fMRI Course, Day 5 1st-Level Analysis

August 4th, 2023



Neuroimaging Initiative (NII)

Consulting for anyone who does neuroimaging



Goals

1. Understand how to do the steps

2. Understand why we did the steps

Both Remember Steps and Apply Concepts







Problem

How to accommodate dozens of labs spread across three campuses?

How to stay current with the latest methods and tools?

How to make sure the ideas "stick"?



Illustrations and demonstrations using data

Goal is for you to analyze your own data

Feedback is highly appreciated!

About Me



fMRI Tutorial #1: Downloading the Data

This book, Andy's Brain Book, is the ReadTheDocs companion to Andy's Brain Blog. It is intended for fMRI beginners, with more advanced imaging techniques being added later on. If this is your first

Overview of The Schedule

Monday	8:30 AM –	Contrasts, Group Analysis &	Andy Jahn		
8/7/2023	12:30 PM	Double Dissociations	University of Michigan		
	4:00 PM- 5:00 PM	Pattern Analysis & Classification via MVPA-virtual but live in 1360 East Hall. MUST be in 1360 for the virtual lecture.	Stephen LaConte Virginia Tech		
Tuesday	8:30 AM -	Pitfalls in fMRI Research	Andy Jahn		
8/8/2023	12:30 PM		University of Michigan		
Wednesday 8/9/2023	8:30 AM – 12:30 PM	Network Analysis & Tools	Scott Peltier University of Michigan Alex Iordan University of Michigan		
Thursday	8:30 AM –	Part 1-	Andy Jahn		
8/10/2023	12:30 PM	Introduction to Open Science	University of Michigan		
		Part 2- BIDS, MRIQC & fMRI Prep	Scott Peltier University of Michigan		
Friday	8:30 AM –	Reproduciibility	Andy Jahn		
8/11/2023	12:30 PM		University of Michigan		

Overview of The Schedule

At regular intervals, I will be asking you to download software and data

This is just to help with the demonstrations; don't worry if you are unable to download or install these!

Today's Agenda

1. Overview of fMRI

2. The BOLD Response

3. Model Fitting and 1st-Level Analysis

4. Other Modeling Options: Parametric Modulation and Finite Impulse Response

Neuroimaging Scene: The Early 1990's



MRIs: More powerful & More widespread



Deoxygenated blood = Lower signal

Oxygenated blood = Higher signal

Blood Oxygenation Level Dependent Signal (BOLD Signal)



ON

250 s

OFF

270 s

ON

190 s

OFF



Kwong et al., 1992

The BOLD Response



The BOLD Response: Duration



Bob Cox, AFNI

The BOLD Response: Convolution



Applet Demonstration of Convolution

https://phiresky.github.io/convolution-demo/

Interim Summary

1. Stimulus transducted into neural firing

2. More neural firing = more oxygen consumption

3. More oxygen consumption = more blood flow

4. More blood flow = greater measured signal

Observed signal is a few steps removed from actual neural activity

What We've Done So Far...

1. Overview of fMRI

2. Preprocessing the individual subject

3. Experimental Designs

4. Timing Files

5. Creating the general linear model (GLM)

Flanker task: Behavioral task adapted for fMRI analysis

Behavioral

* Dependent measure of interest is reaction time
* Can have the same amount of time between trials

* Two dependent measures: reaction time & the BOLD response * Will need differing amounts of time between trials

fMRI







Image from Bob Cox

Linearity



1. Block design (e.g., Kwong et al., 1992)



Advantages: Powerful, easy to design

Disadvantages: Boring, predictable, cannot use complex designs

2. Event-related designs



Advantages: More engaging, can use more complex designs Disadvantages: Less power, susceptible to collinearity

Mixed Designs



Block: State effects; trial: item-related effects Disadvantages: Very sensitive to errors in HRF modeling



Nee et al., 2013

Differing amounts of time between trials (i.e., jitter) are needed to avoid <u>collinearity</u>





Image from AFNI



- Trying to fit data as a sum of basis vectors that are nearly parallel doesn't work well: solutions can be huge
- Exactly parallel basis vectors would be impossible:
 - · Determinant of matrix to invert would be zero



Demonstration of viewing the time-series

Timing Files

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	20.0	2.0	congruent	0.591	correct		
	30.0	2.0	congruent	0.499	correct		
	40.0	2.0	incongrue	0.719	correct		
	52.0	2.0	congruent	0.544	correct		
	64.0	2.0	congruent	0.436	correct		
	76.0	2.0	incongrue	0.47	correct		
	88.0	2.0	congruent	0.409	correct		

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64.0	2.0	congruent_correct
76.0	2.0	congruent_correct
88.0	2.0	incongruent_correct
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The BOLD Response: Convolution



How to Write out Timings?

