FMRI Data Analysis at the Individual Level

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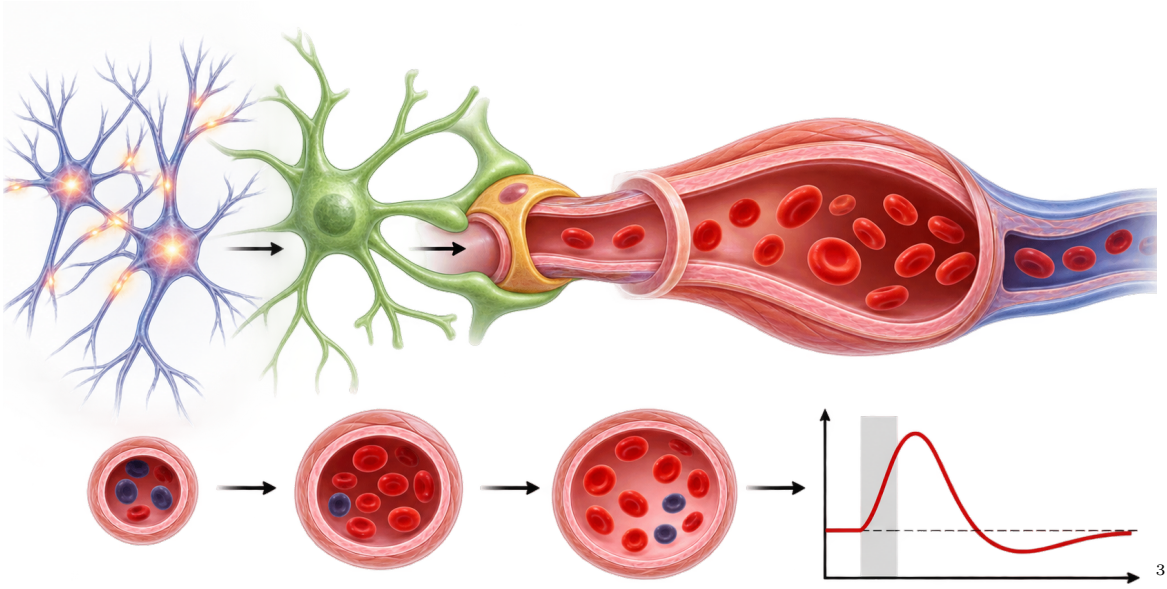
FMRI data analysis: big picture

- Four stages
  1. Experimental design & data collection
  2. Preprocessing & quality control
  3. Modeling
     - ⋆ individual level
     - ⋆ group level
  4. Result reporting

- Modeling
  - ◦ Statistical inference: relationship estimation
    - ⋆ causal inference: experimentally induced effects on BOLD
    - ⋆ correlation: resting-state
  - ◦ Multivariate/predictive: MVPA, encoding/decoding, RSA, machine learning, AI

- Statistical inference
  - ◦ Localization: task ⇒ regional BOLD responses
  - ◦ Network-level inference: requires stronger assumptions/models

FMRI: from neural activity to scanner

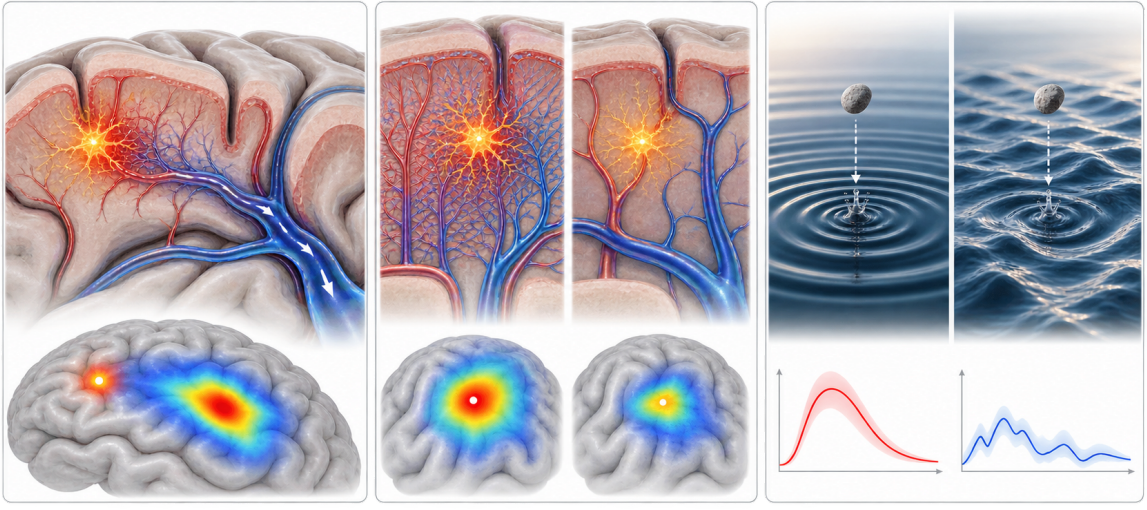


FMRI: challenges in decoding signal – Rosetta Stone problem

spatial (draining veins)

spatial (heterogeneous neurovascular coupling)

temporal (brain state)



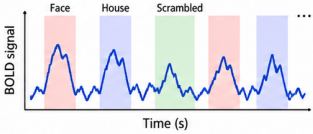
FMRI: three types

Task fMRI

Measure brain responses to controlled experimental tasks.



Example BOLD time series (voxel)



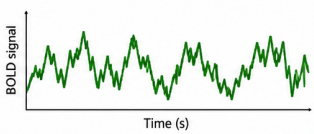
- **Stimuli:** controlled, repeatable conditions (e.g., faces, objects, reward, language)
- **Analysis:** GLM with task regressors; contrast condition-related activity
- **Goal:** identify brain regions engaged by specific cognitive processes

Resting-state fMRI

Measure spontaneous brain activity in the absence of an explicit task.



Example BOLD time series (voxel)



- **Stimuli:** no explicit task (fixation or eyes closed)
- **Analysis:** functional connectivity (e.g., correlation, ICA), network properties
- **Goal:** characterize intrinsic brain networks (e.g., default mode, attention, sensory) and their interactions

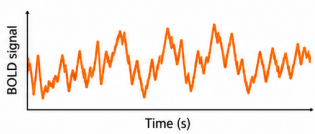
Naturalistic fMRI

Measure brain activity during continuous, real-world stimuli.

