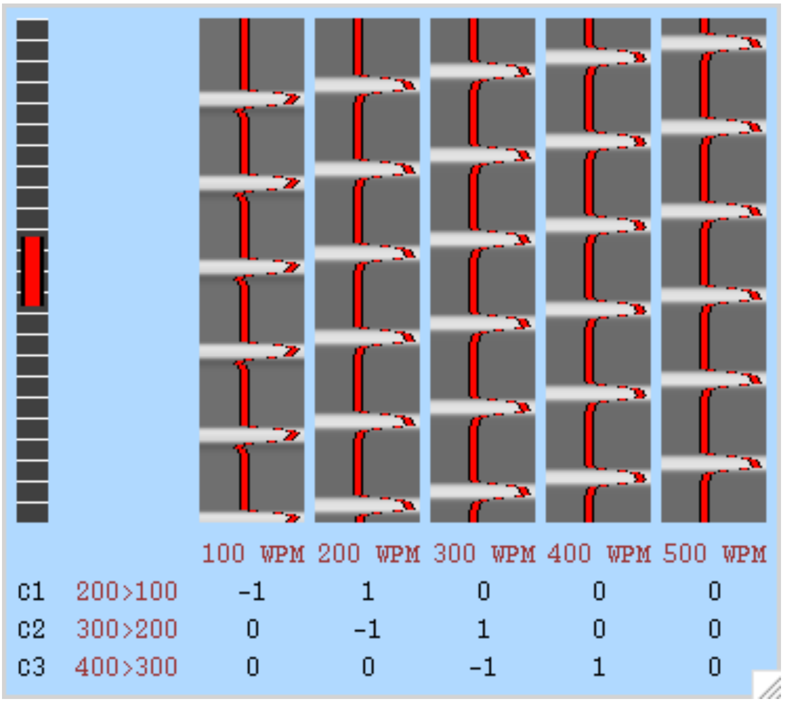
300WPM > 200WPM

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



True story

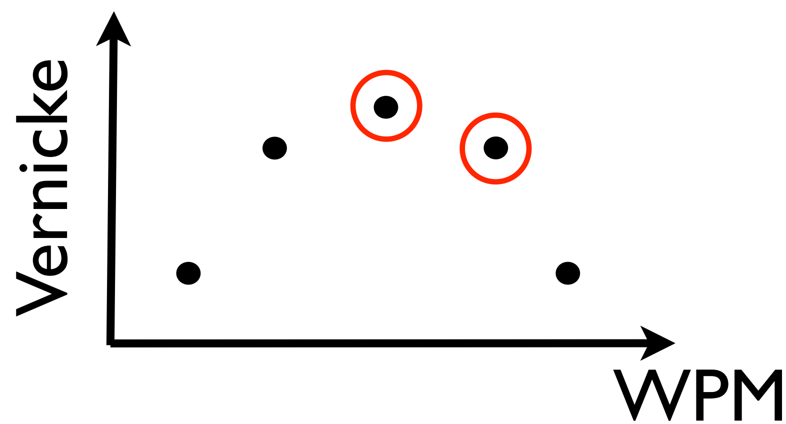
F-contrasts to the rescue



OR

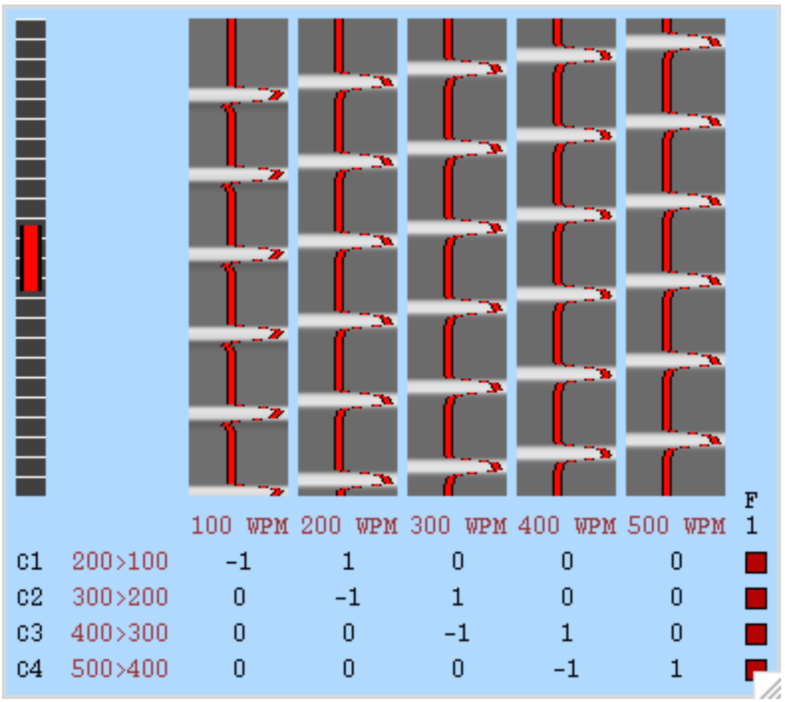
400WPM > 300WPM

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

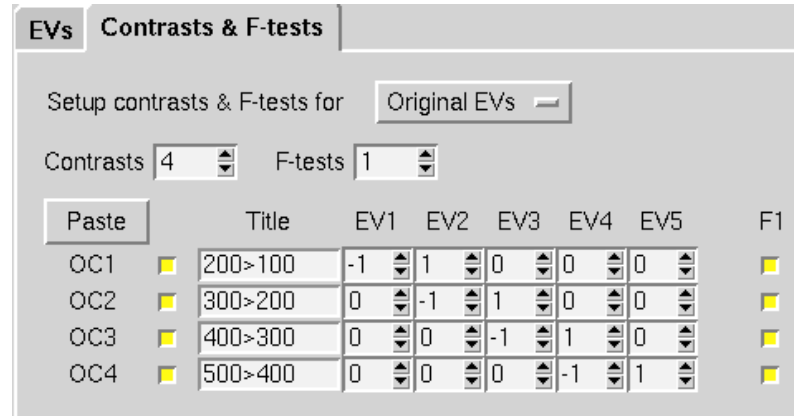


True story

F-contrasts to the rescue

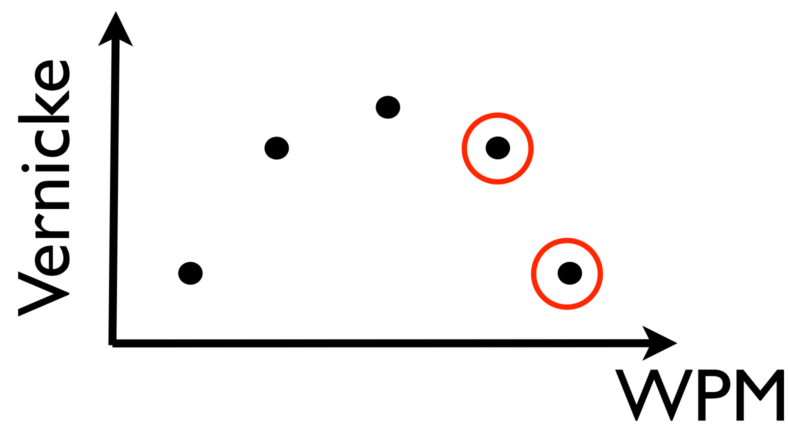


N.B.



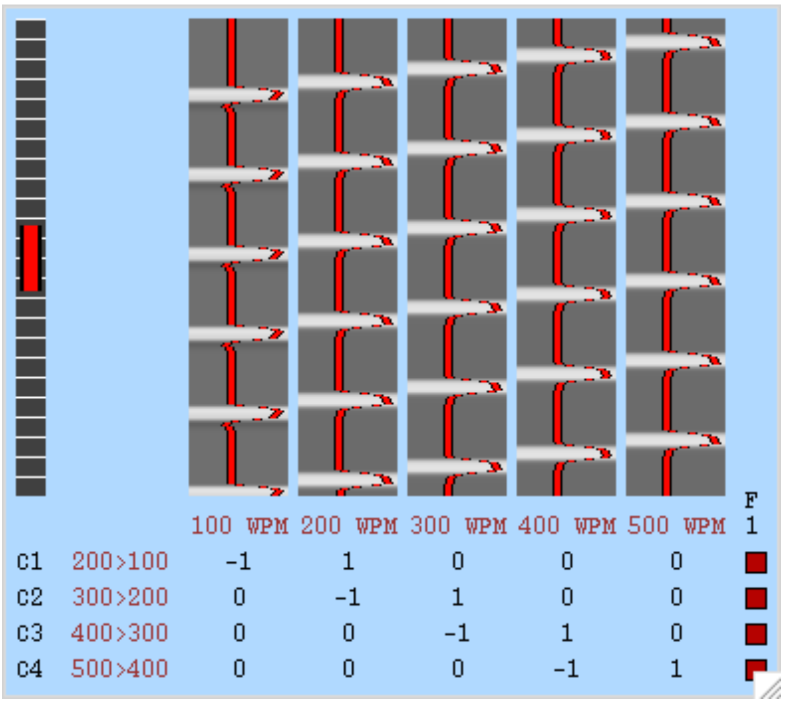
OR

500WPM > 400WPM

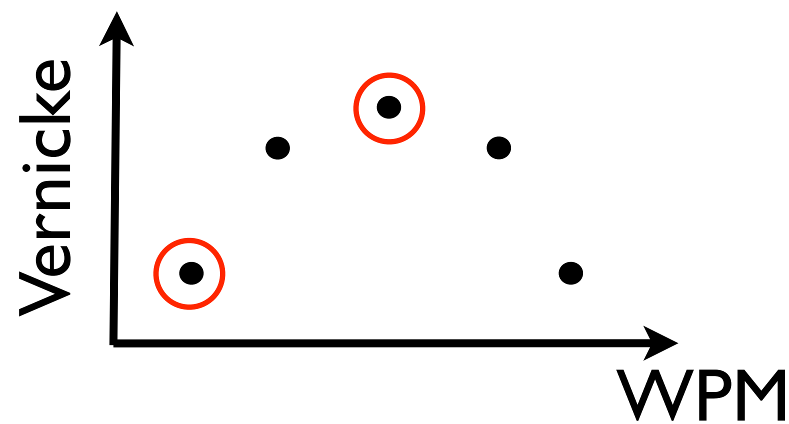


True story

F-contrasts to the rescue

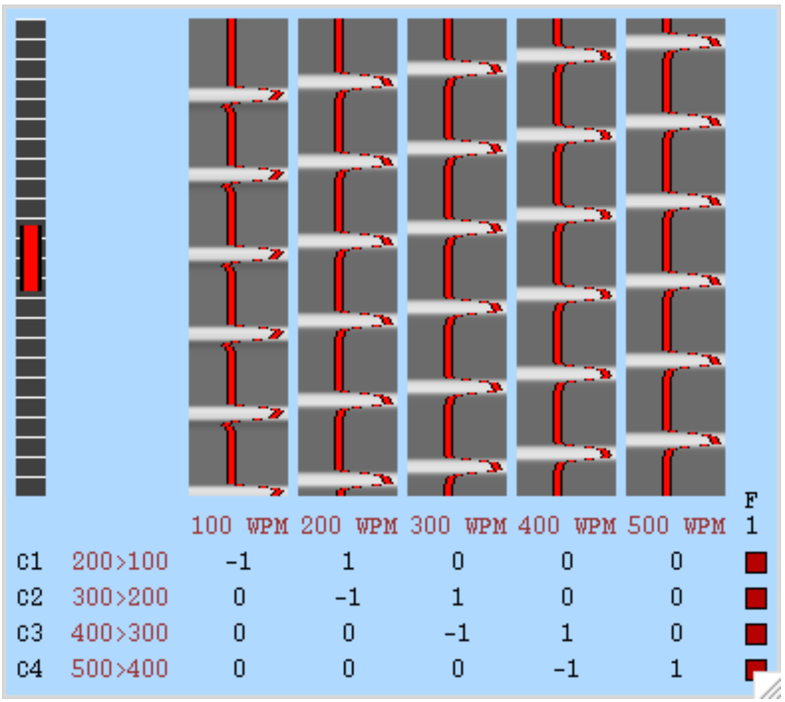


But ... that doesn't span all possible response, what about for example 300>100?