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4	117.27	7.99	98.21	10.02	135.06	7.55	80.69	9.07	
5	152.59	7.54	206.98	7.50	171.38	6.75	189.44	7.07	
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How to Write out Timings?

Depends on what stimulus presentation software you use

My advice: Write the timings in BIDS format (Onset, Duration, Trial Type, etc)

These can be easily edited and imported into any of the major packages


How to Write out Timings?

DS000102 - 🗁 SUB-01 - 🗁 FUNC - 🗋 SUB-01_TASK-FLANKER_RUN-1_EVENTS.TSV

LOWNLOAD

ONSET	DURATION	TRIAL_TYPE	RESPONSE_T	CORRECTNESS	STIMVAR	RSPONSE	STIMULUS	COND
0.0	2.0	incongruen	1.095	correct	2	1	incongruent	cond003
10.0	2.0	incongruen	0.988	correct	2	1	incongruent	cond003
20.0	2.0	congruent	0.591	correct	1	1	congruent	cond001
30.0	2.0	congruent	0.499	correct	1	1	congruent	cond001
40.0	2.0	incongruen	0.719	correct	2	1	incongruent	cond003
52.0	2.0	congruent	0.544	correct	1	1	congruent	cond001
64.0	2.0	congruent	0.436	correct	1	1	congruent	cond001
76.0	2.0	incongruen	0.47	correct	2	1	incongruent	cond003
88.0	2.0	congruent	0.409	correct	1	1	congruent	cond001
102.0	2.0	incongruen	0.563	correct	2	1	incongruent	cond003
116.0	2.0	congruent	0.493	correct	1	1	congruent	cond001
130.0	2.0	congruent	0.398	correct	1	1	congruent	cond001
140.0	2.0	congruent	0.466	correct	1	1	congruent	cond001
150.0	2.0	incongruen	0.518	correct	2	1	incongruent	cond003
164.0	2.0	incongruen	0.56	correct	2	1	incongruent	cond003
174.0	2.0	incongruen	0.533	correct	2	1	incongruent	cond003
184.0	2.0	congruent	0.439	correct	1	1	congruent	cond001

Onset Times Recommendations

No matter how you choose to write them out, you need to verify them

Some scanners acquire a few "dummy scans" at the beginning

If the experiment has a motor response, check that contrast first



Overview of model fitting

Fit the Model at each voxel ("mass univariate")



Uses one or more regressors (independent variables) to predict an outcome measure (dependent variable)

$$Y = \boldsymbol{\beta}_1 X_1 + \boldsymbol{\beta}_2 X_2 + \boldsymbol{\beta}_3 X_3 + \boldsymbol{\varepsilon}$$

Y= Outcome variable

 β = Beta Weights (parameter estimates)

X= Regressor

 ε = Residual

$$Y = \boldsymbol{\beta}_1 X_1 + \boldsymbol{\beta}_2 X_2 + \boldsymbol{\beta}_3 X_3 + \boldsymbol{\varepsilon}$$

Assume that: $Y = GPA, X_1 = IQ, X_2 = Drinks per week, X_3 = Height$

 $GPA = (\beta_1 * IQ) + (\beta_2 * Drinks) + (\beta_3 * Height) + \varepsilon$ $\beta_1 = 0.05^*, \beta_2 = -0.07^*, \beta_3 = 0.01 (not significant)$

IQ and drinks per week contribute to GPA; height doesn't



We can use these numbers to calculate the variance

$$SSE = \sum \left(Y_i - \hat{Y}_i\right)^2 = \sum e_i^2$$

$$\sigma^2 = \frac{\Sigma e_i^2}{N-1}$$

Test statistic

$$t = (\bar{x} - \mu_0) / (s / \sqrt{n})$$

where:

- x = the sample mean
- µ₀ = the hypothesized population mean
- s = the sample standard deviation
- n = the sample size

Deriving a beta weight (β) can be calculated by using linear algebra:

$$Y = X\hat{eta}$$

 $X'Y = (X'X)\hat{eta}$
 $(X'X)^{-1}X'Y = \hat{eta}$

$$\widehat{\operatorname{Var}}[\hat{\beta}] = \hat{\sigma}^2 (X'X)^{-1}$$

t-statistics in fMRI are conceptually similar, but computed slightly differently:

$$t = \frac{c(X'X)^{-1}X'Y}{\sqrt{\hat{\sigma}^2 c(X'X)^{-1}c'}}$$

$$\hat{\sigma}^2 = \frac{e'e}{N-p}$$

where $e=Y-X\hat{eta}=Y-\hat{Y}$

N = Number of time-points p = Number of regressors

Note: t-statistics are calculated at the 1st-level, but usually aren't carried into the 2nd-level analysis

In other words: Magnitude is carried to the group-level, not variance

This can be done in other programs, e.g. AFNI's 3dMEMA



Source: AFNI



Source: AFNI



Source: Jeanette Mumford

Revisiting the HRF



Canonical HRF: Width and delay are fixed, height is estimated as a beta

Why use a double-gamma (e.g., model the undershoot?)





Time



Time











600



Other options

Grand mean scaling: Removes intersession variance, allows for combining data across subjects

Intensity normalization: Forces each volume to have the same mean (not recommended)

$$g_s = \frac{\sum_{n=1}^N g_{ns}}{N}$$

Session-specific grand mean scaling: Multiplies each volume in session s by 100/g_s

Percent Signal Change

Some recommend reporting percent signal change instead of beta weights

More accurate reflection of effect size, more comparable between studies

ROI tool like Marsbar will scale by the overall mean of the voxels in the region

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Module List	Current Module: fMRI model specification	
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Model derivatives

Model HRF Derivatives. The canonical HRF combined with time and dispersion derivatives comprise an 'informed' basis set, as the shape of the canonical response conforms to the hemodynamic response that is commonly observed.

The incorporation of the derivate terms allow for variations in subject-to-subject and voxel-to-voxel responses. The time derivative allows the peak response to vary by plus or minus a second and the dispersion derivative allows the width of the response to vary. The informed basis set requires an SPM{F} for inference. T-contrasts over just the canonical are perfectly valid but assume constant delay/dispersion. The informed basis set compares favourably with eg. FIR bases on many data sets. One of the following options must be selected: * No derivatives



Benefits of time derivative

No interpolation of raw data, may capture variability in BOLD response

Cons: Requires an additional regressor in the model per condition

Other options: Highpass filtering and prewhitening





Highpass filter removes frequencies below a certain threshold



 $Y = X\beta + \epsilon$

$\operatorname{Cov}(\epsilon) =$







$KY = KX\beta + K\epsilon$

Prewhitening

Gauss-Markov assumptions: Normally distributed errors, constant variance, and no temporal autocorrelation

Are fMRI data temporally autocorrelated?

Other options: Individual Modulation

Useful for beta-series correlation, MVPA classification






PROBE

12.0

R





Drawback: Very tedious to implement without scripting!

For AFNI users: Can use 'IM' basis function in 3dDeconvolve

What about nuisance regressors, such as motion?



	Multiple regressors		
Dir	/Users/vincent/Data/tmp/TEST_SYNC/2018/Data/SPM_Labs/Subjects/sub01/func/whyhow/run_01		
Up	/Users/vincent/Data/tmp/TEST_SYNC/2018/Data/SPM_Labs/Subjects/sub01/func/whyhow/		
Prev	/Users/vincent/Data/tmp/TEST_SYNC/2018/Data/SPM_Labs/Subjects/sub01/func/whyhow/		
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Activation map with image registration but *without* using movement estimates as regressors Activation map when also using movement estimates as regressors

Source: AFNI



Perennial Question: How much is too much?

Guideline from days of yore: >1 voxel over entire run, >0.5 voxel between volumes

More important: Does motion correlate with your task?

