STUDY DESIGN AND EFFCIENCY

QUIN MASSEY & DR LISA TEDESCO TRICCAS

PART 1: STUDY DESIGN BY: QUIN MASSEY

OVERVEW

- **1. Main Design Goals**
- 2. Types of Study Design
 - Subtraction
 - Conjunction
 - Factorial
 - Parametric
- **3. Stimulus Presentation Strategies**
 - Blocked Design
 - -Event Related Design
 - -Mixed Design

MAIN GOALS: TO TEST A SPECIFIC HYPOTHESIS

- We want to manipulate the participants experience & behaviour in some way that is likely to produce a functionally specific neural response, and then make an inference.

- Isolate functional processes of interest
- Measure Behaviour
- Collect as much data as possible
- Avoid confounding physiological and psychological artefacts

- Choose stimulus conditions and timing that maximise BOLD signal contrast

WHAT CAN WE MANIPULATE?

- **1. Stimulus Type and Properties**
 - 2. Stimulus Timing
 - **3. Subject Instructions**

chological artefacts at maximise BOLD



K KAFI INFIESI SA SINFIERYPI HESISPER AININE I HEAFI VA I TASKRELATIVE TO ANOTHER TASK A - TASK B

TWO TASK CONDITIONS DIFFERING IN THE PROCESS OF INTEREST

ASSUMPTION OF 'PURE INSERTION': Two or more conditions can be cognitively added with no interactions among the cognitive components of a task (Amaro & Barker, 2006)

Task condition 1: evokes process of interest

Task condition 2: evokes all but the process of interest

If the experiment is looking at the neuronal structures underlying a single process called "N"...

N = [Task with N] - [matched task without N]

STEP BY STEP:

- Find a stimulation activity: "Look at the screen and when you see a word, repeat it."

& a control activity: "When you see a word, do not repeat it."

- You then subtract these two, and identify the difference, which would ideally be the cognitive process of interest (repetition).

 In order for subtraction to work, "pure insertion" is needed. Which is saying when a new cognitive component (repeating) is added to a task (reading), the implementation of the pre existing component (reading) remains unaffected.

- For example, we assume that reading to repeat and reading to read are the exact same thing.

Monti (2021)



Neurochat (2013)

CONJUNCTION: TESTS SEVERAL HYPOTHESES, DETERMINING THE SIGNIFICANCE BETWEEN THE TASK PAIRS SEE SIMILARITIES BETWEEN AREAS

How does Conjunction differ to Subtraction?

- Subtraction looks for activation differences between a pair of tasks that share all but the component of interest, conjunction looks for the commonality in activation differences between two or more pairs of tasks that share only the component of interest.

- Cognitive components that are not common to all task pairs can include interaction terms, and because these effects are discounted, one does not need to depend on pure insertion. Price & Friston (1997)

- Isolate process of interest by finding commonalities between task conditions
 - Task Pair 1: Subtraction isolating A & B
 - Task Pair 2: Subtraction isolating A & C

NOTE CONJUNCTION NUL HYPOTHESIS IS MORESTRICT HAN THE GLOBAL NULL HYPOTHESIS

Conjunction Null Hypothesis

More strict analysis

P = 0.05

Only activation over the p value threshold can reject the null hypothesis & prove overlapping activation

*CONJUNCTION NULL HYPOTHESIS IS IMPORTANT TO HAVE IN SITUATIONS WHEN A STRICT DESIGN & **CONSERVATIVE NULL HYPOTHESIS IS NEEDED***

Global Null Hypothesis

Lenient numerical value & analysis

Allows researchers to indicate trends

Shows a more directional effect

Friston et al. (1996)



PARAMETRIC - COGNITIVE DEMAND OF TASK VARIES SYSTEMATICALLY WITH BOLD SIGNAL **LINEAR - ADAPTATION, COGNITIVE DIMENSIONS** NON LINEAR - POLYNOMINAL EXPANSIONS, NEUROMETRIC