True story

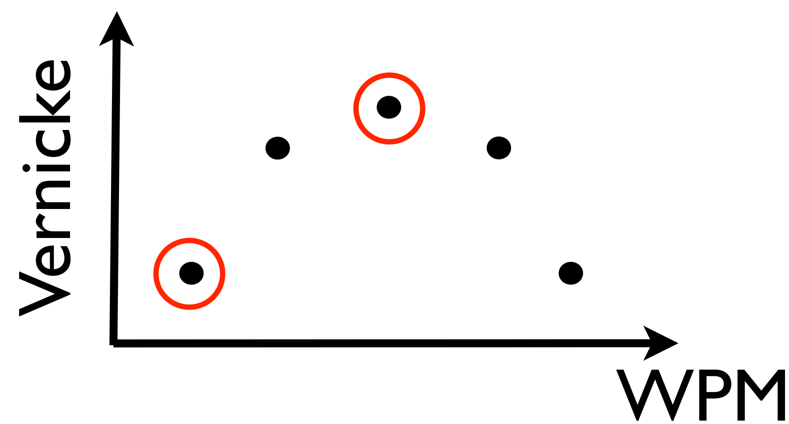
F-contrasts to the rescue



		100 WPM	200 WPM	300 WPM	400 WPM	500 WPM	F 1
C1	200>100	-1	1	0	0	0	
C2	300>200	0	-1	1	0	0	
C3	400>300	0	0	-1	1	0	
C4	500>400	0	0	0	-1	1	

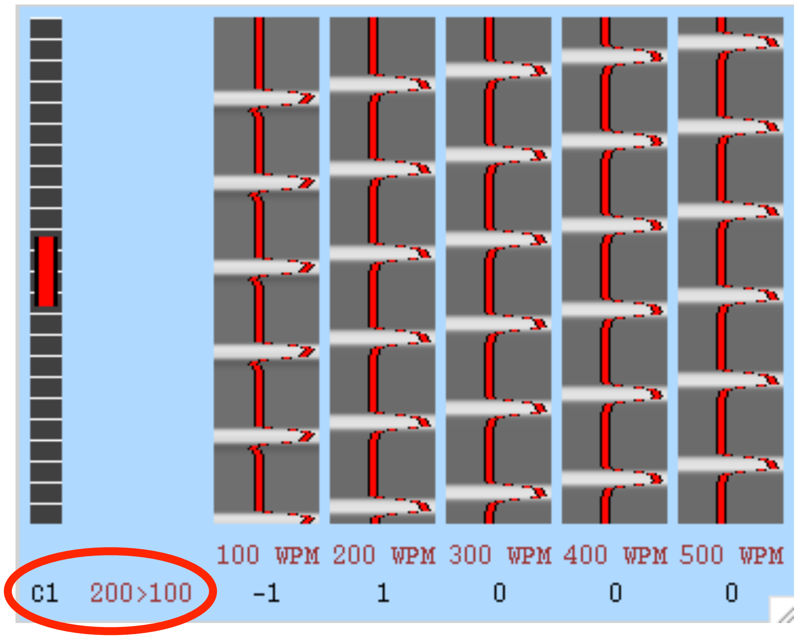
300>100 implies
200>100 AND/OR 300>200
which we have covered

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



True story

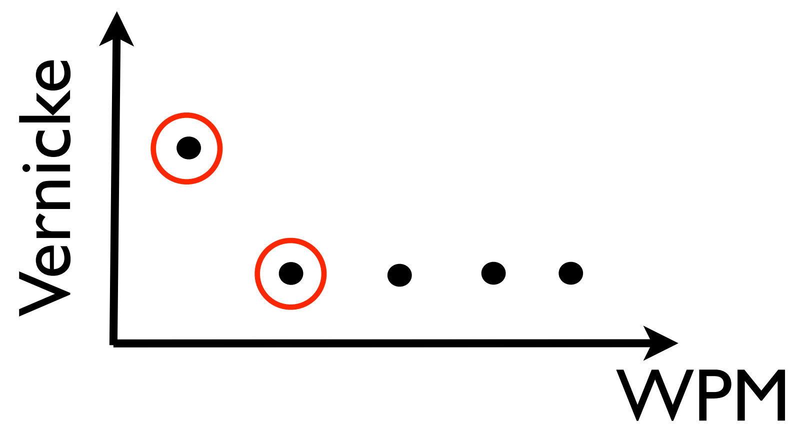
F-contrasts to the rescue



This *t*-contrast asks "where is 200>100?"

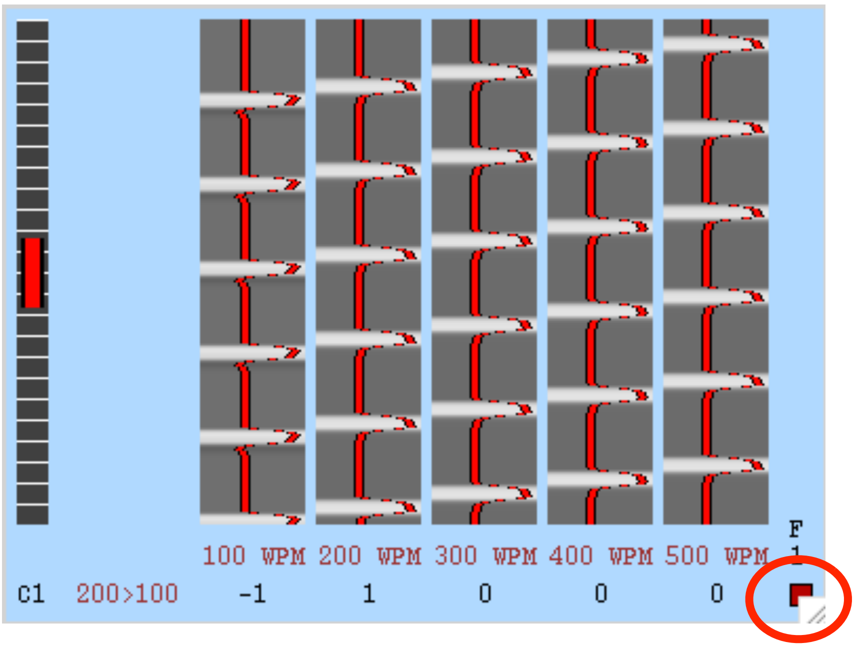
F-contrasts are bi-directional

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



True story

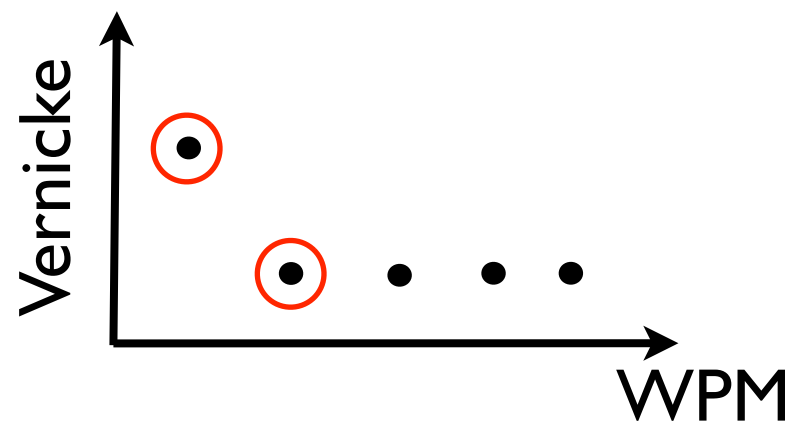
F-contrasts to the rescue



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?



True story

Advanced Analysis: Parametric Designs

Summary:

- Important to have separate EVs (and parameters) per level of stimulus, otherwise assuming an exact linear response
- Linear trends require contrasts that are centred about zero and with even intervals
- Going beyond linear trends can be done with F-tests to look for arbitrary response shapes

Advanced Analysis: 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?

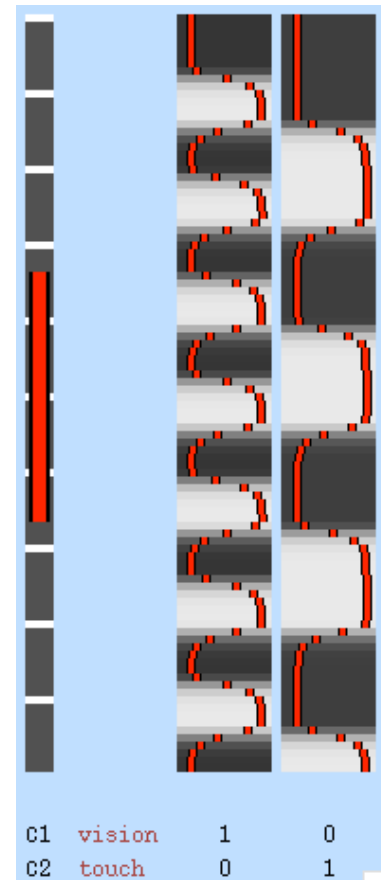
Solution:
- Specific regressors
- Contrast masking

Multisensory study

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

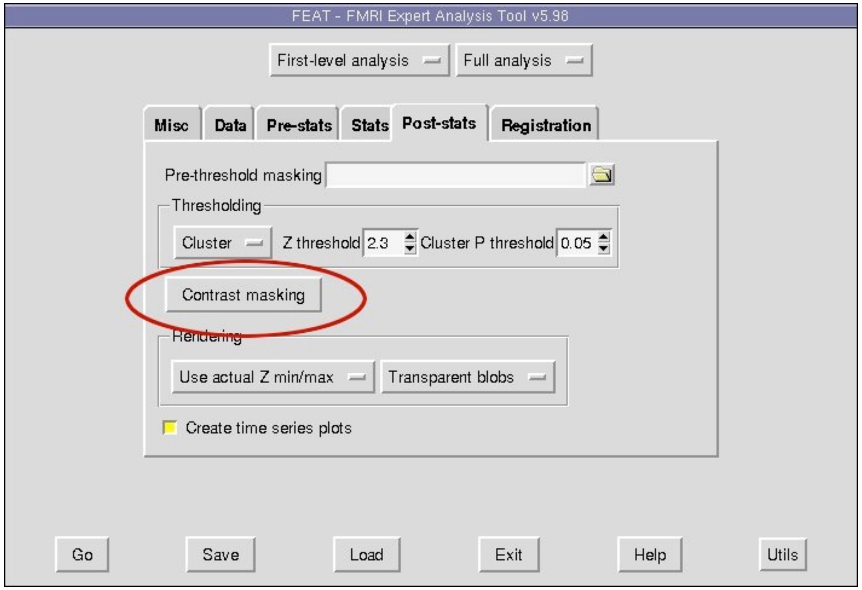
- Can generate simple contrasts for:
- vision activation/deactivation [1 0]
- touch activation/deactivation [0 1]
- differences in responses [1 -1]

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



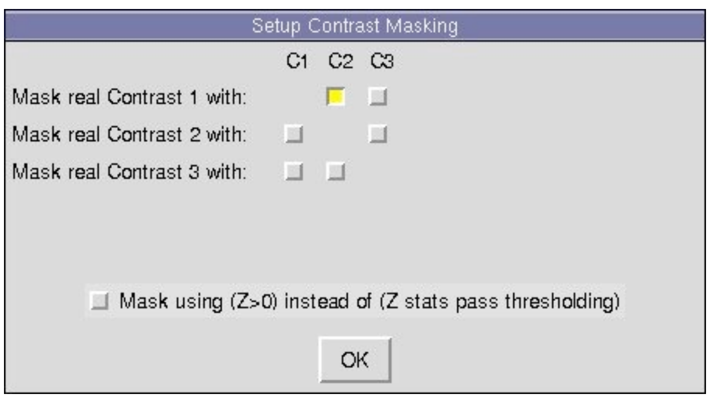
Contrast Masking

- 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

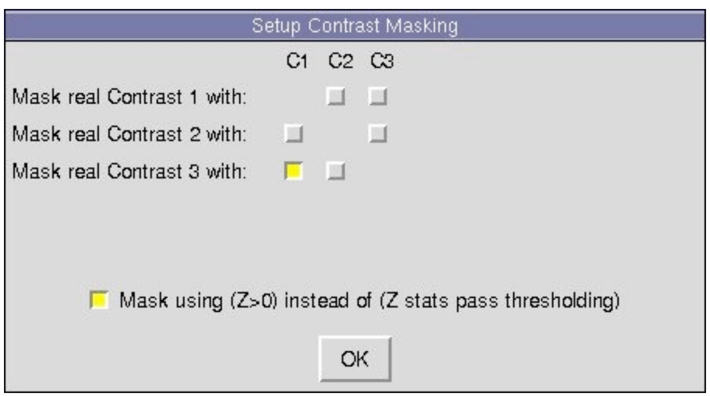
- Often it is of interest to identify regions showing significant effects in multiple contrasts (e.g. responds to visual AND tactile stimulations)
- This can be achieved by masking a thresholded z image for a chosen contrast using the thresholded z image from one or more other contrasts.



