# Granger Mediation Analysis for Multiple Time Series

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Slides viewable on web:
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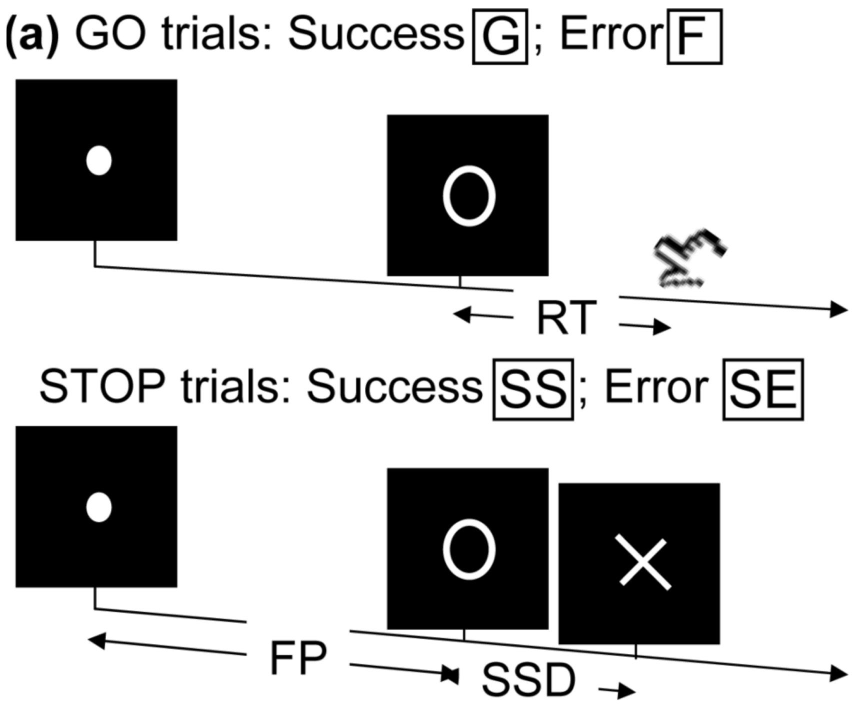
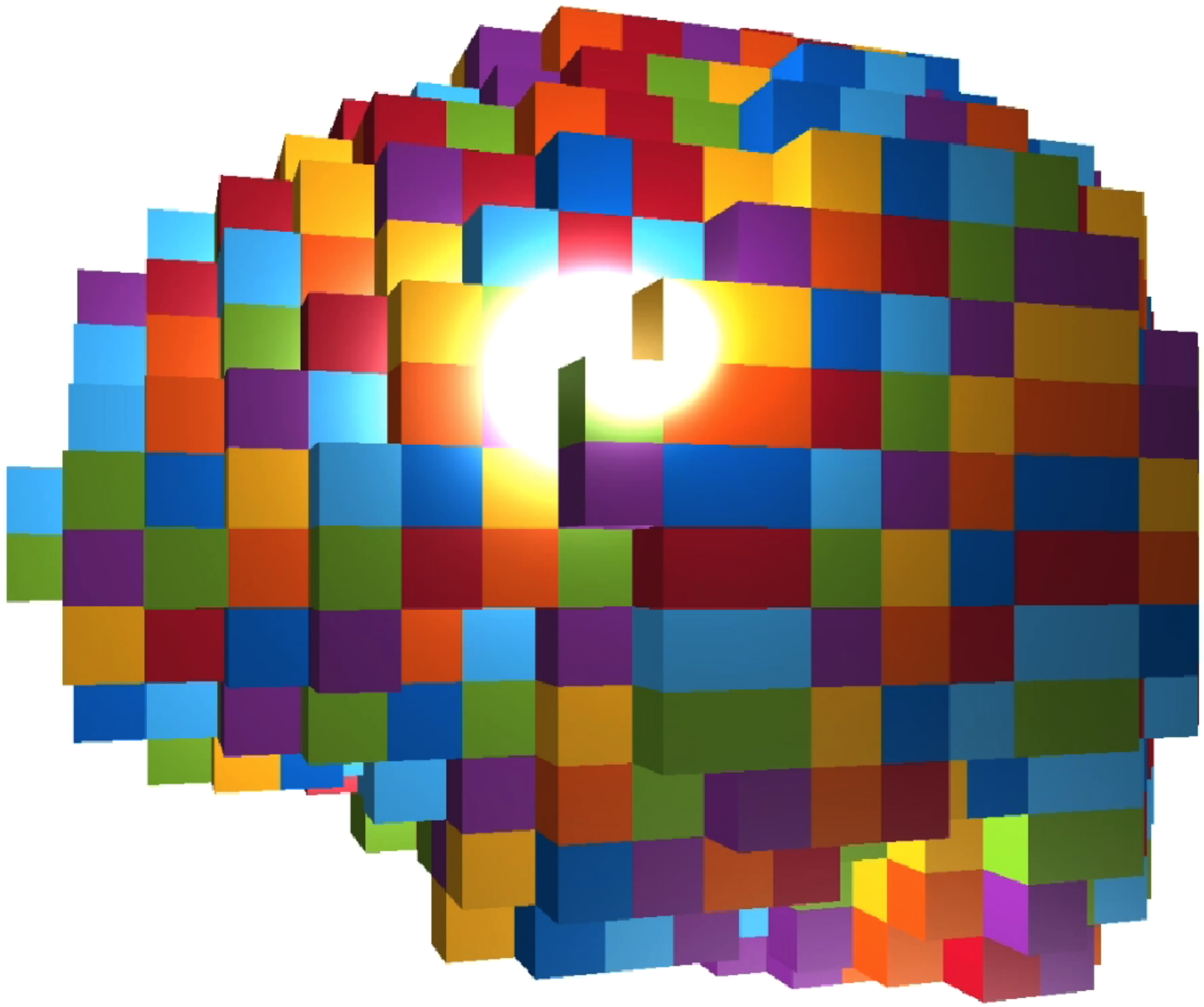
# fMRI Experiments