FUNCTIONS, MODEL BASED REGRESSORS

EXAMPLE : (SEIDMAN ET AL., 1998)

TASK 2: RESPOND IF A IS PRECEDED BY 3 LETTERS, THEN Q (ABCDQ)

TASK 1: RESPOND IF A IS PRECEDED BY Q (A, Q)

BASELINE: RESPOND TO ALL LETTERS

- INCREMENTALLY INCREASES THE DIFFICULTY OF TASKS **THROUGH A "STEP"** INCREASE

- ALLOWS DISSOCIATION **BETWEEN AREAS FUNCTIONALLY ASSOCIATED** WITH TASKS AND OTHER **'MAINTENANCE' AREAS**









FACTORIAL : TWO OR MORE FACTORS, AND THEIR DIFFERENT LEVELS ARE MATCHED

TESTS FOR INTERACTIONS

Interactions: When the effects of one factor depend on the levels of a second factor.

Main Effect: Effect of one factor alone

'...perform a task where the cognitive components are intermingled in one moment, and separated in another instance...' (Amaro & Barker, 2006)



2 X 2 DESIGN 2 FACTORS X 2 LEVELS = 2 CONDITIONS - FACH FACTOR HAS 2 LEVELS

X2	Factors: X & Y
X2 Y1	Levels: X1, X2, Y1, Y2
X2 Y2	Conditions: X1Y1, X1Y2, X2Y1, X
	X2 X2 Y1 X2 Y2



Monti (2021)

EXAMPLE:

Gender

Does a new drug decrease migraine attacks, is it more effective in males or females?

-Using the 2 x 2 chart, you can see all of the possible interactions between the two factors, dosage and gender. The interactions can also be seen on a graph, which is a combination of the individual factors main effects.

	Low	High
Male	Male Low Dose	Male High Dose
Female	Female Low Dose	Female High Dose

Dosage

Main Effects



A) Block Design



B) Event-Related

C) Mixed Block/ Event-Related



BLOCK DESIGN ALTERNATING BETWEEN DIFFERENT TASK CONDITIONS

CONDITION ONE





PROS:

-Avoids rapid task switching (e.g. patients)

-Fast and easy to run

-Good signal to noise ratio

-Strong detection & statistical power

Maximises: data variability due to experimental manipulation (between-conditions variability)

Minimises: other sources of data variability (within-conditions variability)

CONS:

-Habituation

-Signal drift

-Poor choice of conditions

that cannot be







-Expectancy effect

- baseline as many preclude meaningful
- -Cant have many tasks conducted repeatedly

WHEN THE SUBJECTS **EXPECT A GIVEN RESULT AND UNCONSCIOUSLY AFFECTS THE** OUTCOME

Huettel (chapter 9)



TASKAVS_NO TASK

SQUEEZE **RIGHT HAND**



30 SEC REST

SQUEEZE **RIGHT HAND**



SQUEEZE **LEFT HAND**

> By continuously moving through tasks, you can distinguish differential activation between conditions. However, it does not allow identification of activity common in both tasks.

By resting, it shows more activity associated with the task, but may introduce unwanted results







EVENT RELATED DESIGN: EVOKE PROCESS OF INTEREST TRANSIENTLY BY BRIEF PRESENTATION OF INDIVIDUAL STIMULI



PROS:

Task order and spacing is randomised (as long as the hemodynal response can reach baseline before the next trial)

Allows real world testing & trial by trial sorting based on subject response

Eliminates predictability

Can look at novelty, priming & temporal dynamics of response

CONS:

mic	Lower statistical power (small signal change)
ct	More complex design and analysis (e.g. timing/baseline issu
	Evoke smaller changes in BOLD signal
2	Possibly larger switching costs between tasks

Huettel (chapter 9)





- The subject was presented with a picture of a house, and then a picture of a person. The participant was asked to tap his left index finger for the house, and tap his right for the person.