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

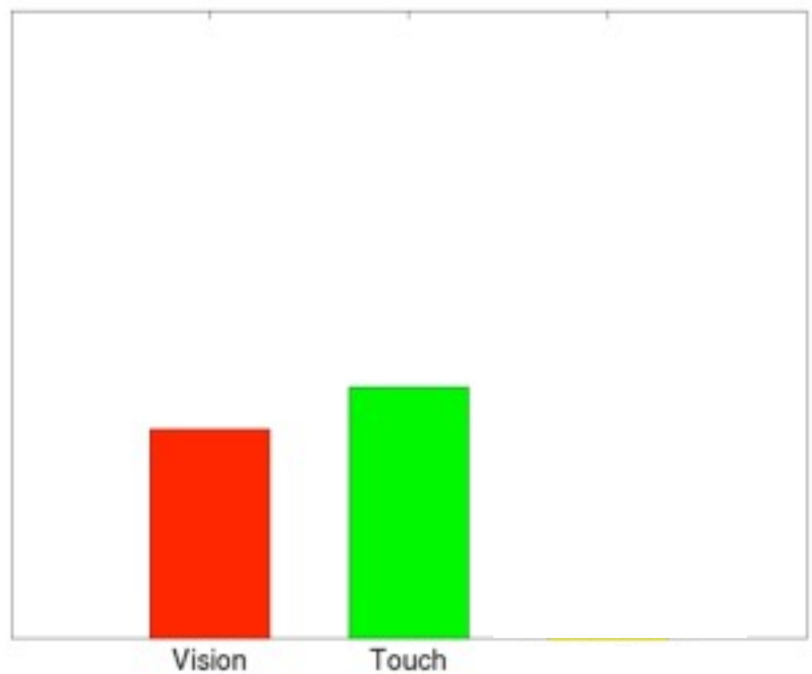
Factorial design

	No Vision	Vision
No Touch		
Touch		

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

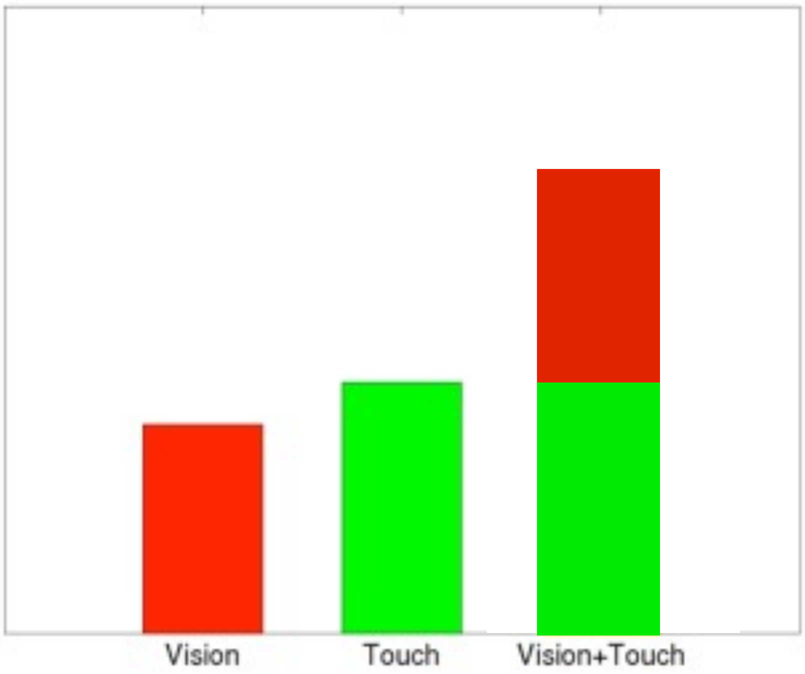
No Interaction Effect

	No Vision	Vision
No Touch		
Touch		



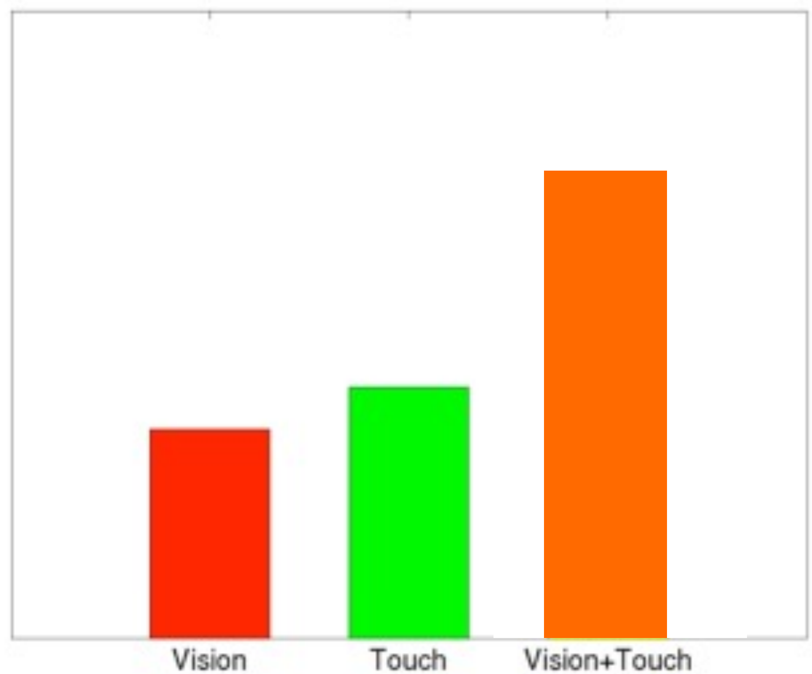
No Interaction Effect

	No Vision	Vision
No Touch		
Touch		



No Interaction Effect

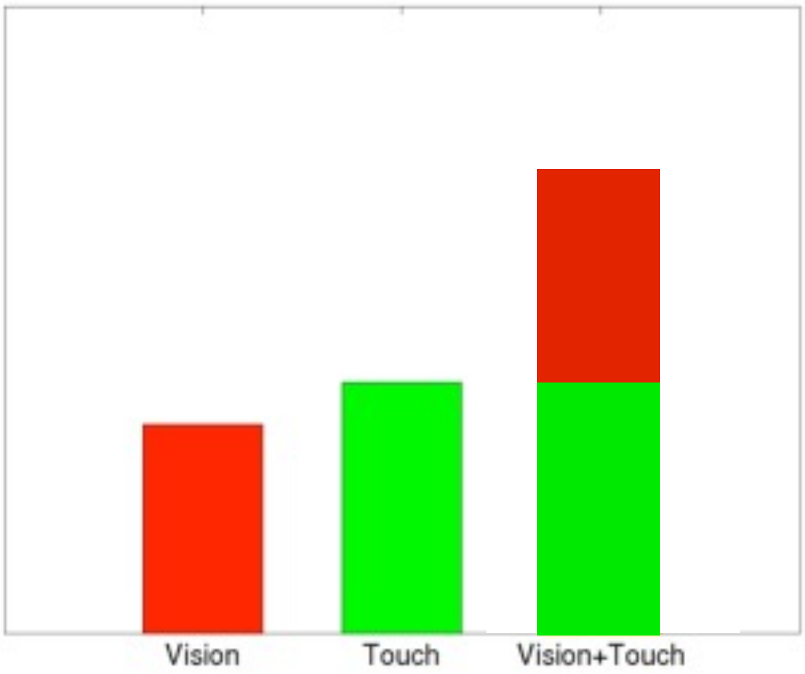
	No Vision	Vision
No Touch		
Touch		



No interaction - effects add linearly

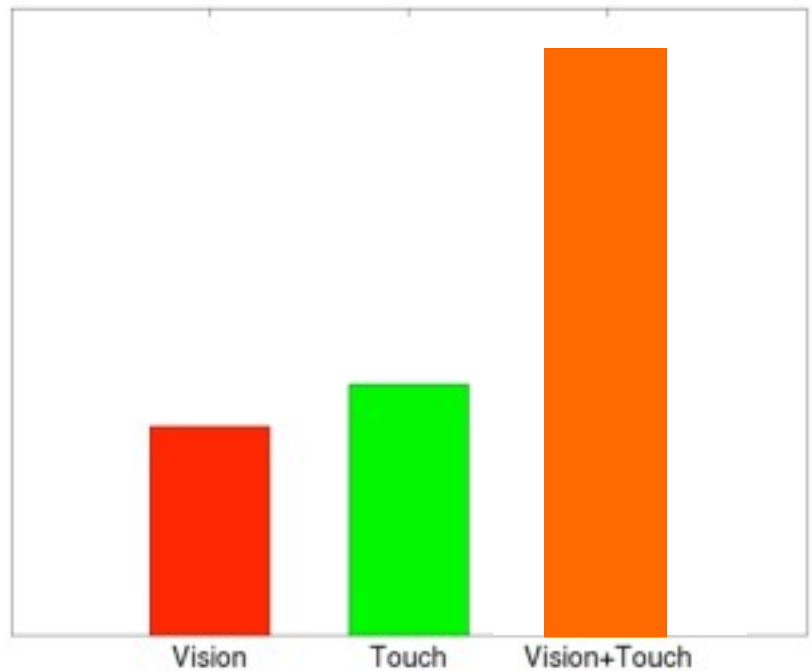
Positive Interaction Effect

	No Vision	Vision
No Touch		
Touch		



Positive Interaction Effect

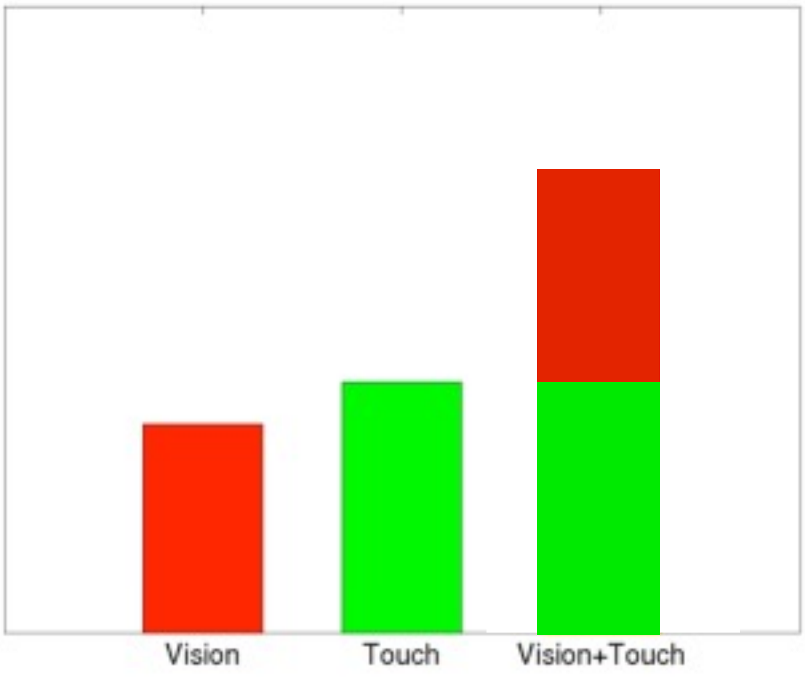
	No Vision	Vision
No Touch		
Touch		



Positive interaction - "superadditive"