- Task fMRI: performs tasks under brain scanning
- **Randomized** stop/go task:
  - **press** button if "go";
  - **withhold** pressing if "stop"
- Not resting-state: "do nothing" during scanning

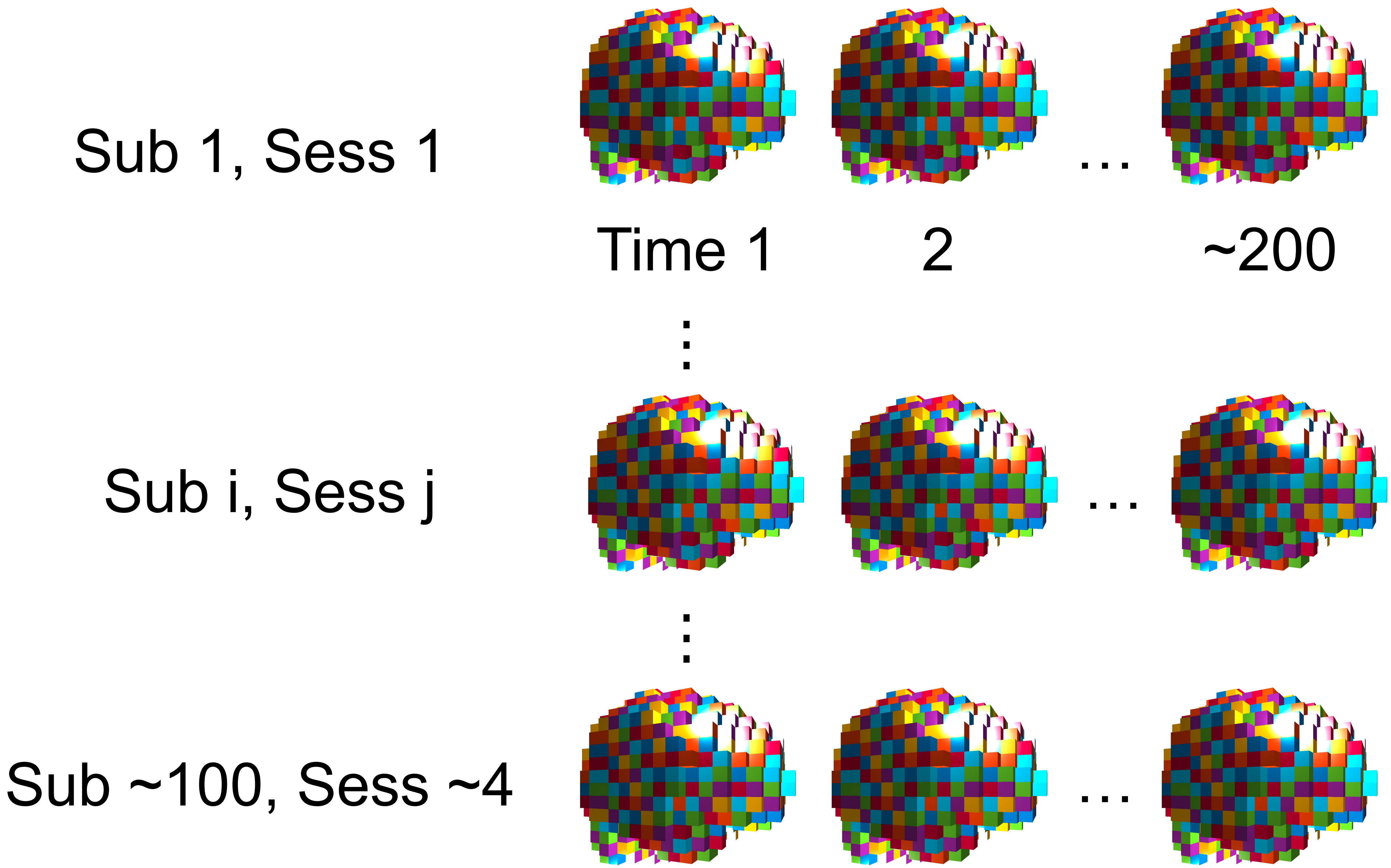
**Goal: infer brain activation and connectivity**

*Image source: NSF*



**fMRI data**: blood-oxygen-level dependent (BOLD) signals from each **cube**/voxel (~millimeters), $10^5 \sim 10^6$ voxels in total.