Other nuisance regressors: DVARS, Framewise Displacement (FD)

Derivative Variance (DVARS) measures abrupt global signal changes from volume to volume (Power et al., 2011)

Volumes that exceed a specified threshold are flagged for scrubbing: Inserting that volume as a regressor into the GLM







Before we begin the Demo: SPM Terms for Analysis

1st-Level Analysis: Individual subject (all runs within the subject)

2nd-Level Analysis: Group-Level Analysis (all subjects within the experiment)

A contrast is simply one condition's beta weight subtracted from another

e.g., A-B

General recommendations: Model everything that is related to the task, and don't model any baseline events (e.g., implicit baseline)

. Subject/Session Scans Conditions	300 files	
Condition Name Onsets	WhyFace 9169 117.2590563 152.5798844 225.1941691]	
Time Modulation Parametric Modulations	9262 7.674989138 8.015399588 8.542317722] No Time Modulation	
Orthogonalise modulations	Yes	

Example: Pos/Neg/Neu images



Onset time (s)	Duration (s)	Description
11	4	Negative
17	.5	Face
27.5	4	Neutral
33.5	.5	Face

Example: Where is Pos activation greater than Neg activation?

Contrast weights for each side should sum to +1 and -1

	Pos IAPS	Neg IAPS	Neu IAPS	Face after Pos	Face after Neg	Face after Neu
PosIAPS > NegIAPS	1	-1	0	0	0	0

Where is Pos activation greater than Neu activation?

	Pos IAPS	Neg IAPS	Neu IAPS	Face after Pos	Face after Neg	Face after Neu
PosIAPS > NegIAPS	1	-1	0	0	0	0

Where is both Pos and Neg activation greater than Neu activation?

	Pos IAPS	Neg IAPS	Neu IAPS	Face after Pos	Face after Neg	Face after Neu
PosIAPS > NegIAPS	1	-1	0	0	0	0

Where is average face activation greater than baseline?

	Pos IAPS	Neg IAPS	Neu IAPS	Face after Pos	Face after Neg	Face after Neu
PosIAPS > NegIAPS	1	-1	0	0	0	0

Contrast weights need to be weighted for number of runs as well



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	Delete existing contrasts	No

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Smooth	DEP
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Contrast Manager	DEP

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Replicate over sessions	Replicate&Scale
Delete existing contrasts	No

1st-level setup: Demonstration

Other Experimental Modeling Options

Parametric Modulation

Finite Impulse Response (FIR)

Why do these types of analyses?

Parametric Modulation

Uses Auxiliary Behavioral Information (ABI)

Continuous (or several finely graded) ABI levels

Parametric modulators are estimated <u>in addition</u> to the regressor they modulate

Parametric Modulation

Example: Light intensity

Regressor for a "Light" trial, and also a regressor for the intensity of the light









Fig. 1. (A) An illustration of the event-related task design. During each trial, the participant was presented for 3 s with a display showing the size of the potential gain (in green) and loss (in red). After the accept or reject response, a variable interval was presented to allow for optimal deconvolution of fMRI responses to each trial (27). Gambles were not resolved during scanning. The values of gain loss for each trial and were sampled from the gain/loss matrix, as shown here for two example gambles; a gamble from each cell in this 16×16 matrix was presented during scanning, but the data were collapsed into a $4 \times$ 4 matrix for analysis. All combinations of gains and losses were presented. ISI,



interstimulus interval. (B) Color-coded heatmap of probability of gamble acceptance at each level of gain/loss (red indicates high willingness to accept the gamble, and blue indicates low willingness to accept the gamble). (C) Color-coded heatmap of response times (red indicates slower response times, and blue indicates faster response times).

tion (22).

Examination of regions of interest in the striatum and VMPFC from the gain/loss conjunction analysis (Fig. 3) revealed that these

eu physiological response to

Fig. 3. Conjunction analysis results. (A) Map showing regions with conjointly significant positive gain response and negative loss response (P < 0.05, whole-brain corrected, ineach individual map) (see also table S1). Red pixels indicate regions showing significant conjunction; green circles highlight clusters included in the respective heatmaps to the right. L, left; R, right. (B) Heatmaps were created by averaging parameter estimates versus baseline within each cluster in the conjunction map for each of the 16 cells (of 16 gambles each) in the gain/loss matrix; color coding reflects strength of neural response for each condition, such that dark red represents the strongest activation and dark blue represents the strongest deactivation.

sitivity to losses versus gains) is highly correlated across risky and riskless contexts (23). Therefore, we surmise that a similar mechanism may contribute to other manifestations of loss aversion.