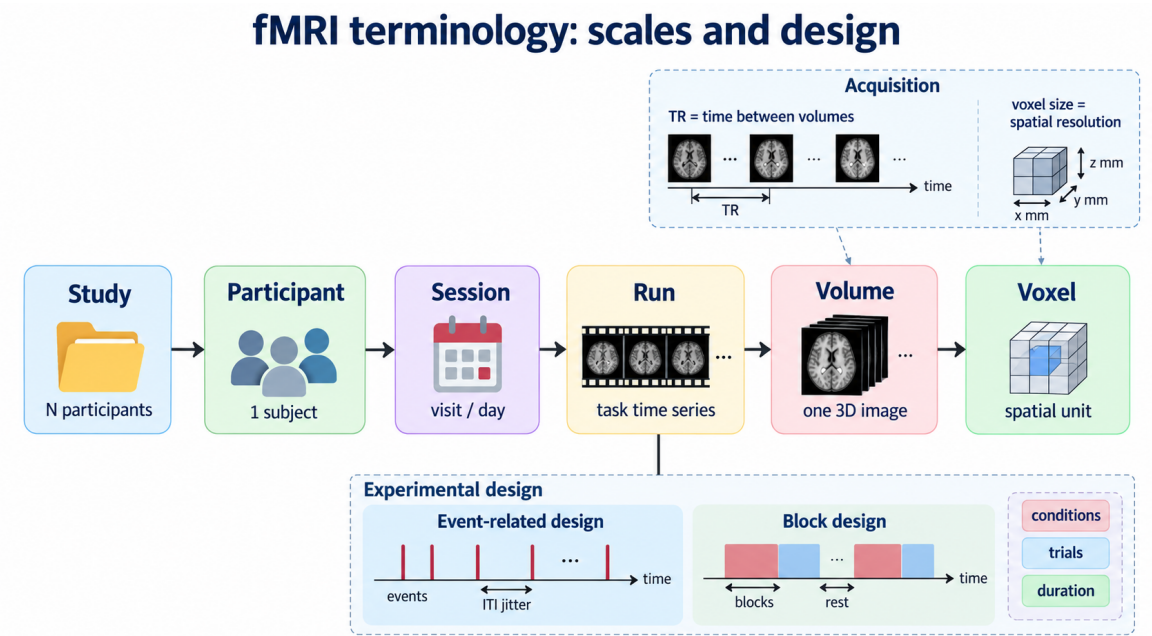


Examples:
movie watching
story listening
natural speech
social interaction
virtual reality
...

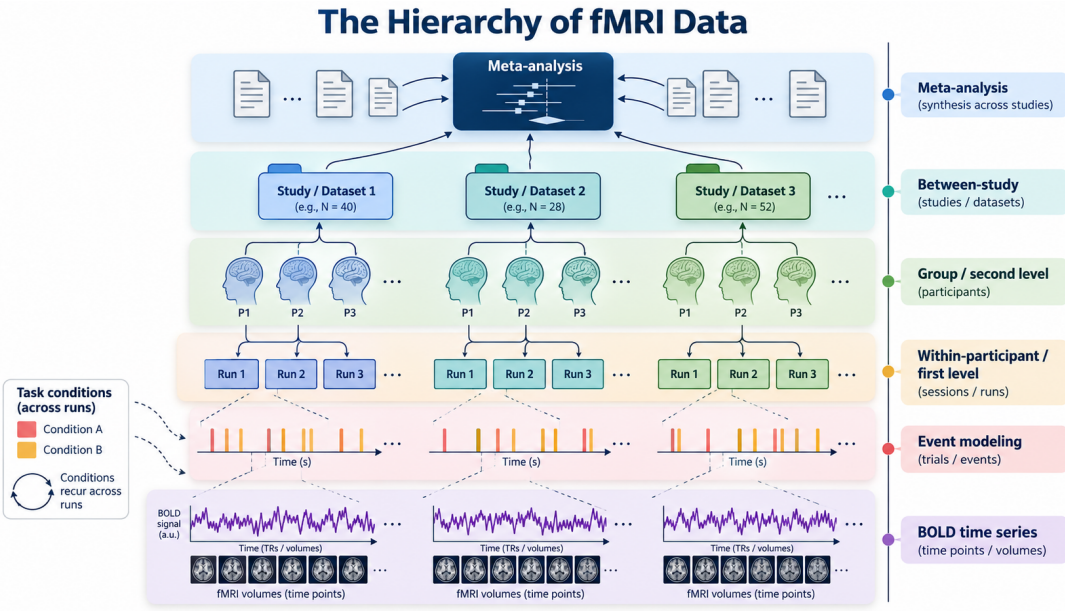
Example BOLD time series (voxel)



- **Stimuli:** continuous, complex, real-world input (e.g., movies, narratives, speech, interactions)
- **Analysis:** encoding/decoding models, inter-subject correlation, representational analyses
- **Goal:** understand how the brain processes natural, ecologically valid information


fMRI terminology: scales and design
Acquisition
TR = time between volumes
time
TR
voxel size = spatial resolution
z mm
y mm
x mm
Study
N participants
Participant
1 subject
Session
visit / day
Run
task time series
Volume
one 3D image
Voxel
spatial unit
Experimental design
Event-related design
events
ITI jitter
time
Block design
blocks
rest
time
conditions
trials
duration

Task FMRI: data hierarchy



Task FMRI: how to model observed data?

Experimental design: a toy example

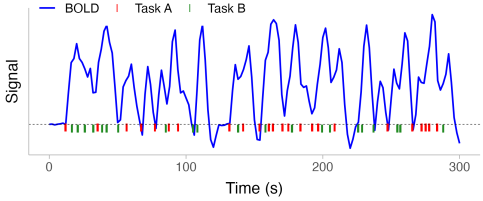
- task – 2 conditions: happy & sad
- sampling: #participants (40); #trials (30) per condition

Data structure: individual level

- 4-dimensional: space (3D voxels) + time
- massive univariate analysis: time series at each voxel

Research/analytical goal

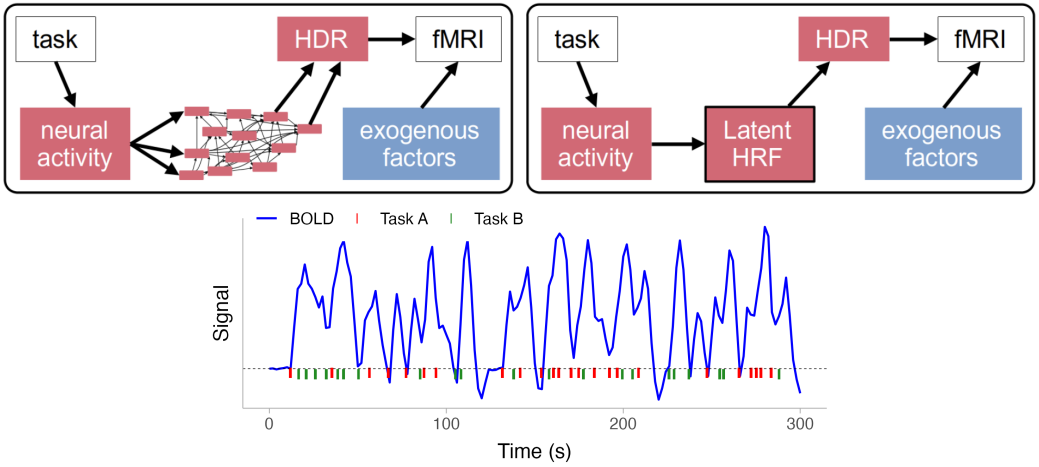
- estimand: response difference between conditions at each region
- estimation: hemodynamic response under each condition
- localization: regions showing response difference