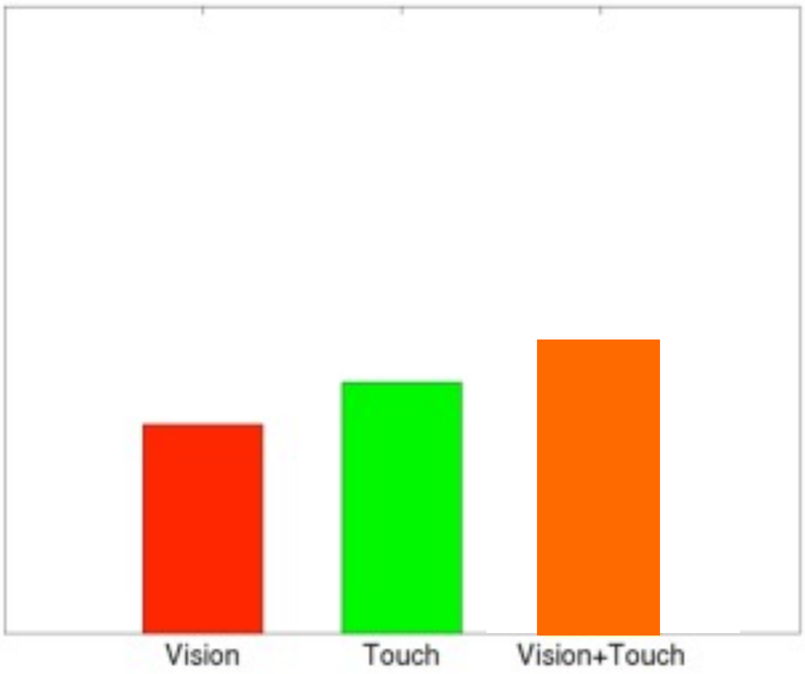
Negative Interaction Effect

	No Vision	Vision
No Touch		
Touch		



Negative Interaction Effect

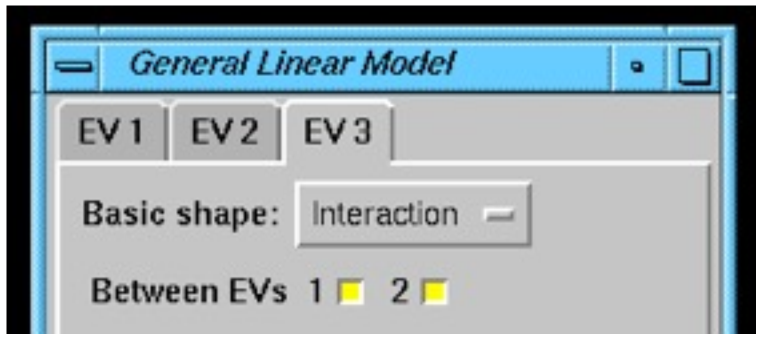
	No Vision	Vision
No Touch		
Touch		



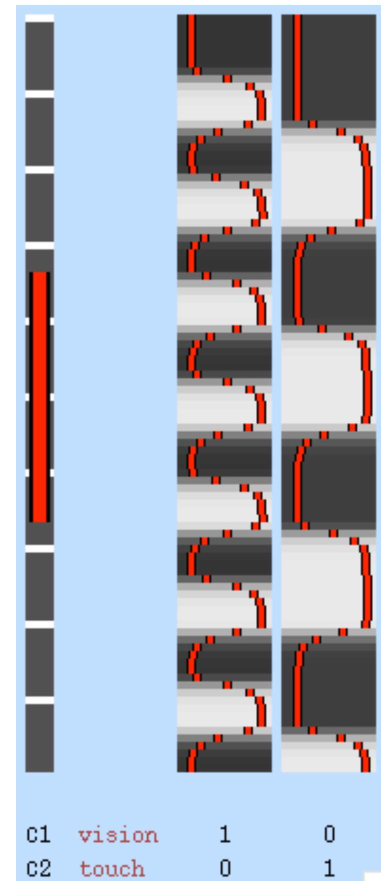
Negative interaction
- "subadditive"

Modelling Interactions Between EVs

	No Vision	Vision
No Touch		
Touch		

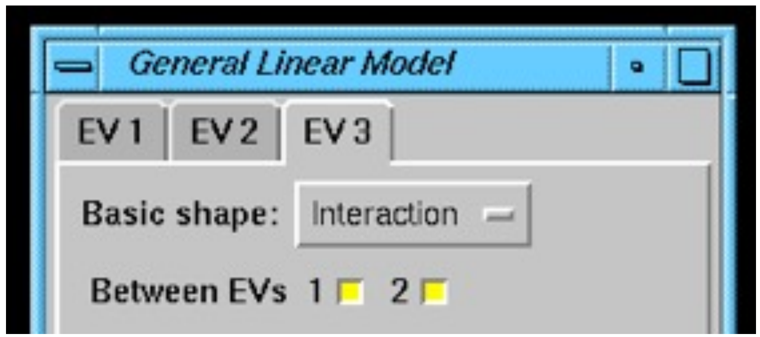


- EV1 models vision on/off
- EV2 models touch on/off

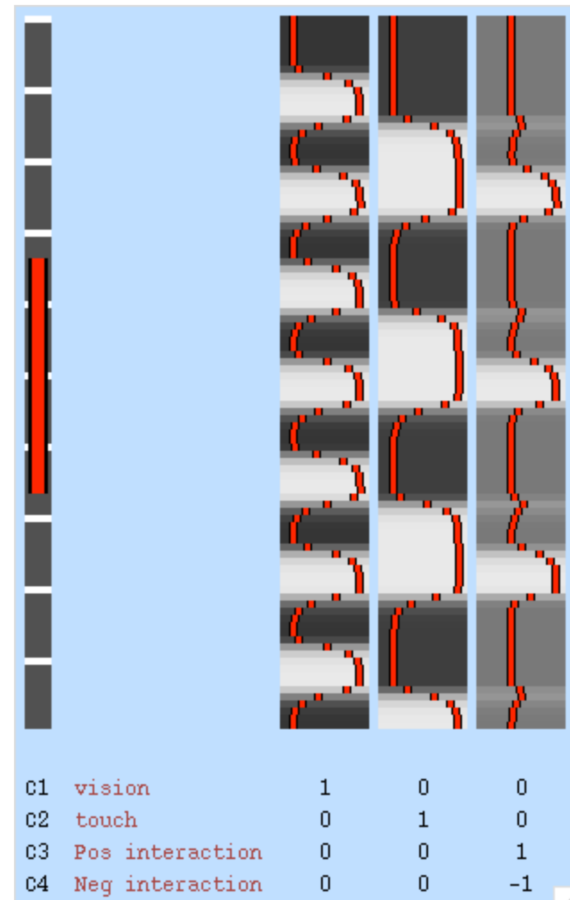


Modelling Interactions Between EVs

	No Vision	Vision
No Touch		
Touch		



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



Advanced Analysis: Factorial Designs and Interactions

Summary:

- Contrast masking allows questions of the form "A *and* B" to be asked
    - F-tests ask "A or B or both"
- Factorial design covers different combinations including the interaction
- Interaction can be positive, negative or none and is tested using an extra EV and a simple contrast

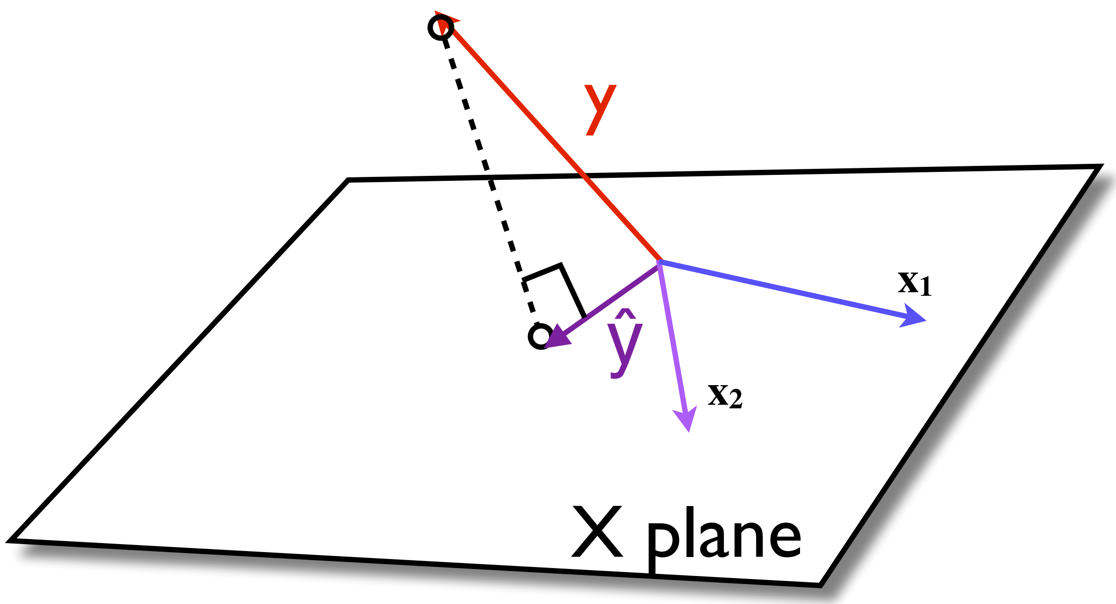
Advanced Analysis: Correlation of EVs and Design Efficiency

Correlation of EVs

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

- Start by looking at first-level examples:
  - correlation and rank deficiency
  - design efficiency tool

Geometric vue



vectors

$$\begin{bmatrix} x_1 \end{bmatrix}$$

vector in a 1-dimensional space

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$$

vector in a 3-dimensional space

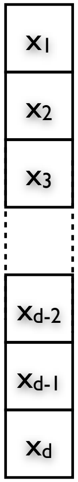
$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_{d-2} \\ x_{d-1} \\ x_d \end{bmatrix}$$

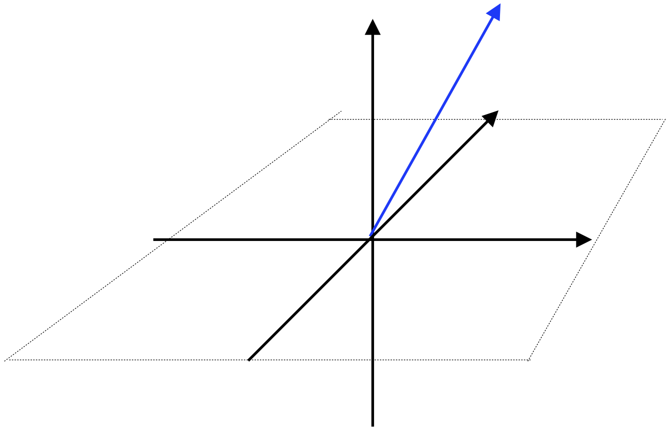
vector in d-dimensional space

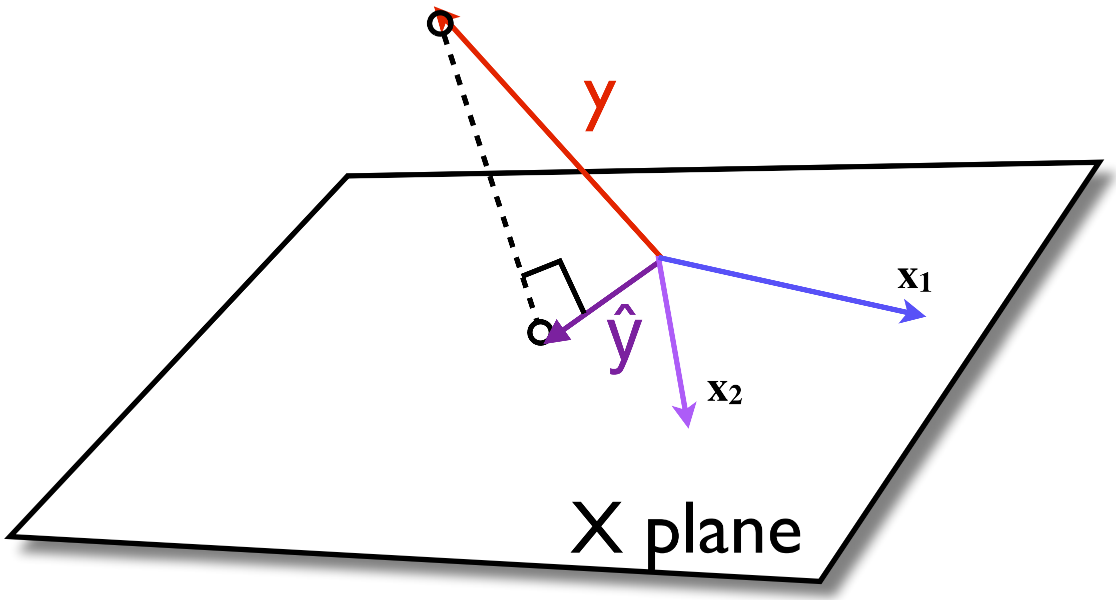
The world in >3 dimensions ?????