The arrows indicate the "rest" in between tasks. The "rest" is just long enough for the hemodynamic response to fully move up, and return back to the baseline.





MIXED DESIGN: COMBINATION OF BLOCK AND EVENT RELATED DESIGN

Stimulus present in regular blocks: >1 type of event per block



EVENT : ITEM RELATED PROCESSES (BUTTON PRESS) BLOCK : STATE RELATED PROCESSES (ATTENTION)

VWhite -

Within task block, the subject is presented with a video of different numbers, with a letter appearing within the sequence. The subject is told to press the button when a letter is presented.





WHICHEVER STUDY DESIGN YOU CHOOSE IN BOTH, Design or stimulus presenting strategies, it all depends on your question.

Part 2: Efficiency and optimisation of fMRI designs

MFD 2022 Dr Lisa Tedesco Triccas



Good fMRI design requires two criteria

1. <u>Appropriate</u>

e.g. induces subject to do or experience the psychological state that you want to study (psychological)

2. <u>Efficient</u>

e.g. effectively detects brain signals related to those psychological states (statistical)

You can have a great psychological experiment with huge neuronal response, but be completely unable to identify this in fMRI-signal because you can't disassociate the BOLD signal

Content

- General advice
- Terminology
- Challenges with BOLD IR
- Stimulus timing: One condition
 - Fourier Transformation
 - High-pass filtering
- Stimulus timing: Two/more conditions
- Different efficiencies for different contrasts
- Correlation between regressors



General advice

1. Scan for as long as possible

- Avoid fatigue, habituation and discomfort
- Statistical power (40-60 mins)
- Group analysis: number of subjects

2. Keep subject as busy as possible

- Minimise the time subjects are not engaged in a task
- Breaks in scanning
- disrupts the spin equilibrium
- reduce efficiency of any temporal filtering
- "session" effects



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Challenges with BOLD Impulse response

- BOLD impulse response (IR)
 - Haemodynamic Response Function (HRF): relation between burst of neuronal activity and BOLD signal
 - Typical response: peak at 4-6s, initial undershoot at 10-30s, returns to baseline at 25-32s (Malonek & Grinvald, 1996)
- Main challenges:
 - 1. Delayed and dispersed BOLD response
 - 2. Low frequency noise



Terminology

- Trials: replication of a condition
 - Components of a trial: bursts of neural activity, or periods of sustained neural activity
 - (event)
- Stimulus Onset Asynchrony (SOA): time between onset of two different stimuli (Long vs short)
- Inter-Trial Interval (ITI): time between the onset of successive trials
- Inter-Stimulus Interval (ISI): time between the offset of one component and the onset of the next



• For example, a working memory trial can consist of a stimulus (event), a retention interval (epoch) and a response



Optimising efficiency: stimulus timing

Temporal convolution model

Stimulus x IR = Predicted fMRI data

- The following examples will use this model
- Stimulus timing
 - You want trials to be temporally close to limit ITI
 - In order to be sensitive to differences between trials close together in time (i.e., <20 s), you can either
 - **Fix SOA** but vary the order of trials
 - Fix the order but vary the SOA



GLM: Y(data) = X(design matrix) . β (parameters) + ϵ (error)



Stimulus timing: Single condition vs baseline



Fixed SOA

• SOA = 16s



• SOA = 4s











○ Even less efficient – "raised baseline"



Varied SOA- Stochastic Design

• Minimal SOA of 4's, but only a 50% probability of an event every **4**s



Predicted fMRI Data



- Only half stimuli used compared to 4s SOA, but more efficient.
- **Reason**:
 - Larger variability in signal
 - Good ability to estimate the shape of the BOLD IR



Varied SOA- Blocked design

 Blocked design: vary the SOA in a systematic fashion (block of 5 stimuli every 4s with 20s rest)





- Even more efficient than a stochastic design
- Why? explained using the Fourier transform of each function

Fourier transform

Operation which converts functions from time to frequency domains



The Fourier transform (FT) process is like the musician hearing a tone (time domain signal) and determining what note (frequency) is being played.