Modeling challenges

- input: timing; output: time series
- Rosetta Stone: input ⇒ output?
- separation: tasks, nuisances, noise

Task FMRI: decoding the Rosetta Stone

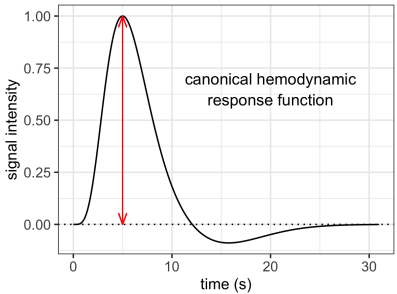


Decoders for latent HRF (hemodynamic response function)

- standard kernel or basis function: "canonical" HRF
- micro-rulers: flexible basis functions or splines
- standard kernel with adjustments: "canonical" HRF + derivatives

Task FMRI: canonical HRF

Standard kernel: shape-fixed HRF



- $h(t) = 5.7t^5e^{-t}/\Gamma(6) - 0.95t^{15}e^{-t}/\Gamma(16)$
- double gamma
- 2 phases: overshoot & undershoot
- overshoot peaks at 5s
- overshoot / overall duration: 12 / 32s
- undershoot depth: 9% of peak; no initial dip

How is the kernel created?

- constants (e.g., $\Gamma(6)$, $\Gamma(16)$): universal?
  - phenomenological, empirically motivated
  - not mechanistically physiological
- empirically informed via PCA: Friston et al. (1998)
  - $5.7t^5e^{-t}/\Gamma(6)$: peak (rapid rise + slow decay)
  - $0.95t^{15}e^{-t}/\Gamma(16)$: undershoot
  - HRF: large gamma - smaller delayed gamma

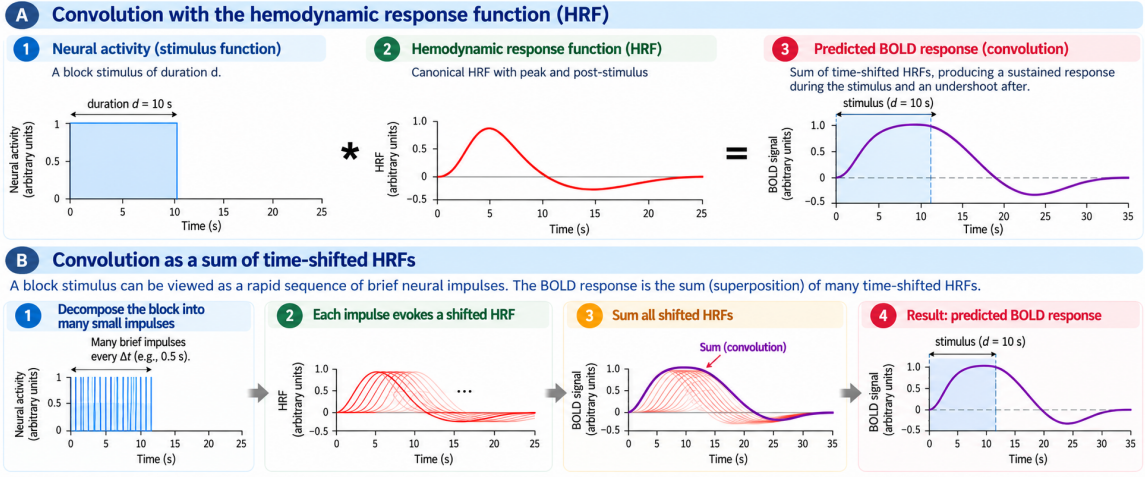
AFNI kernel 1: basis GAM

- $\text{GAM}(t;p,q) = (\frac{t}{pq})^p exp(p - \frac{t}{q})$: Cohen (1997)
- default parameters: $p = 8.6,\ q = 0.547$
- peak of 1 at $pq = 8.6 \times 0.547 \approx 4.70$ s
- overshoot only; no undershoot

AFNI kernel 2: basis TWOGAM

- $\text{GAM}(t;p_1,q_1) - \text{GAM}(t;p_2,q_2)$
- similar to canonical HRF

Task FMRI: creating a predictor through convolution



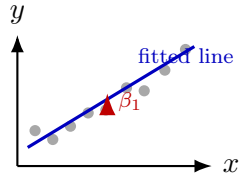
Task FMRI: from canonical HRF to predictors

Predictor/regressor (constructed ruler): assumed response to neural activity

- canonical HRF as a kernel: conceptually an impulse response function
  - produced by an idealized, infinitesimally brief burst of neural activity
- response with a neural activity of duration d at k-th trial:
  - stimulus represented by a boxcar: $s(t) = \begin{cases} 1, & t_k \le t < t_k + d, \ t = 1, 2, ..., T; \\ 0, & \text{otherwise.} \end{cases}$
  - predictor construction via convolution: $x(t) = (s * h)(t) = \int_{t_k}^{t_k+d} s(\tau)h(t-\tau)d\tau = \int_{t_k}^{t_k+d} h(t-\tau)d\tau$
  - data discretely collected: convolution in a summation form $x_n = \sum_i s_i h(n-i)\Delta t$
  - assumptions
    - ⋆ linearity / superposition: responses add approximately linearly
    - ⋆ time invariance: expected response kernel is assumed stable over modeled period
    - ⋆ homogeneity: trials under same condition share a common expected response
    - ⋆ boxcar assumption: stimulus duration functions as a proxy for duration of modeled neural drive
- implementations using 3dDeconvolve in AFNI
  - BLOCK(d,1)
  - GAM, TWOGAM, SPMG1
- other modeling options: modulation across trials
  - amplitude: -stim_times_times_AM2 (e.g., stimulus valence, behavior)
  - duration: dmUBLOCK(-d) (e.g., varying trial duration, RT)

Task FMRI: from predictors to estimated responses

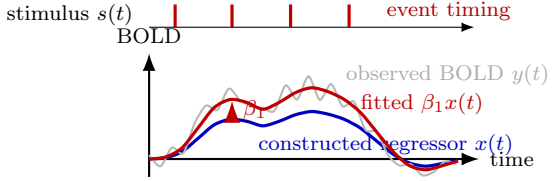
Conventional regression



$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i$$

- x_i, y_i: height of father and son
- x_i: index order usually irrelevant
- β_1: change in y per unit x
- β_1 interpretability: association
- regression: which is x or y?
- causation: prior knowledge