в Striatum 3 20 Potential Loss 10 10 15 20 10 20 30 40 Potential Gain (\$) R Ventromedial prefrontal cortex 5 0 Potential Loss (\$) -5 10 -10-15 15 -20 -25 20

20

30

Potential Gain (\$)

40

10

y = 12

v = 40



Fig. 4. Scatterplot of correspondence between neural loss aversion and behavioral loss aversion in ventral striatum [Montreal Neurological Institute coordinates (*x*, *y*, *z*): 3.6, 6.3, 3.9; center of gravity in millimeters]. Regression line and *P* value were computed with the use of robust regression by iteratively reweighted least squares to prevent the influence of outliers; however, this regression also remained highly significant (*P* = 0.004) when the extreme data point (top right-hand corner) was removed from the analysis. β_{loss} and β_{gain} are the unstandardized regression coefficients for the loss and gain variables, respectively.

Parametric Modulation: Mean Centering



Courtesy of Bob Spunt

Parametric Modulation: Other Considerations

Orthogonalizing the regressors as part of the design

Orthogonalizing as part of the GLM

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Should be set to "No"

Why?



Mumford et al., 2015

Why?



Demonstration of Parametric Modeling Setup

Other Experimental Modeling Options

Parametric Modulation

Finite Impulse Response (FIR)
Other Experimental Modeling Options

Parametric Modulation

Finite Impulse Response (FIR)

Basis functions such as the HRF assume a stereotypical shape



Source: mri-q.com

But what if we don't want to assume a shape?

Example: You want to see whether the peak for condition A is later than the peak for condition B

Another example: You think the overall shape of the BOLD response is different between patients and controls, even though the amplitude is the same

You specify the window length and number of timepoints

e.g.: 20s window, 10 timepoints

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Statistical analysis: Design

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 $\label{eq:gray-bound} (\operatorname{gray} \to \beta \ \operatorname{not} \ \operatorname{uniquely} \ \operatorname{specified})$

Design description...

Basis functions : Finite Impulse Response Number of sessions : 2 Trials per session : 2 2 Interscan interval : 2.00 [s] High pass Filter : [min] Cutoff: 128 [s] Global calculation : mean voxel value Grand mean scaling : session specific Global normalisation : None





Image by Karthik Ganesan



Nee et al., 2013

Demonstration of FIR Modeling Setup

One of the most versatile tools is the image calculator

Every package has one (AFNI, FSL, MRtrix, etc.)

Simple to do basic arithmetic on a 3D image



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Copyright (c) 1991.1994-2020		A string is entered.	•	



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forwa	rd {mm}	0				
up	{mm}	0				
pitch	{rad}	0				
roll	{rad}	0				
yaw	{rad}	0				
resi	ze {x}	1				
resi	ze {y}	1				
resi	ze {z}	1				
Set C	Drigin	Reorie	ent			

File: ./1stLevel/beta_0002.nii Dimensions: 53 x 63 x 52 Datatype: float32 Intensity: Y = 1 X spm_spm:beta (0002) - Sn(1) Con*bf(1) Vox size: -3 x 3 x 3 Origin: 27 38.3 24.3 Dir Cos: 1.000 0.000 0.000 1.000 0.000 Full Volume

 World Space
 Image: Trilinear interp.

 Auto Window
 Add Overlay...