Fourier transform



https://www.youtube.com/watch?v=spUNpyF58BY



- FT plots magnitude as a function of frequency
- The BOLD IR acts as a low pass filter and attenuate higher frequencies
- Block design more efficient because the majority of signal is "passed" by the IR filter



Sinusoidal modulation: Most efficient design





- Majority of signal passed by the IR, not filtered out.
- Stimulus frequency should be best aligned with the dominant frequency of the IR (.03 Hz) or 1 waveform in 32 seconds
- Issue: Practically, it would not be possible for most designs which have discrete events rather than modulated changes





Problem: low frequency noise



- Two main components of fMRI noise:
 - o low-frequency "1/f" noise
 - o background "white noise"
- Causes: scanner drift, gradual changes in physical parameters
- Solution: High-pass filter
- Goal: maximise the loss of noise and minimise the loss of signal

Consequences of high pass-filtering



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- The high-pass filter would cause issues with design blocks that are too long
- Block designs are only efficient when the block length is short
- Issue with block design: subject may become aware of blocking and alter strategy/attention
- Compromise between efficiency and predictability

Revisiting the stochastic design













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- The high-pass and low-pass filter discussed create a single band-pass filter or 'efficient HRF"
- Minimal SOA of 4's, but only a 50% probability of an event every 4s
 - randomised SOA "spreads" the signal energy across a range of frequencies
 - \circ Majority of signal is passed \rightarrow reasonably efficient design
- Best practice for event related designs
Stimulus timing: 2 or more conditions



General Linear Model



- Efficiency(e) is the ability to estimate β (parameters), given the design matrix (X)
 for a particular contrast (c) and the given noise variance (σ²)
- $e(\sigma^2, c, X) = {\sigma^2 c^T (X^T X)^{-1} c}^{-1}$
 - The efficiency for each contrast is different
 - High covariance (correlation)
 between regressors can reduce
 efficiency.

Different efficiency for different contrasts

no mask

standard mask





- A fully randomised design with two eventtypes (A and B, let's say no mask/standard mask)
 - Long SOAs (16-20s) are optimal for <u>common effect (A+B)</u>

• Short SOA's are optimal for the <u>differential</u> <u>effect</u> (A-B)

- Trade off: The optimal SOA depends on the specific contrast of interest.
- What about when you want to be sensitive to both contrasts?

Marini et al., 2021









Reducing the trade off: null events



- Null events: "fixation trials" allow for selective averaging
- Purpose: buy us efficiency for detecting the common effect (A+B) even at short SOAs with a small reduction of efficiency for detecting the differential effect (A-B)
- This is equivalent to the stochastic design – randomises SOA between the events of interest







Correlation between regressors



- Efficiency can be considered in terms of the correlation between regressors.
 - Differential effect (A-B) has a high negative correlation
 - Common effect (A + B) has low variance
- Corresponds to different efficiency for different contrast



Reducing correlation between regressors



- Issue: High correlation between two regressors means that the parameter estimate for each one will be estimated inefficiently
- Solution:
 - <u>C -- Keep stimulus-response interval</u> fixed at 4s, but only cue a response on a random half of trials.
 - It will reduce correlation between the regressors and increases efficiency

Conclusions

STUDY DESIGN:

- Subtraction : Task A Task B
- Conjunction: Looks for commonality in activation differences
- Parametric: Task increases in difficulty
- Factorial: Test for interactions

STIMULUS PRESENTING DESIGN:

- Blocked design sustained stimuli
- Event related event related stimuli
- Mixed design combination of the two.