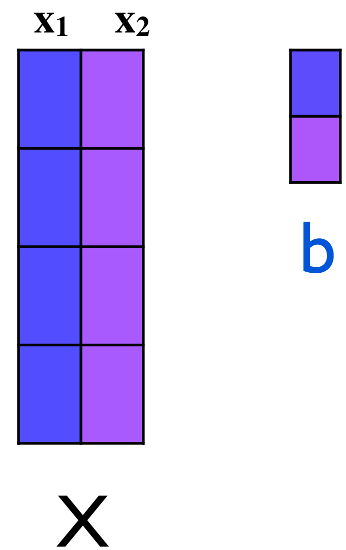
vectors

This “arrow” picture is also useful in d-dimensions, as any vector is in effect one-dimensional.





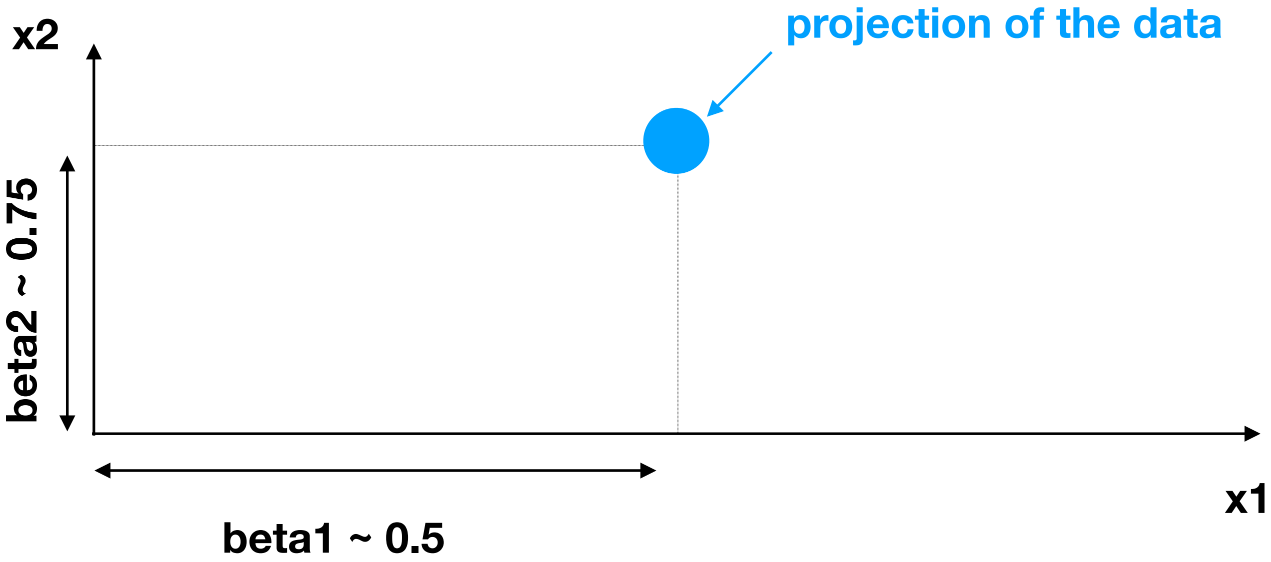


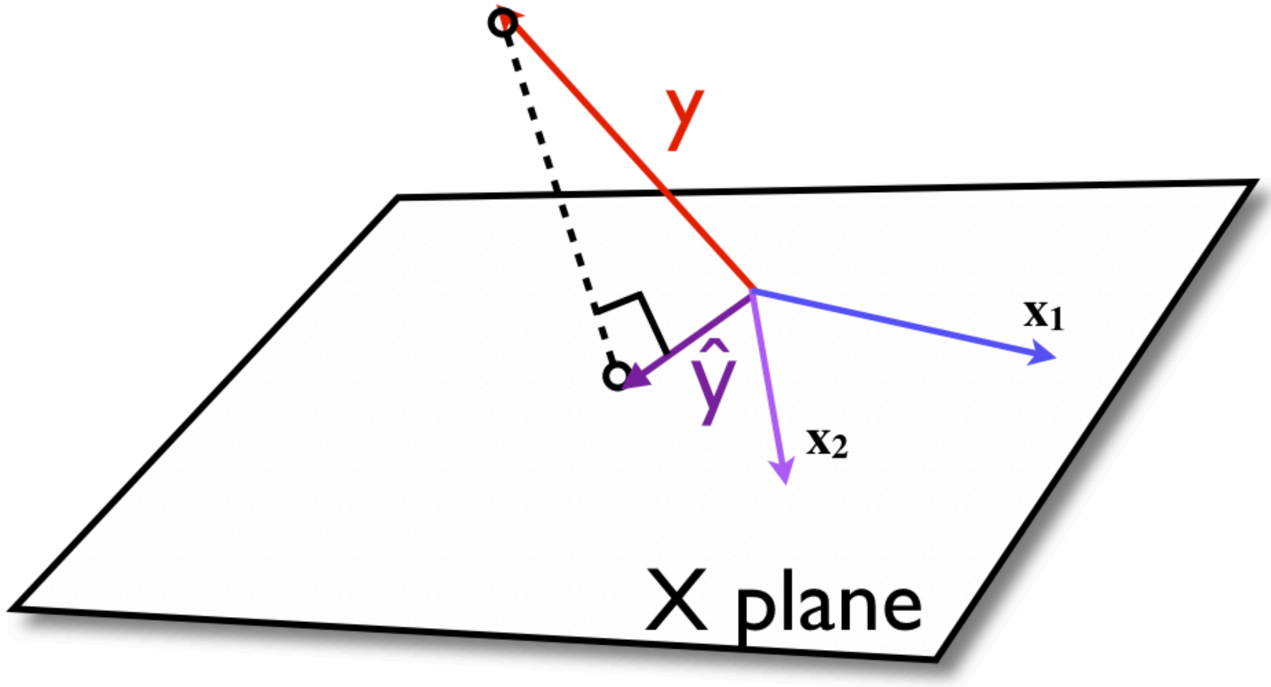


b = pinv(X) * y

ŷ = X*b

b are the coordinates of ŷ in the (x_1,x_2) coord system of the X plane


projection of the data
x2
x1
beta2 ~ 0.75
beta1 ~ 0.5



- b tells us "how much" of each regressor we need to approximate y
- But what about "uncertainty"?

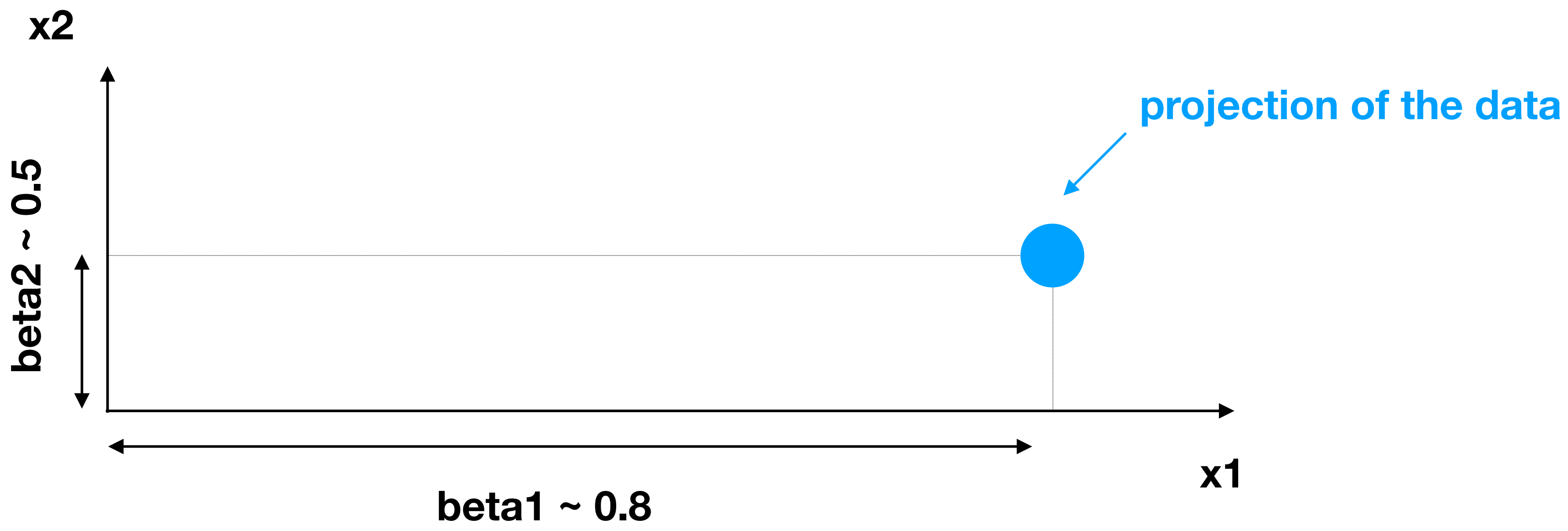
$$y = X*b + \text{error}$$

GLM with error term

$$y = (X+\text{error})*b$$

Same model

Analysing the error in b (parameter estimates) same as analysing what happens when we slightly alter X