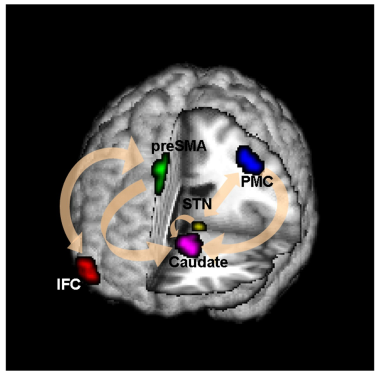
# Multilevel fMRI Studies

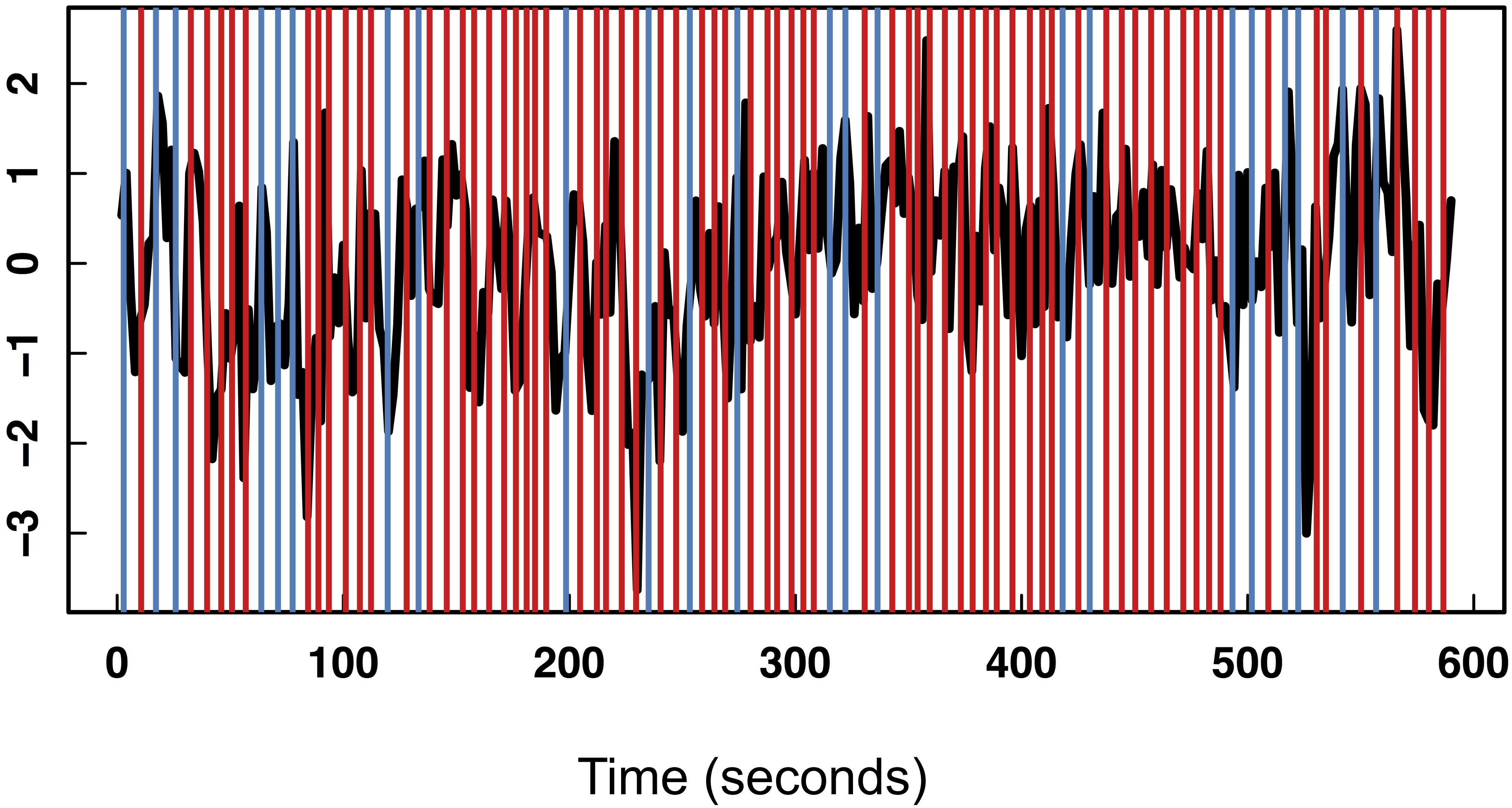



**Large, multilevel** (subject, session, voxel) data

e.g. $1000 \times 4 \times 300 \times 10^6 \approx 1$ trillion data points

# Raw Data: Motor Region

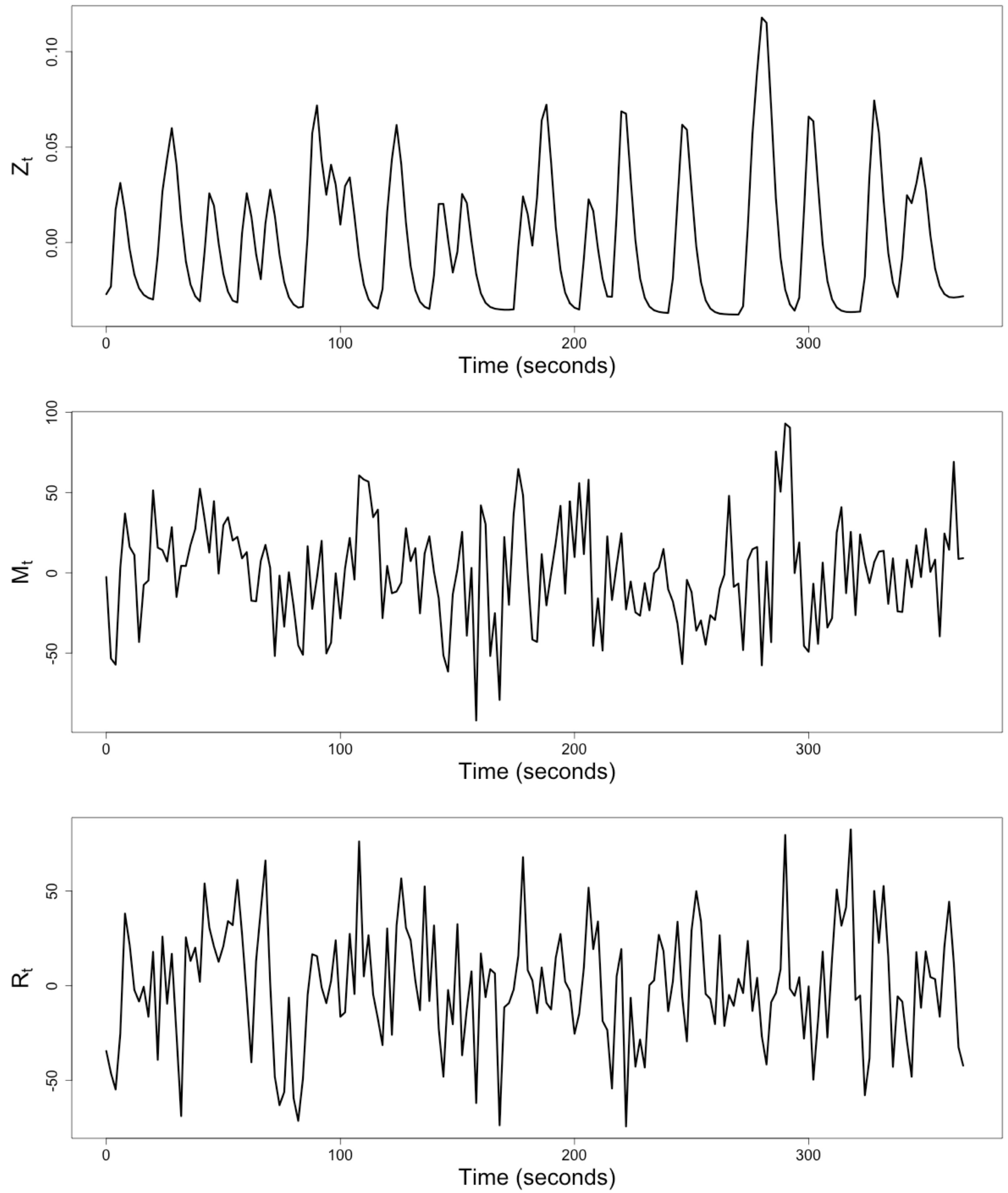



**Black**: fMRI BOLD activity

**Blue**: stop onset times; **Red**: go onset times

Image sources: Duann, Ide, Luo, Li (2009): J Neuro; Luo, Small, Li, Rosenbaum (2012): JASA




$Z_t$ : Stimulus onsets convoluted with Canonical HRF

$M_t$ , $R_t$ : fMRI time series from two brain regions

# Review: Granger Causality/VAR

- Given two (or more) time series $x_t$ and $y_t$

$$x_t = \sum_{j=1}^{p} \psi_{1j} x_{t-j} + \sum_{j=1}^{p} \phi_{1j} y_{t-j} + \epsilon_{1t}$$

$$y_t = \sum_{j=1}^{p} \psi_{2j} y_{t-j} + \sum_{j=1}^{p} \phi_{2j} x_{t-j} + \epsilon_{2t}$$