File Edit View Insert Tools Desktop Window SPM Figure Help Image: Specific Spec			hics	112 (7771): Graph	SP						••
Crosshair Position Origin mm: 0.0 30.0 30.0 vx: 27.0 48.3 34.3 Intensity: 0.375347 right (nm) 0 forward (mm) 0 pitch (rad) 0 origin: 27 38.3 24.3 Dirensity: 1.000 1.000 0.000 pitch (rad) 0 yw (rad) 1 Yordif Space Trilinear interp. Auto Window Add Overlay			Help	SPM Figure	ktop Window	ls Desk	Тос	Insert	View	Edit	File
Crosshair Position Origin mm: 0.0 30.0 30.0 vx: 27.0 48.3 34.3 Intensity: 0.375347 right {mm} 0 forward {mm} 0 optich {rad} 0 resize {x3 1 Set Origin Reorient											
Crosshair Position Origin mm: 0.0 30.0 30.0 vx: 27.0 48.3 34.3 Intensity: 0.375347 right {mm} 0 forward {mm} 0 up {mm} 0 pitch {rad} 0 roit {rad} 0 yaw {rad} 0 resize {x} 1 resize {y} 1 Set Origin Reorient											
mm: 0.0 30.0 30.0 vx: 27.0 48.3 34.3 Intensity: 0.375347 right (mm) 0 forward (mm) 0 up (mm) 0 pitch (rad) 0 vox (rad) 0 vaw (rad) 0 resize (x) 1 resize (z) 1 Set Origin Reorient		.nii	e: ./Inc-Con_Session	File	Drigin	C	sition	shair Po	Cros		
vx: 27.0 48.3 34.3 Intensity: 0.375347 right {mm} 0 forward {mm} 0 up {mm} 0 pitch {rad} 0 roll {rad} 0 yaw {rad} 0 resize {x} 1 resize {z} 1 Set Origin Reorient		x 52	Dimensions: 53 x 63			0.0 30.0	0.0 3		mm:		
Intensity: 0.375347 right (mm) 0 forward (mm) 0 up (mm) 0 pitch (rad) 0 roll (rad) 0 yaw (rad) 0 resize (x) 1 resize (x) 1 resize (z) 1 Set Origin Reorient			Datatype: int16			18 3 34 3	27.0		vx:		
Interisty: 0.3/334/ right {mm} 0 forward {mm} 0 up {mm} 0 pitch {rad} 0 yaw {rad} 0 resize {x} 1 resize {y} 1 Set Origin Reorient		0184054 X	Intensity: $Y = 0.0$			375347	_,.0		Inter		
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Image: Section of the section of th			-p u			0		t {mm3	righ		
Origin: 27 38.3 24.3 up (mm) 0 pitch (rad) 0 roll (rad) 0 yaw (rad) 0 resize (x) 1 resize (z) 1 Set Origin Reorient Set Origin Reorient		3	Vox size: -3 x 3 x			0		rd from	forture		
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roll [rad] 0 yaw [rad] 0 resize {x} 1 resize {y} 1 resize {z} 1 Set Origin Reorient		1.000 0.000	0.000			0		h {rad}	pito		
yaw {rad} 0 resize {x} 1 resize {y} 1 resize {z} 1 Set Origin Reorient		0.000 1.000	0,000		_	0		{rad}	rol		
resize {x} 1 resize {y} 1 resize {z} 1 Set Origin Reorient			0.000			0		/ {rad}	yav		
resize {y} 1 Full Volume Hide Crosshair resize {z} 1 World Space Trilinear interp. Set Origin Reorient Auto Window Add Overlay						1		ize {x}	res		
resize {z} 1 World Space Trilinear interp. Set Origin Reorient Auto Window Add Overlay		Hide Crosshair	lume 🗘	Full Vol		1		ize {y}	res		
Set Origin Reorient Auto Window	٥	Trilinear interp.	Space 0	World S		1		ize {z}	res		
		Add Overlay	/indow 0	Auto Wi	t	Reorient		Origin	Set		
	_							.5			

Demonstration

Preview of Today's Lab

Dataset collected by Emily Falk; 2x2 factorial design



Preview of Today's Lab

Block design



Preview of Today's Lab

ourrent module. mini model specific	
Name Onsets Durations Time Modulation Parametric Modulations	HowFace 284 135.0593544 171.3800147 243.0883199] 4532 10.7859291 8.894711134 9.210554915] No Time Modulation
Orthogonalise modulations	Yes
Name Onsets Durations Time Modulation	HowHand 6296 80.6916593 189.4403629 264.5608179] 313 10.45648544 9.137848595 10.19211621] No Time Modulation
Orthogonalise modulations	Yes
Multiple conditions Regressors Multiple regressors High-pass filter Factorial design	eLab/sub05/func/whyhow/run_01/rp_run_01.txt 128
Basis Functions . Canonical HRF Model derivatives	No derivatives
Model Interactions (Volterra) Global normalisation Masking threshold	Do not model Interactions None 0.8
Explicit mask Serial correlations	AR(1)
Current Item: Directory	