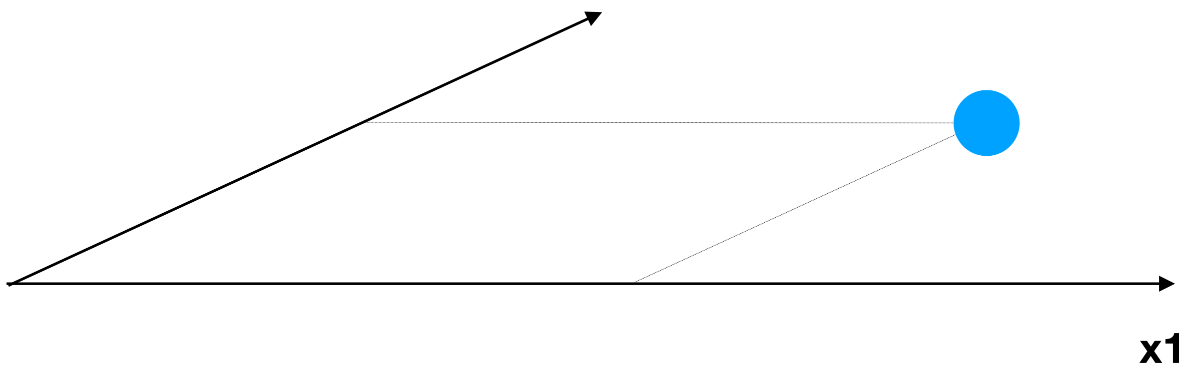

x2
projection of the data
beta2 ~ 0.5
x1
beta1 ~ 0.8

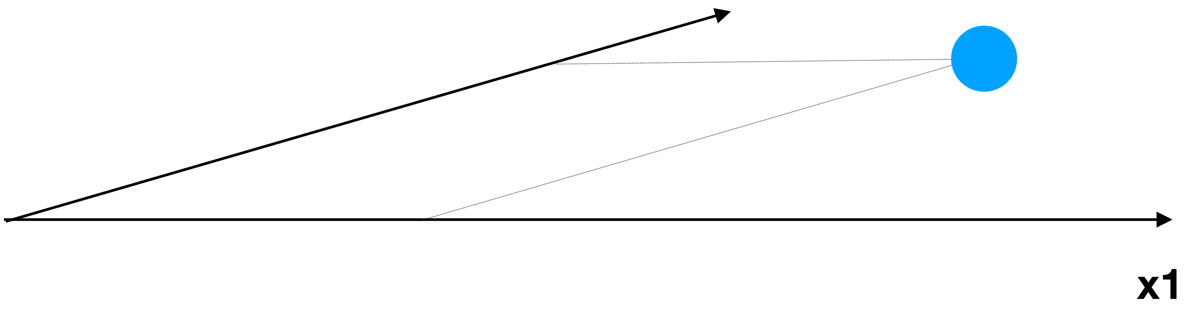

x1

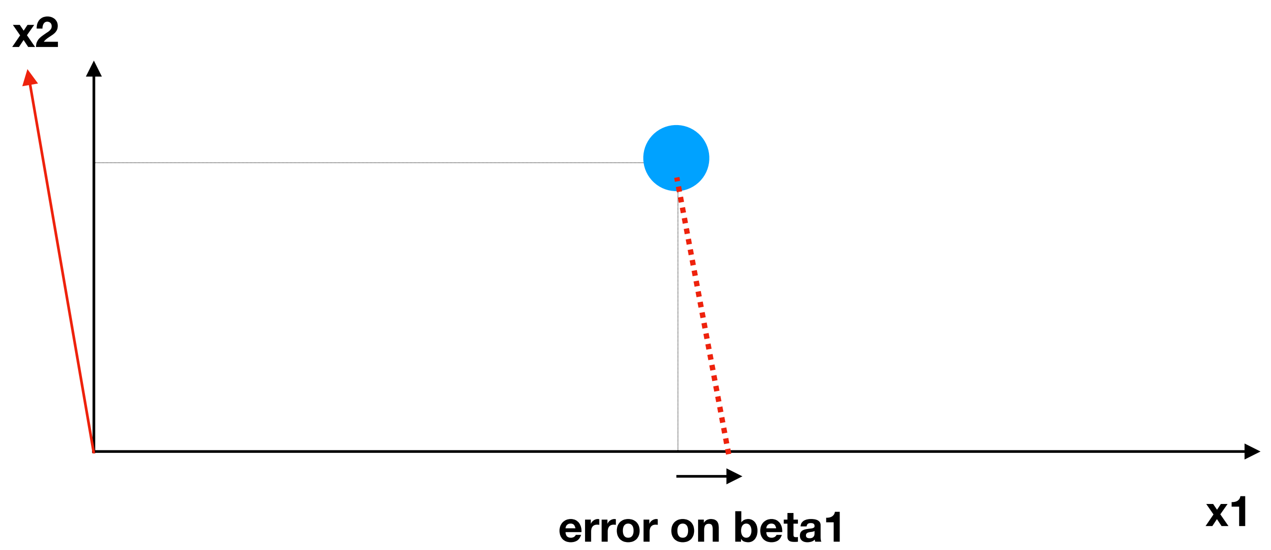

x1

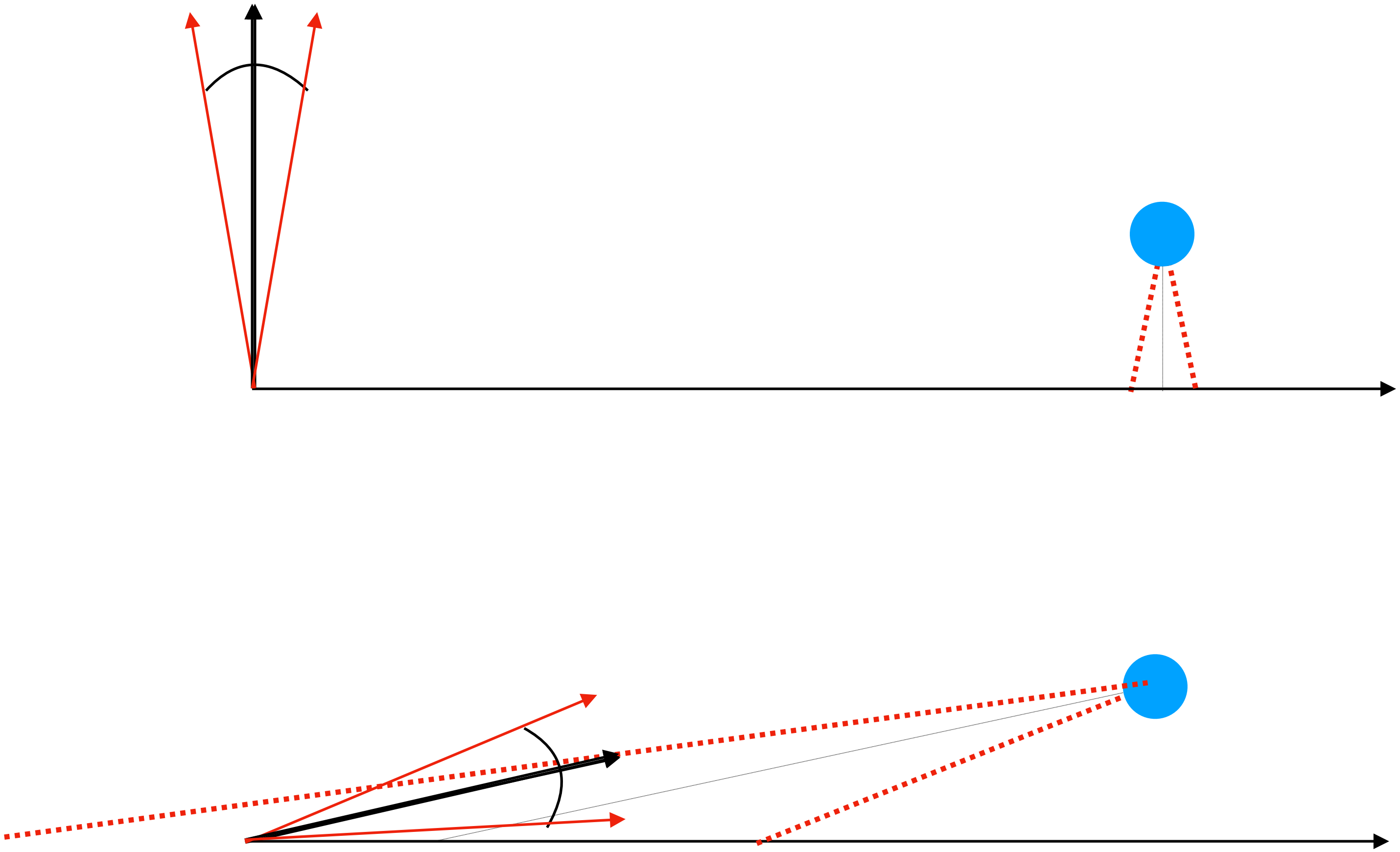

x1


x1


x1

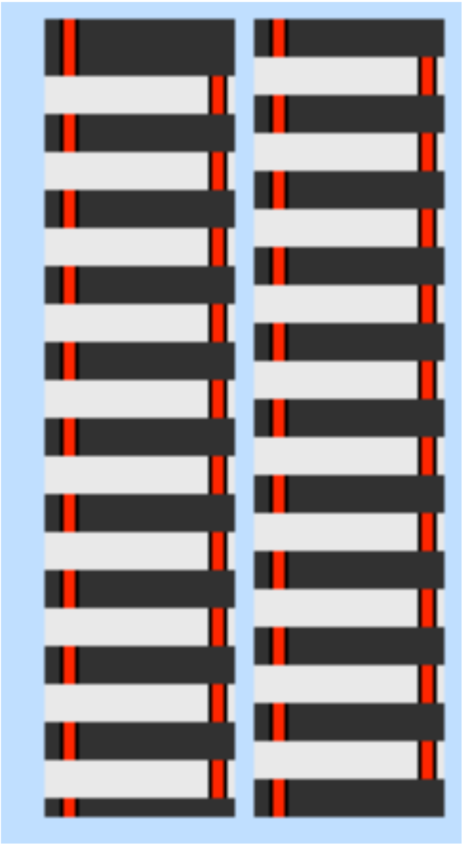

x1

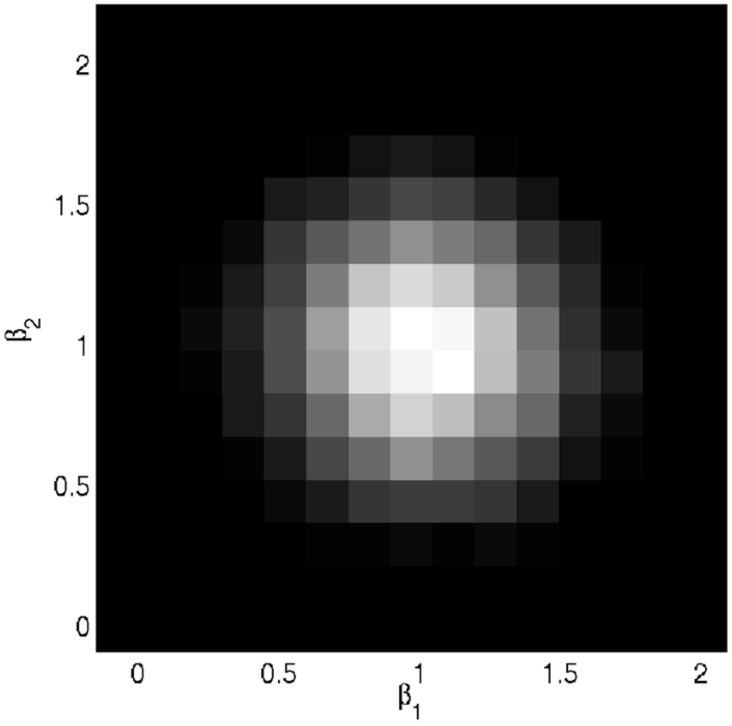

x2
error on beta1
x1



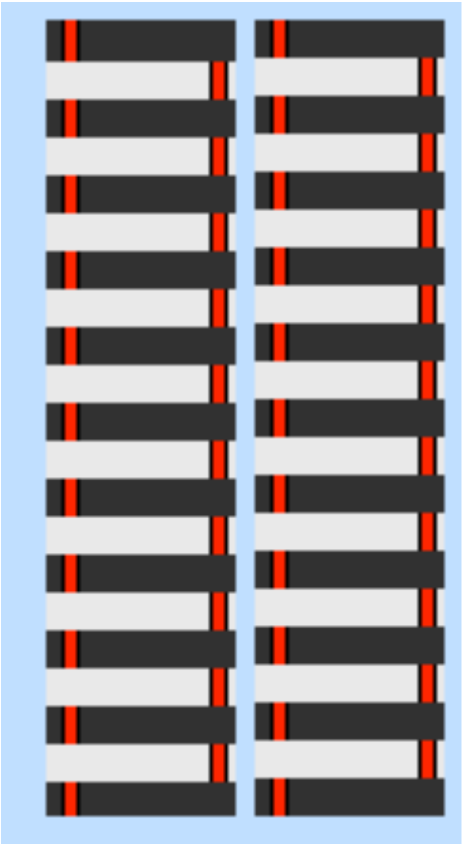
Look at what happens to std(b) when we have correlated regressors!