- Also called vector autoregressive models
- $y$ Granger causes $x$ if $\phi_{1j} \neq 0$ [Granger, 69]
- Models **pair-wise** connections not **pathways**

Google Scholar

granger causality neuroimaging

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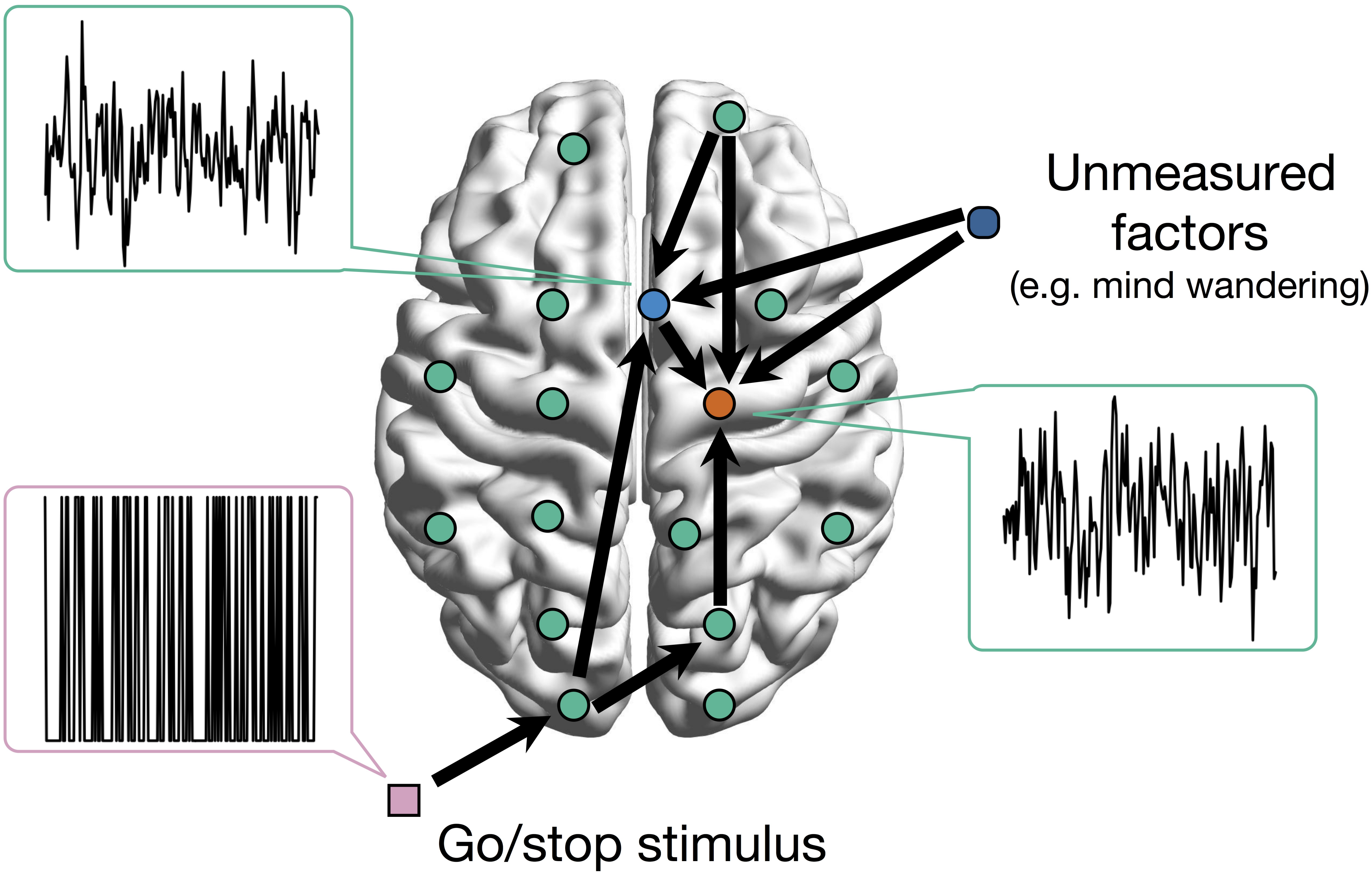
# Granger Causality/VAR