FMRI time-series regression



Event timing + assumed HRF → time-ordered predictor waveform $x(t)$

$$x(t) = s(t) * h(t)$$

$$y(t) = \beta_0 + \beta_1 x(t) + \epsilon(t),\ t = 1, 2, ..., T$$

$x(t)$**: constructed "ruler"**; **shape** fixed by design + HRF
β_1**: scalar amplitude**, how strongly the voxel follows ruler $x(t)$
Scaling convention matters: rescaling $x(t)$ rescales β_1

Same regression formulation, different predictor

conventional x_i: observed; index order irrelevant
FMRI $x(t)$: constructed in time t; integrity of temporal sequence maintained
model: time series regression; usually termed as GLM

Task FMRI: what does the regression coefficient mean?

$$y(t) = \beta_0 + \beta_1 x(t) + \epsilon(t) \quad \Longrightarrow \quad \boxed{[\beta_1] = \frac{[y]}{[x]}}$$

Raw FMRI signal

$y(t)$: in **arbitrary scanner units**

- depends on scanner/acquisition: 1000-3000
- varies across voxels/region, runs & individuals
- raw β_1 (e.g., 37.2) $\Rightarrow$ in arbitrary units

Render $y(t)$ meaningful units

Scale each voxel's time series within a run:

- $y^*(t) = 100\, y(t)/\overline{y} \;\Rightarrow\; \overline{y^*(t)} = 100$
- fluctuations: relative to **temporal mean**
- regressor $x(t)$: properly scaled
- $\beta_1 \approx$ BOLD percent signal change
- $\beta_1 = 1.2 \quad \Rightarrow \quad \sim 1.2\%$ response

Important qualifications

- **Local-mean scaling** Temporal mean as proxy for baseline
- **Good approximation** Percent signal change: relative to temporal mean, with negligible inaccuracy
- **Regressor scaling matters**

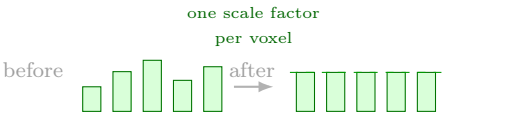
  β interpretability: properly normalizing $x(t)$
- **Scale runs/sessions separately**

  Different arbitrary intensity scales; allowing concatenated analyses

Task FMRI: local-mean vs grand-mean scaling

Voxelwise temporal-mean scaling

Each voxel uses its own temporal baseline

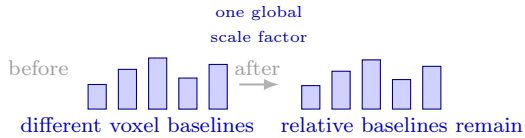


$$\bar{y}_v = \text{mean}_t\{y_v(t)\}, \qquad y_v^*(t) = 100\,\frac{y_v(t)}{\bar{y}_v}$$

- fluctuations: relative to voxel's **own baseline**
- each voxel mean is ~ 100
- with appropriate regressor scaling:
  $\beta \approx$ **local BOLD % signal change**
- visualization: region differences disappeared
- result reporting: effect estimates
- effect quantification: promoting cross-study comparisons and reproducibility

Grand-mean scaling

One reference value for the whole run/session



$$G_s = \text{mean}_{v,t}\{y_v(t)\}, \qquad y_v^*(t) = C\,\frac{y_v(t)}{G_s}$$

- global factor: data on a common intensity scale
- visualization: region differences maintained
- β remains in **global-scaled units**
- no percent signal change interpretation
- effect estimates not reported
- difficulty for cross-study meta-analysis

Task FMRI: regression model more generally

$$y(t) = \beta_0 + \theta x_{\text{drift}}(t) + \beta_1 x_{\text{cond}_1}(t) + \beta_2 x_{\text{cond}_2}(t) + \gamma x_{\text{motion}}(t) + ... + \epsilon(t),\ t = 1, 2, ..., T$$

vector-matrix form $\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$

- time series vector $\boldsymbol{y} = (y_1,\ ...,\ y_T)'$
- design/model matrix $\boldsymbol{X} = (\mathbf{1},\ \text{drifts},\ \boldsymbol{x}_1,\ \boldsymbol{x}_2,\ ...)$
- nuisance regressors / regressors of no interests
  - drifts: modeled by Legendre polynomials
  - motions: 6/12/24 components, censoring
  - tasks of no interest: error trials, instruction periods
  - others: cardiac/respiratory recordings, tissue-specific signals (WM, CSF), ...
- residuals $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0},\ \Sigma)$
- statistical inference for effects of interest
  - point estimate $\widehat{\beta}_1,\ \widehat{\beta}_2,\ \widehat{\beta}_1 - \widehat{\beta}_2$
  - uncertainty: standard error $\widehat{\sigma}$; $t = \widehat{\beta}/\widehat{\sigma}$
  - other statistics: F, R^2

parameter estimation: $\beta_1,\ \beta_2$

- least squares (3dDeconvolve)
  - residuals: assuming white noise $\epsilon(t)$ ($\Sigma = \boldsymbol{I}$)
  - many effects not accounted for $\Rightarrow$ underestimated $\widehat{\sigma} \Rightarrow$ inflated t, but pointed estimates remain unbiased
- restricted maximum likelihood (3dREMLfit)
  - residuals: assuming temporal correlation ARMA(1,1)
  - accuracy for temporal correlation structure: complex (specific acquisition (e.g., TR), region, model specification, etc.)
  - reflecting modeling challenges: so much effects swept under the rug of residuals (cross-trial variability, endogenous/exogenous effects, ...)

Task FMRI: from regression coefficients to the scientific contrast

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon} \qquad \boldsymbol{\beta} = (\beta_0,\ \beta_{\text{happy}},\ \beta_{\text{sad}},\ \beta_{\text{motion}},\ \ldots)'$$

A contrast encodes scientific question

Happy response

$$\theta = \boldsymbol{c}'\boldsymbol{\beta} = [0\ 1\ 0\ 0\ \cdots]\boldsymbol{\beta} = \beta_{\text{happy}}$$

Happy − Sad

$$\theta = \boldsymbol{c}'\boldsymbol{\beta} = [0\ 1\ \ -1\ 0\ \cdots]\boldsymbol{\beta}$$

Average task response

$$\theta = \boldsymbol{c}'\boldsymbol{\beta} = [0\ \tfrac{1}{2}\ \tfrac{1}{2}\ 0\ \cdots]\boldsymbol{\beta}$$

A regression coefficient corresponds to a **model column**
A contrast specifies the **estimand** from those columns