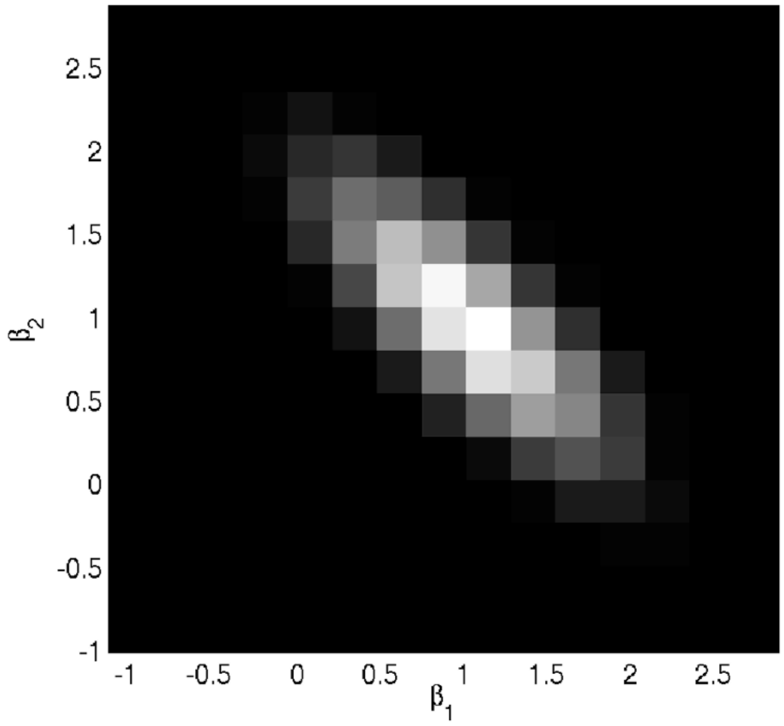
Why do we want an orthogonal design?



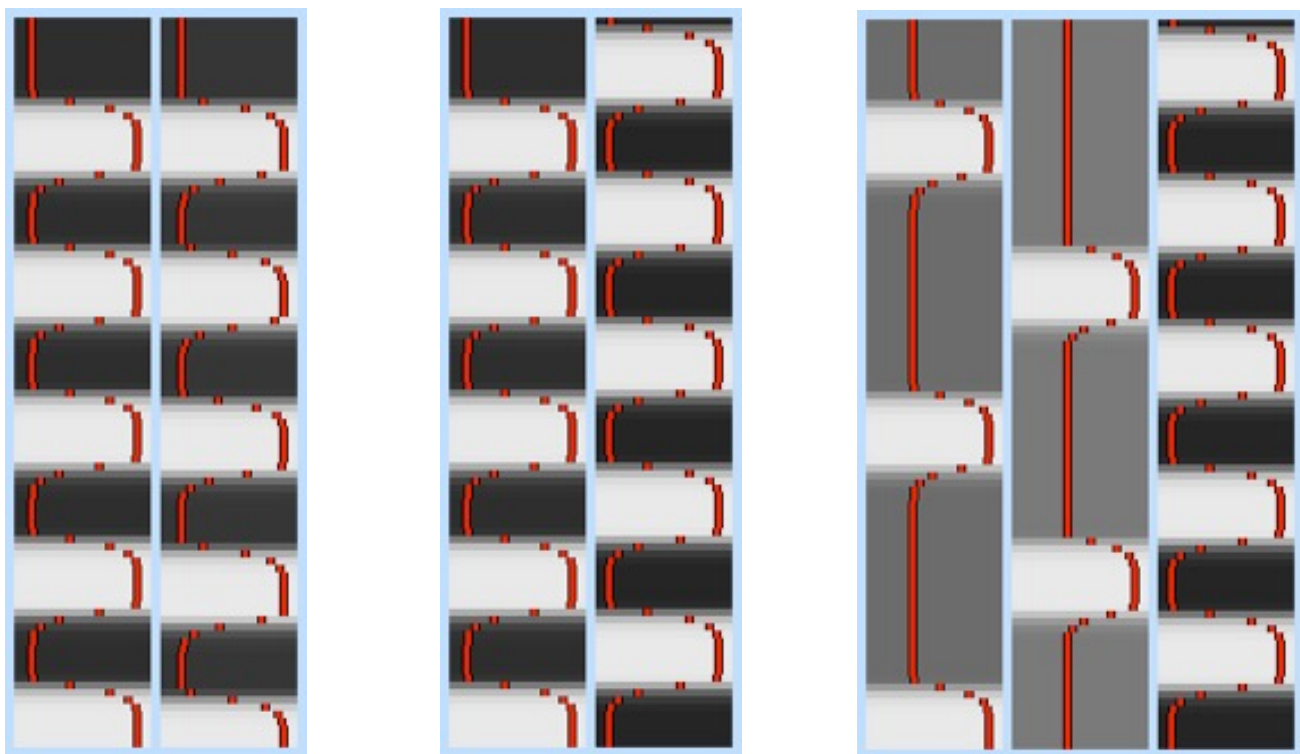


Why do we want an orthogonal design?



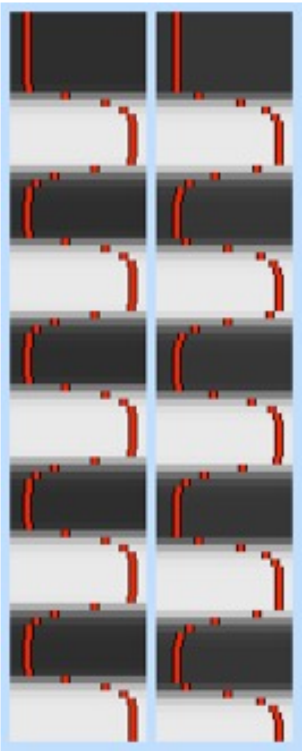


Correlation of EVs: First-level designs



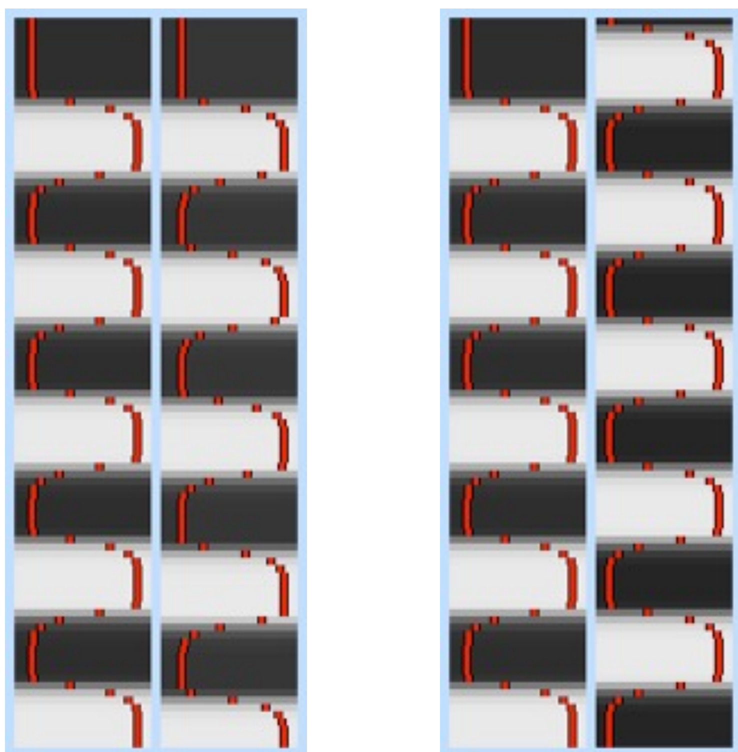
Design Matrix Rank Deficiency

- 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!



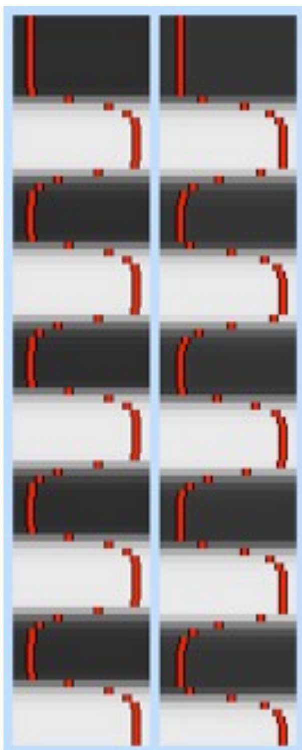
Design Matrix Rank Deficiency

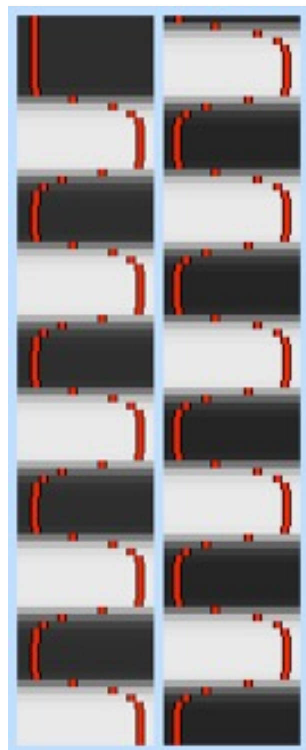
- A design matrix is rank deficient when a linear combination of EVs is exactly zero
  - Model can fit exactly the same signal in multiple ways!
- e.g. visual and tactile stimulations are exactly opposed
  (so no baseline)



Design Matrix Rank Deficiency

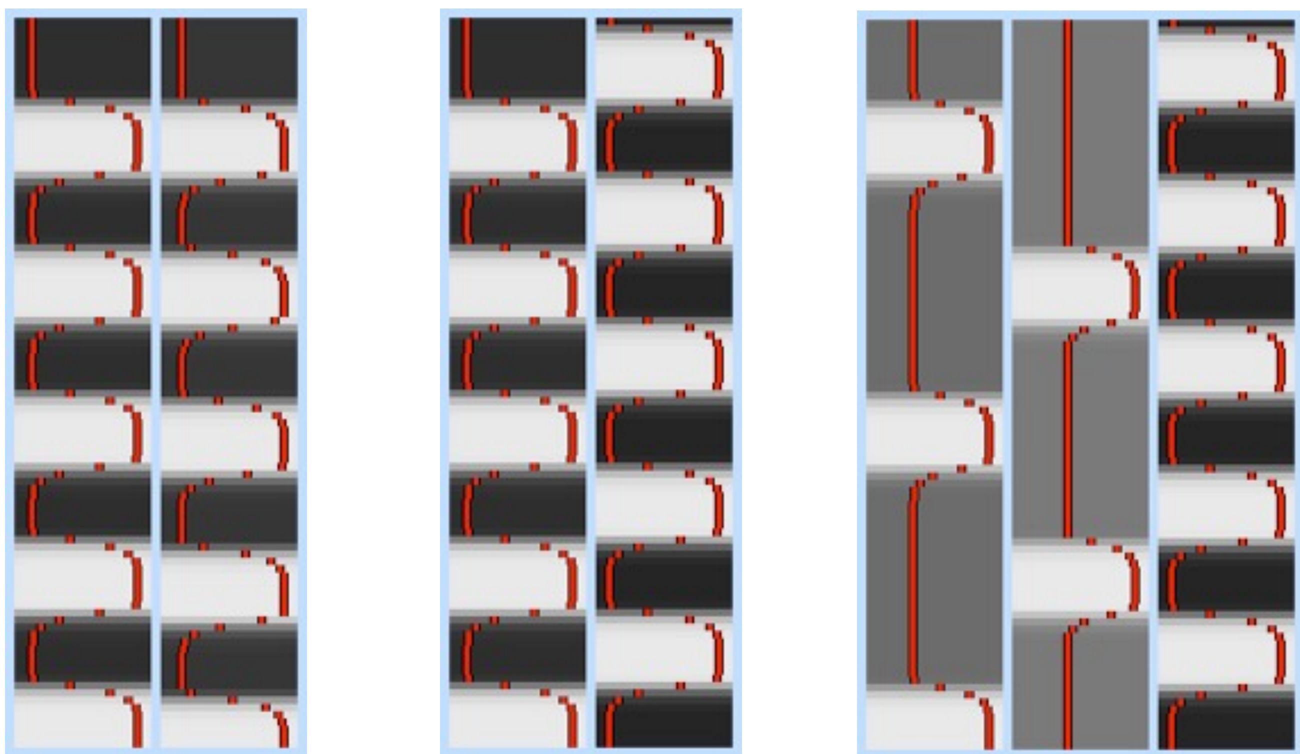
- A design matrix is rank deficient when a linear combination of EVs is exactly zero
  - Model can fit exactly the same signal in multiple ways!
- e.g. visual and tactile stimulations are exactly opposed (so no baseline)