1. Consider efficiency **before** experiment prioritise study design being appropriate for the research question

2. Block design (short block length ~20sec) are most efficient

 Stochastic designs are also useful in specific contexts - For specific inferences linked to particular events at particular times

 Different contrasts have different efficiencies – bridge the gap with null events

5. Correlation between regressors should be considered and minimised to improve efficiency









References

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- http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency
- **Previous MfD slides**
- SPM course slides (2016)

Thank you: Dr Sara Bengtsson

Part 2: Efficiency and optimisation of fMRI designs

MFD 2022 Dr Lisa Tedesco Triccas

Good fMRI design requires two criteria

1. <u>Appropriate</u>

e.g. induces subject to do or experience the state that you want to study e.g psychological

2. <u>Efficient</u>

e.g. effectively detects brain signals related to those psychological states (statistical)

You can have a great psychological experiment with huge neuronal response,

but unable to identify this in fMRI-signal because you cannot disassociate the BOLD signal

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- General advice
- Terminology
- Challenges with BOLD IR
- Stimulus timing: One condition
 - Fourier Transformation
 - High-pass filtering
- Stimulus timing: Two/more conditions
 - Different efficiencies for different contrasts
 - Correlation between regressors

General advice

1. Scan for as long as possible

- $\,\circ\,$ Avoid fatigue, habituation and discomfort
- Statistical power (40-60 mins)
- $\circ\,$ Group analysis: number of subjects

2. Keep subject as busy as possible

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 - $\,\circ\,$ disrupts the spin equilibrium
 - $\circ\,$ reduce efficiency of any temporal filtering
 - \circ "session" effects



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Terminology



- Trials: replication of a condition
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 - For example, a working memory trial can consist of a stimulus (event), a retention interval (epoch) and a response (event)
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Optimising efficiency: stimulus timing

• Temporal convolution model

Stimulus x IR = Predicted fMRI data

- $\circ~$ The following examples will use this model
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Stimulus timing: Single condition vs baseline



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 <u>Not efficient</u> - Low variability of the signal

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- Only half stimuli used compared to 4s SOA, but more efficient.
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 - It will reduce correlation between the regressors and increases efficiency
Conclusions

STUDY DESIGN:

• Factorial: Subtraction : Task A – Task B

→can look at multiple factors in an experiment

- Parametric: Task increases in difficulty
- Conjunction: Looking for similarities in brain activation for multiple different regions.

STIMULUS PRESENTING DESIGN:

- Blocked design sustained stimuli
- Event related event related stimuli
- Mixed design combination of the two.

1. Consider efficiency **before** experiment prioritise study design being appropriate for the research question

2. Block design (short block length ~20sec) are most efficient

3. Stochastic designs are also useful in specific contexts - For specific inferences linked to particular events at particular times

4. Different contrasts have differentefficiencies – bridge the gap with nullevents

5. Correlation between regressors should be considered and minimised to improve efficiency

What is the main difference between Subtraction and Conjunction designs?

A.Conjunction looks for activation differences between a pair of tasks that share all but the component of interest, and Subtraction looks for the commonality in activation differences between two or more pairs of tasks that share only the component of in

B. Pure insertion is not required for subtraction but is for conjunction.

C. Nothing, they are the same.

D. Subtraction looks for activation differences between a pair of tasks that share all but the component of interest, and Conjunction looks for the commonality in activation differences between two or more pairs of tasks that share only the component of i

What two designs make up the "mixed design"

A Factorial and Block

B Factorial and Parametric

C Block and Event-Related

D Event-Related and Conjunction

Stimulus Onset Asynchrony (SOA) is

A Time between onset of two different stimuli

B Time between the offset of one component and the onset of the next **B**

C Time between the onset of successive trials

D Frequency between onset of two different stimuli

Which is the most efficient design from the following?

A Blocked design with fixed SOA

B Stochastic design with varied SOA

> C Blocked design with varied SOA

None of the above

References

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- Previous MfD slides
- SPM course slides (2016)
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