Effect estimate ≠ statistical evidence

Effect estimate $\widehat{\theta} = \boldsymbol{c}'\widehat{\boldsymbol{\beta}}$:
magnitude and direction of the effect

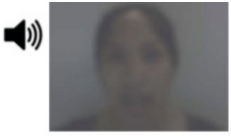
Uncertainty and t statistic

$$\mathrm{SE}(\widehat{\theta}) = \sqrt{\boldsymbol{c}'\widehat{\mathrm{Cov}}(\widehat{\boldsymbol{\beta}})\boldsymbol{c}}, \qquad t = \frac{\widehat{\theta}}{\mathrm{SE}(\widehat{\theta})}$$

t measures effect magnitude relative to uncertainty

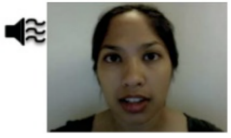
Task FMRI: an illustrative case – speech perception study

- 2 task conditions: audiovisual speech via video



(1) **Auditory-Reliable**

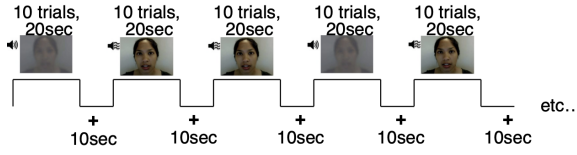
Example: Subjects can clearly *hear* the word "cat," but the video of a woman mouthing the word is degraded.



(2) **Visual-Reliable**

Example: Subjects can clearly *see* the video of a woman mouthing the word "cat," but the audio of the word is degraded.

- 3 runs, each run containing
  - 10 blocks: alternating with 5 auditory-reliable conditions and 5 visual-reliable conditions
  - each block (20 s): 10 stimuli (1s interleaved with 1s interval)
- data information
  - TR = 2s, time series: 150 time points per run × 3 runs
  - voxel size: 2.75 × 2.75 × 3.0 mm

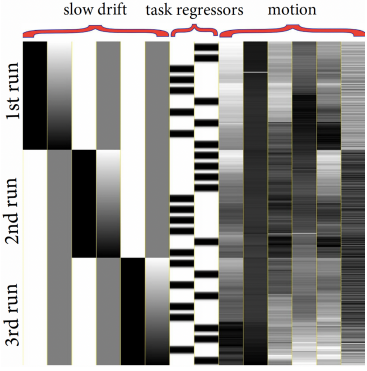


Task FMRI: an illustrative case – assuming fixed HRF

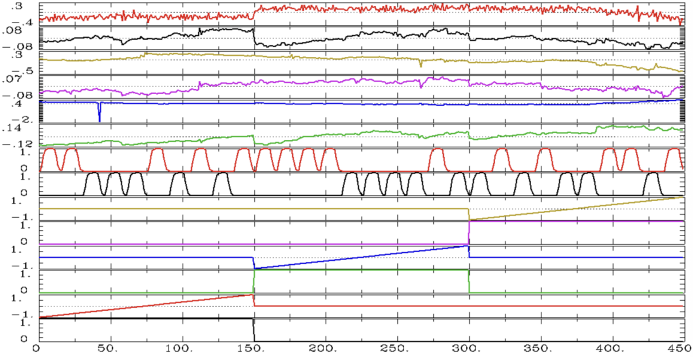
$$y(t) = \beta_0 + \theta x_{\text{drift}}(t) + \beta_1 x_{\text{cond}_1}(t) + \beta_2 x_{\text{cond}_2}(t) + \gamma x_{\text{motion}}(t) + ... + \epsilon(t)$$

vector-matrix form $\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$

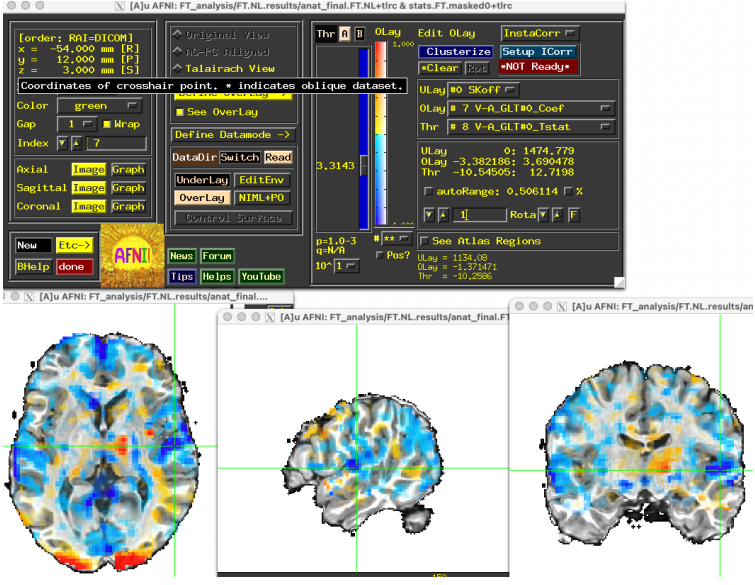
design matrix shown in grayscale



design matrix shown in curves



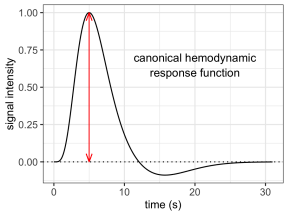
Task FMRI: an illustrative case – result visualization



Modeling: how accurate is canonical HRF?

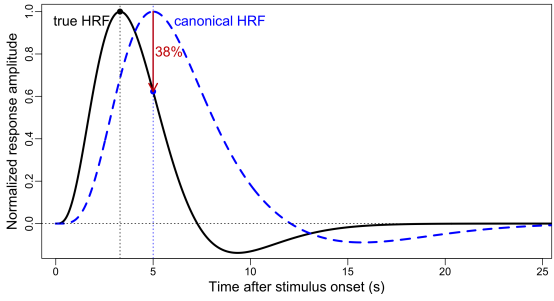
Conventional approach

- (onset+duration) $\otimes$ HRF: regressor
- HRF: rigid kernel
- efficient: 1 regressor/scalar



Rosetta Stone problem: accuracy

- HRF as a kernel: not well-calibrated
- price for efficiency: biased/attenuated effect estimates and/or reduced sensitivity
- $t = \widehat{\theta}/\mathrm{SE}$: compromised efficiency



- response profile: more than peak!

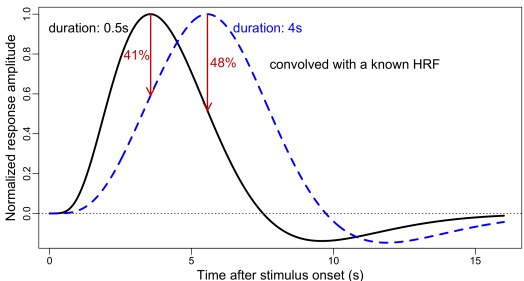
Modeling: Should stimulus duration always be convolved?