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

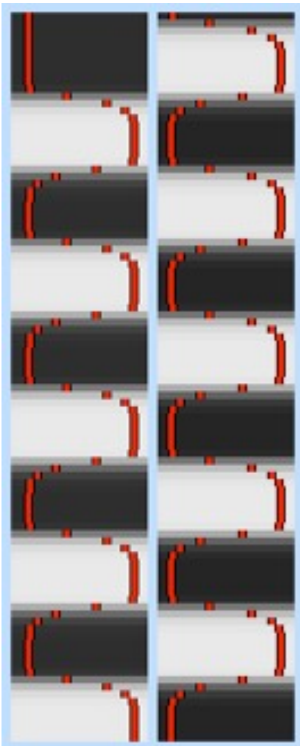
Close to Rank Deficient Design Matrices

- **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

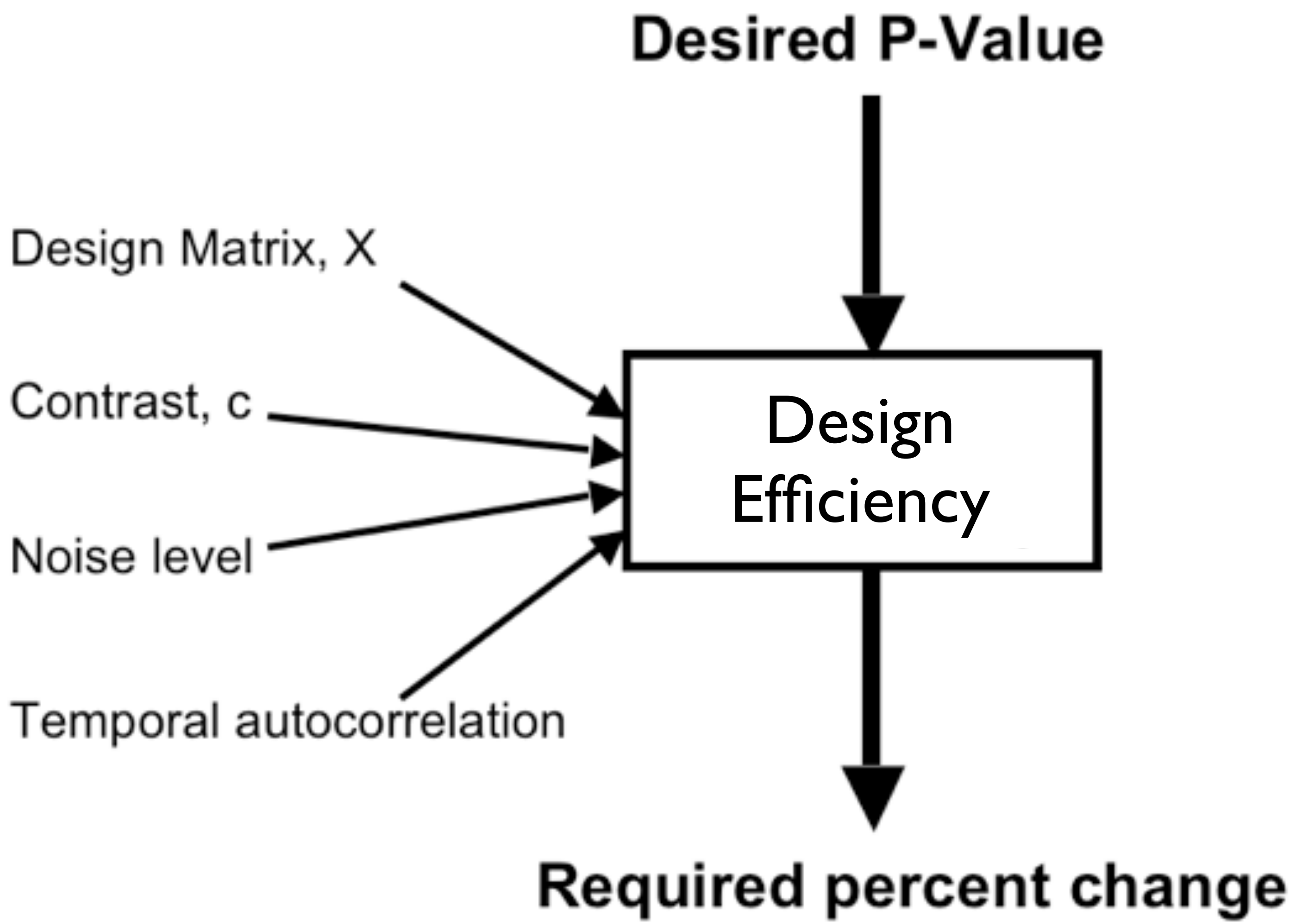
  e.g. may need a lot of data to determine how two EVs with very similar timings best combine to explain the data.

When do we have a problem?

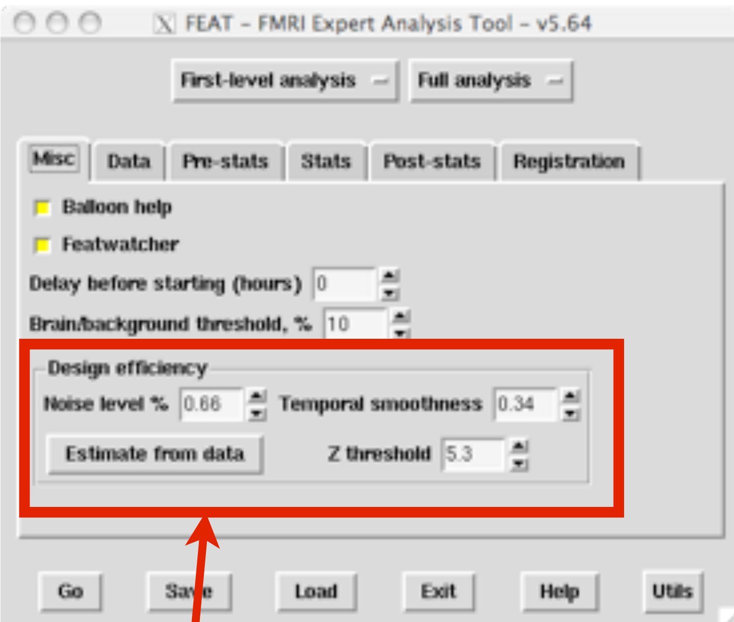


- Depends on SNR, and **also** the contrasts we are interested in:
- [1 -1] e.g. vis-tact??
- [1 1] e.g. average response??
- [1 0] or [0 1] ?? e.g. visual? or tactile?

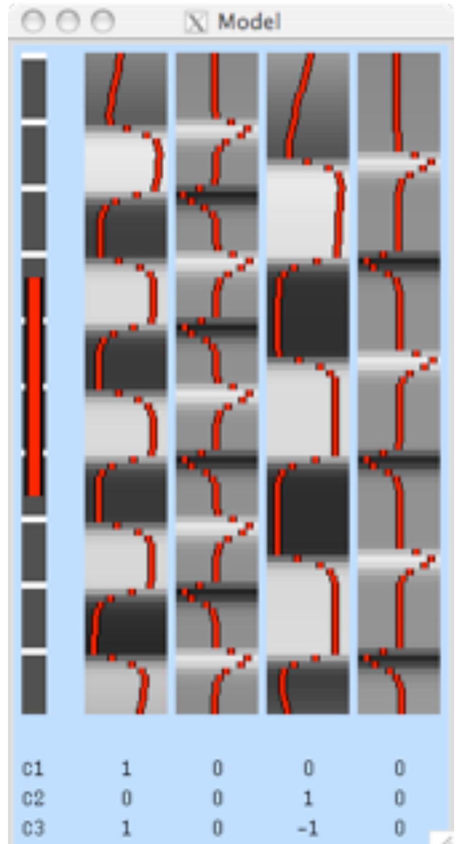
Design Efficiency



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!

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 …

Orthogonalisation

Orthogonalisation

DON'T DO IT!

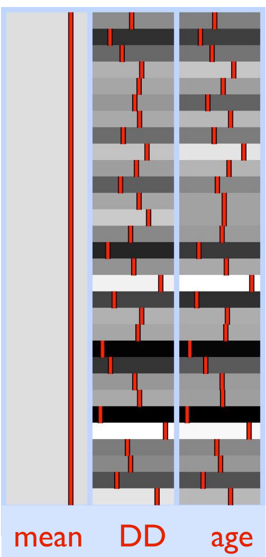
A better alternative to orthogonalisation

- 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

t-test



[0 1 0]

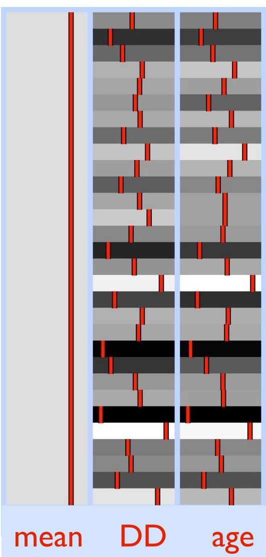
A t-test for a single EV is determined only by variability in BOLD signal that *cannot* be accounted for by other EVs.

This is a ***conservative*** result: only when DD can *uniquely* explain the measurements will there be a significant result.

A better alternative to orthogonalisation

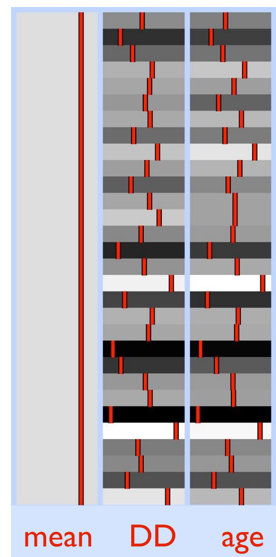
- Consider a case example:
  - Disease Duration (DD) + age (demeaned)
    - where we want to 'correct' for age

t-test



[0 1 0]

F-test



[1 0 0]
[0 1 0]
[0 0 1]

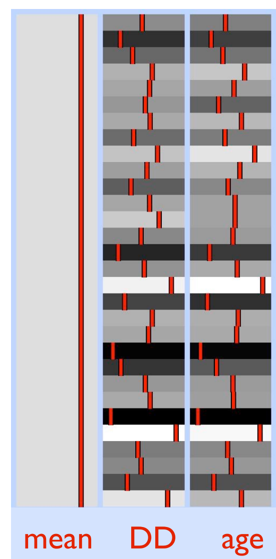
A better alternative to orthogonalisation

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

F-test

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.



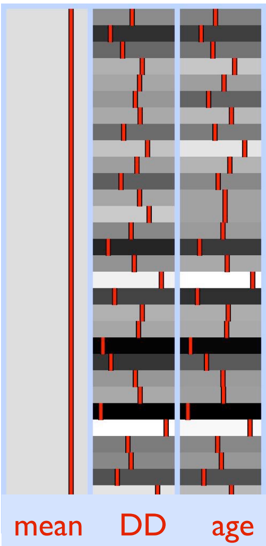
[1 0 0]

[0 1 0]

[0 0 1]

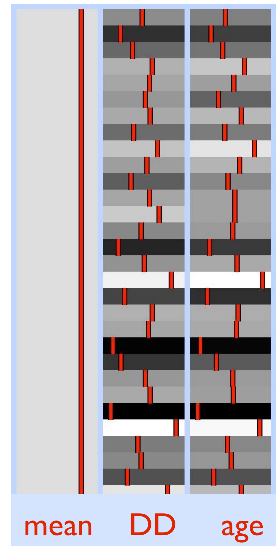
A better alternative to orthogonalisation

t-test



[0 1 0]

F-test



[1 0 0]

[0 1 0]

[0 0 1]

<u>Results (a fairly typical example with strong correlation)</u>:

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

<u>Interpretation</u>: 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.

<u>Follow on</u>: 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).

Advanced Analysis: Correlated EVs

Summary:

- Correlation of EVs makes it difficult for the GLM to assign unique contributions and often leads to no significant results
- Extreme correlation gives rank deficiency
- Problem of correlation depends on the contrast
- Design efficiency gives required % BOLD change to get a significant result *per contrast* (like power calc.)
- Can also get info about where correlations are
- Orthogonalisation: DON'T DO IT!
- In practice consider F-tests for combined explanatory results as well a t-test (unique contributions)
- Try to break correlations through planning/recruitment

That's All Folks