Conventional approach

- (onset + duration) $\otimes$ HRF: regressor
- implicit assumptions
  - neural onset=stimulus onset
  - neural duration=stimulus duration
  - kernel: canonical HRF

2 hypothetical scenarios

- seeing scary face: stimulus duration $d = 0.5$ s
- solving $27 \times 11 = ?$: stimulus duration $d = 4$ s



Treating stimulus duration as the duration of latent neural drive

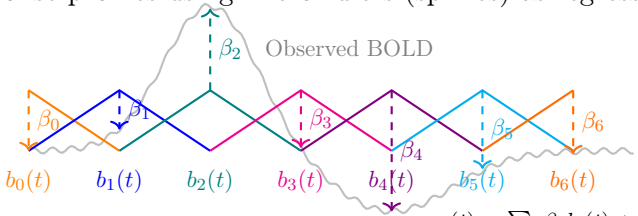
- an assumption: approximation for sustained processes
- inaccurate when neural engagement begins later, terminates earlier, persists afterward, or varies across trials
- cost: under-estimation
- $t = \widehat{\theta}/\mathrm{SE}$: compromised efficiency

Combined impact

- miscalibrated HRF & inaccurate proxy for duration
- underestimation: exacerbated
- accuracy problem

Task FMRI: moving beyond a fixed HRF

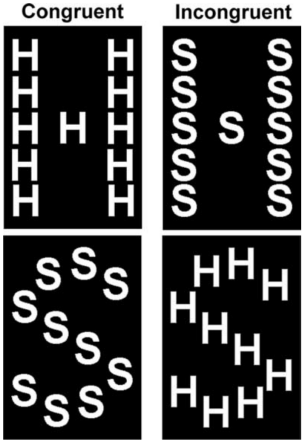
- estimating response profiles using micro-rulers (splines) as regressors



- events vs blocks: no single fixed canonical-HRF is imposed
  - trial duration: used to specify response span (TR=2s: $d = 2\text{s} \rightarrow 16\text{s}$; $d = 6\text{s} \rightarrow 20\text{s}$)
- implementation in AFNI
  - linear splines (tents) TENT(b,e,k): e.g., TENT(2,16,8)
  - cubic splines CSPLIN(b,e,k): CSPLIN(2,16,8)
- advantages
  - flexibility can reduce model bias
  - improved sensitivity outweighs the loss of precision
  - visual verification (cf, assumptions of "canonical" HRF)
- challenges: complexity in design, analysis, computation

Chen, G, Taylor, PA, Reynolds, RC, Leibenluft, E, Pine, DS, Brotman, MA, Pagliaccio, D, Haller, SP, 2023. BOLD response is more than just magnitude: improving detection sensitivity through capturing hemodynamic profiles.

Task FMRI: another illustrative case



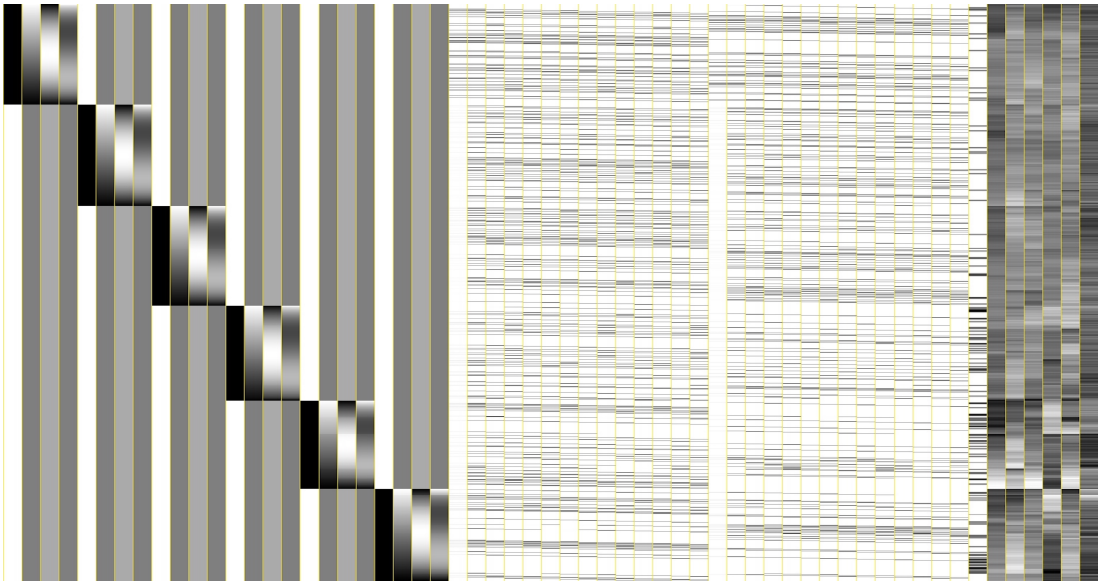
Experiment: global-local selective attention task

- 2 conditions: attention – congruent & incongruent
- 2 groups: 44 health volunteers & 43 bipolar disorder
- 288 trials per condition; TR: 1.25 s; average ITI ≈ 4.0s
- 6 runs
- error trials

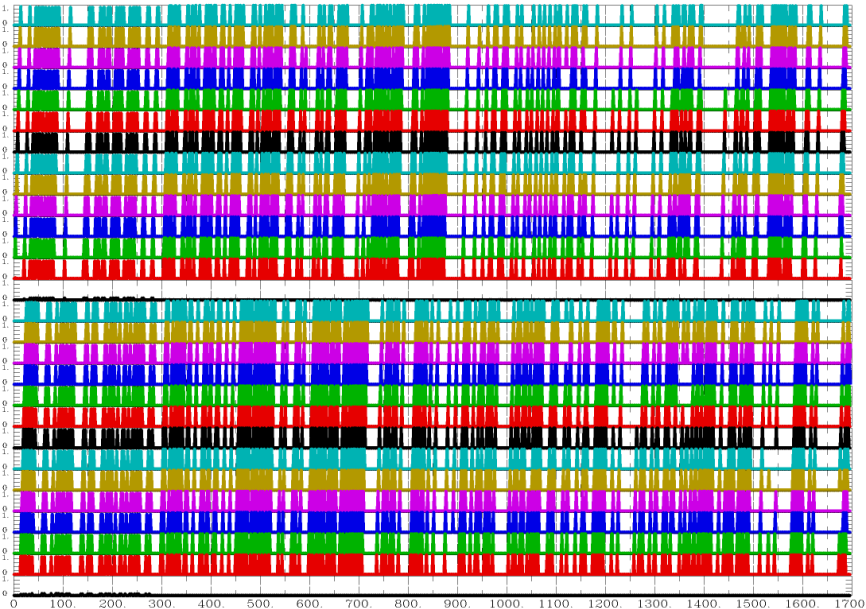
Individual level

- estimated HDRs: sampled at 14 time points - stim_times ... TENT(-2.5,13.75,14) or TENT(1.25,13.75,11)

Task FMRI: estimating response profiles



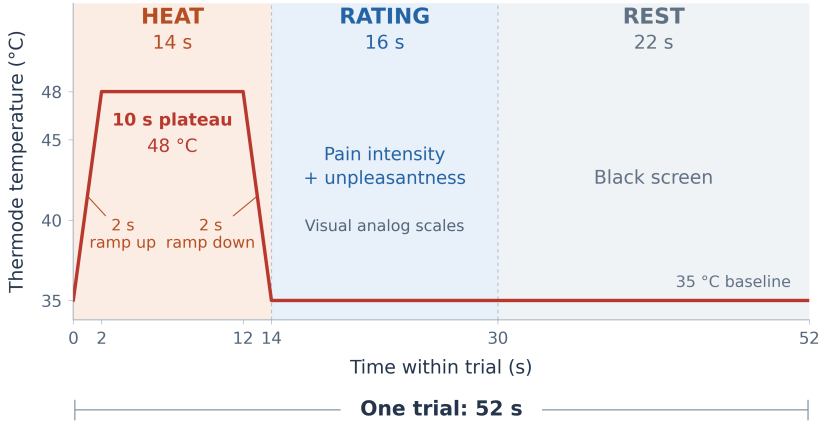
Task FMRI: estimating response profiles



Task FMRI: estimating response profiles



Task FMRI: third illustrative case – pain study



Research Question: pain sensitivity $\Uparrow \rightarrow$ regional response $\Uparrow$ or $\Downarrow$?

boxcar approach: challenges

- how to handle two ramp periods?
- assuming no habituation?

response profile estimation

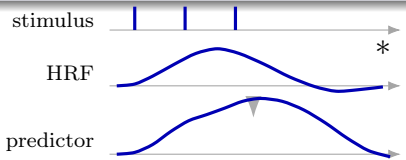
- TR=2s: TENT(2,24,12)
- directly addressing challenges of boxcar approach

Task FMRI: convolution vs deconvolution

Convolution: assume HRF shape

$$x(t) = s(t) * h(t)$$

Known stimulus timing + assumed HRF → predicted BOLD regressor.

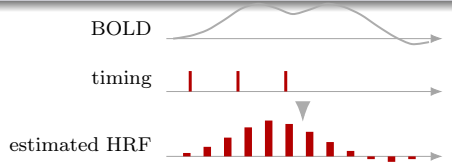


Forward model: shift + overlap + sum

Deconvolution: estimate HDR profile

$$y(t) \approx S\mathbf{h} + \epsilon(t)$$

Known timing + observed BOLD → estimated response profile.



Inverse problem: recover response shape

Multiplication / division analogy is exact in frequency domain:

$$y(t) = s(t) * h(t) + \epsilon(t) \quad \leftrightarrow \quad Y(f) = S(f)H(f), \qquad H(f) = \frac{Y(f)}{S(f)}$$

Deconvolution: usually estimated by regression / regularization rather than literal division

Fixed HRF

fewer parameters ⇒ greater efficiency

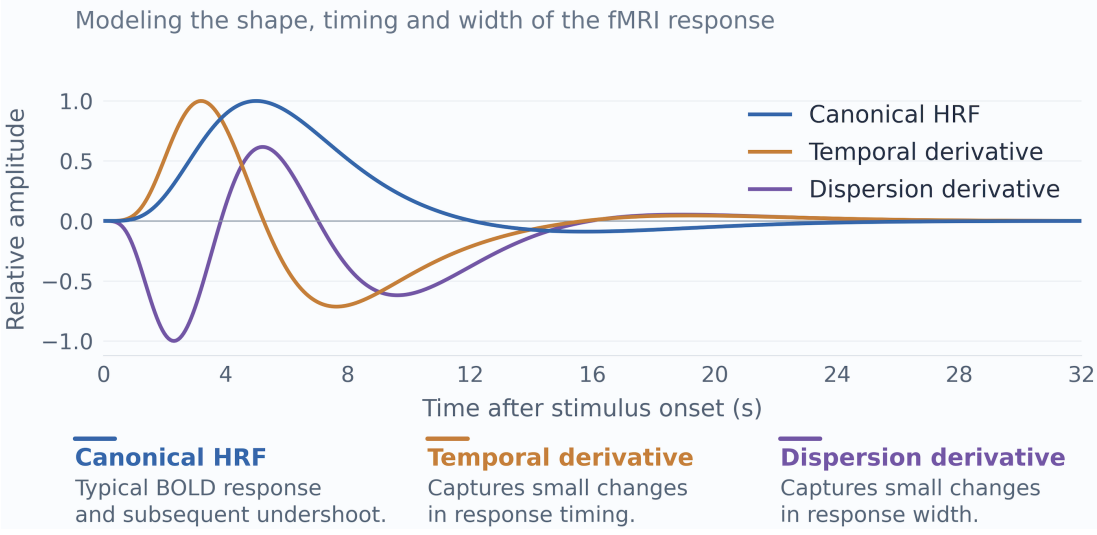
simple • powerful • vulnerable to HRF mismatch

Estimated HDR

more parameters ⇒ greater flexibility

shape/timing estimated • noisier • more data needed

Task FMRI: canonical HRF with adjustments

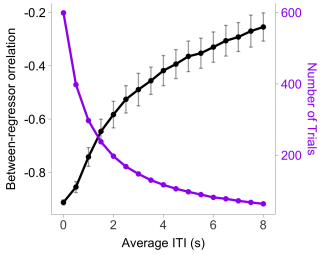


AFNI implementatin: SPMG2, SPMG3

Timing and sampling: Is collinearity always a problem?

Tug of war:
trials vs collinearity

- ITI ↓ ⇔ trials ↑ ⇔ $|\rho|$ ↑

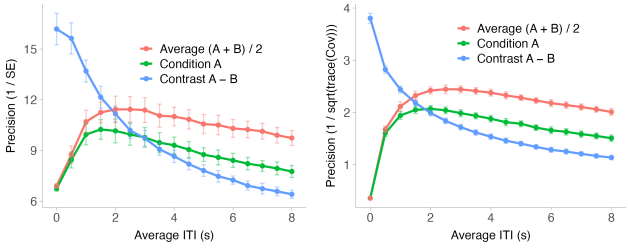


- any sweet spot?
- who to judge? precision: 1/SE

Collinearity: property

- high collinearity ≠ bad design

What simulations reveal



- contrast: ITI ↓ ⇒ precision ↑
- all effects: ITI ≈ 2 s

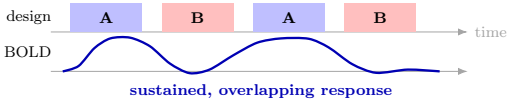
Design efficiency depends

- on the estimand
- not on collinearity alone

Task FMRI block vs event-related designs

Block design

Similar trials grouped into sustained epochs

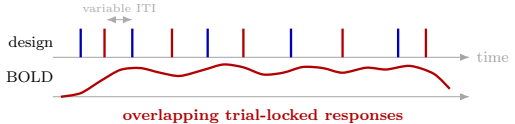


- **Strength:** high efficiency for detecting sustained condition differences
- **Simple:** fewer transitions and usually fewer parameters
- **Limitation:** less flexible for trial-specific effects or HRF-shape estimation
- adaptation, anticipation, and block context may become part of the measured effect

Best suited to: "Does condition A evoke a different *sustained response* than condition B?"

Event-related design

Brief trials are intermixed in time



- **Strength:** separates effects of intermixed trial types
- **Flexible:** supports trial-level covariates, behavioral sorting, and flexible HRF estimation
- jitter/randomization can improve separation of overlapping responses
- often less detection-efficient than a block design for a simple condition contrast

Best suited to: "How does the response differ across *individual trial types, timing, or behavior*?"

Randomization: sub-TR onsets & cross-individual sequence

Randomization: protection against design dependence

Trials synchronized to TR?

jittered onsets

↓

richer temporal sampling

↓

improved HRF sampling/estimability

Same stimulus sequence for all participants?

randomize or counterbalance sequence across participants

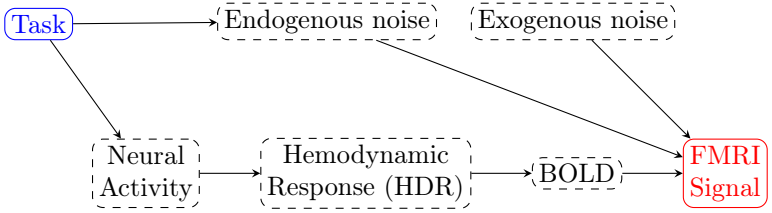
↓

less dependence on one arbitrary sequence

↓

more robust/generalizable population estimate

Task FMRI: challenges



Neural activity ⇒ BOLD: translation accuracy – Rosetta Stone problem

- neurovascular coupling: varying across regions
- draining veins: reducing spatial specificity
- ongoing brain state: producting cross-trial variability

Endogenous noises

- task-invoked physiological changes and motion

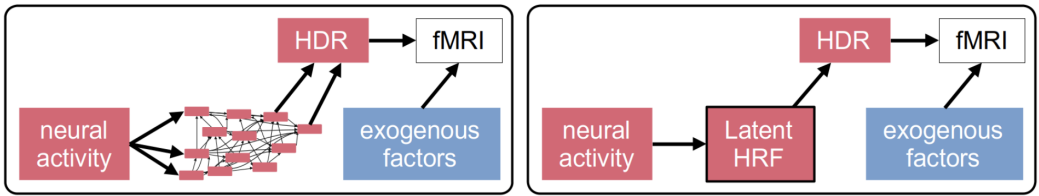
Exogenous noises

- ongoing brain state, motion, heart beat, breathing, draining veins, thermal and scanner noise

Modeling challenges

- model misspecification
- trial-level estimation: difficult
- spatial relatedness ignored: massive univariate analysis
- common information across the brain ignored

Resting-state FMRI: focusing on cross-region correlations

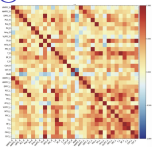


Modeling: mainly focusing on cross-region correlations

$$y(t) = \beta_0 + \theta x_{\text{drift}}(t) + \gamma x_{\text{motion}}(t) + ... + \epsilon(t)$$

- purely observational: no experimentally imposed event sequence provides an external reference
- estimand: correlation; regression: as a denoising process
  - band-pass filtering: often approximately 0.01–0.1 Hz
  - physiological recordings
  - tissue-based components
- residuals $\epsilon(t)$ for follow-up correlation computation
  - seed-based: correlations between seed region and rest of the brain
  - correlations among a list of selected regions

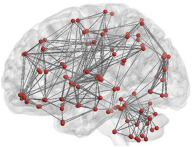
Resting-state: what it reveals—and what it cannot



ROI × ROI matrix
pairwise associations



Circos representation
circular visualization



Region map
spatial pattern of correlation structure

Wide applications

- reproducible cross-region associations
- biomarker discovery
- BWAS: associations with cognition, behavior, development, aging, and disease
- clinical targeting

Two distinct inferential limits

Measurement distortion

- noises ⇒ biased estimation of correlations
- group comparisons: vulnerable to distortion

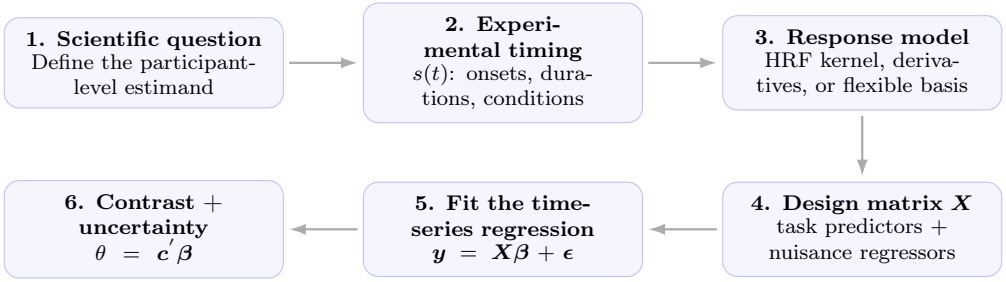
Causal non-identifiability

Correlation does not mean causation

graph metrics, gradients, and topology are descriptive, but don't by themselves resolve the identification problem

Chen et al, 2026. Navigating Correlation, Causation, and Interpretation in Resting-State fMRI. Nature Communications. In press.

Individual-level task FMRI: the whole story



Model construction: $s(t) \xrightarrow{h(t)} x(t) = s(t) * h(t) \implies \boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{\epsilon} \implies \widehat{\theta} = \boldsymbol{c}'\widehat{\boldsymbol{\beta}}$

BOLD $\neq$ neural activity
Indirect vascular proxy; the neural-to-BOLD mapping varies in space and time.

The HRF is a model
A canonical kernel is a useful assumption, not the physiological ground truth.

Design sets identifiability
Timing, randomization, jitter, and collinearity determine what can be separated.

Effect is not evidence
$\widehat{\theta}$ describes magnitude; SE and t quantify uncertainty/evidence.

Individual-level analysis converts each voxel's BOLD time series into an individual-specific estimate of the scientific effect — with uncertainty.