- Granger Causality (VAR) popular for fMRI
    - About **8000** google scholar results on "granger causality neuroimaging"
- Models multiple **stationary** time series
- AR($p$) (small $p$) fits fMRI well [Lingdquist, 08]
- **Not** for **non-stationary**/task fMRI
- **Cannot** model stimulus effects

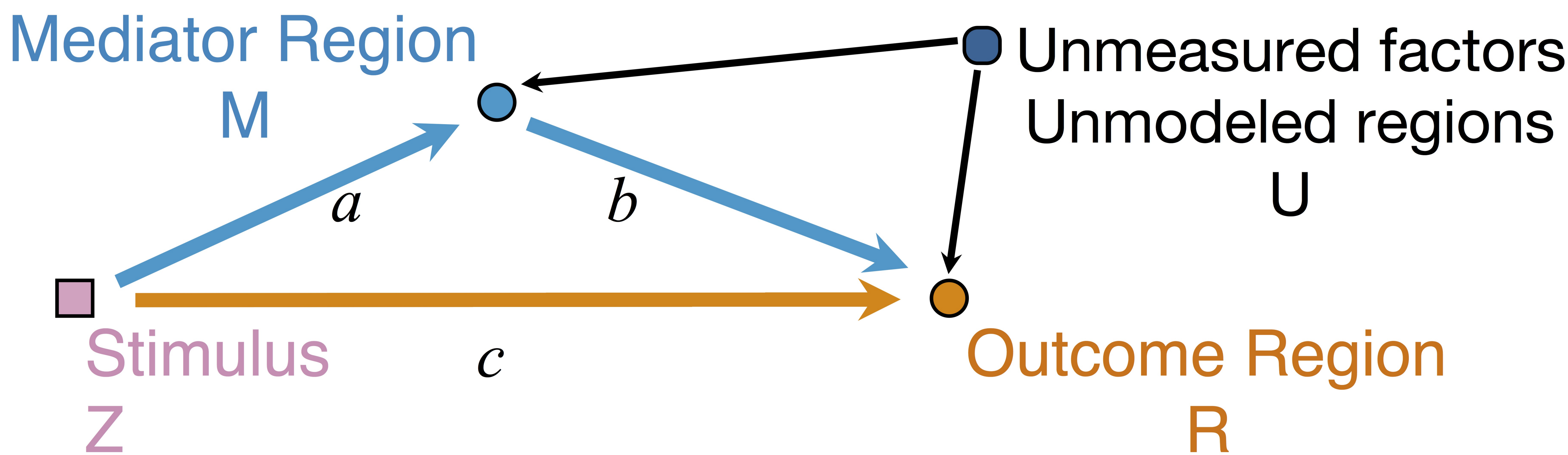
# Conceptual Model with Stimulus




**Goal**: quantify effects stimuli → preSMA → PMC regions

[Duann, Ide, Luo, Li (2009). J of Neurosci]

# Model: Mediation Analysis and SEM




$$M = Za + \overbrace{U + \epsilon_1}^{E_1}$$
$$R = Zc + Mb + \underbrace{Ug + \epsilon_2}_{E_2}, \quad \epsilon_1 \perp \epsilon_2$$

- **Indirect** effect: $a \times b$; **Direct** effect: $c$
- Correlated errors: $\delta = \mathrm{cor}(E_1, E_2) \neq 0$ if $U \neq 0$

# Mediation Analysis in fMRI

- Mediation analysis (usually assuming $U = 0$)

  [Baron&anp;Kenny, 86; Sobel, 82; Holland 88; Preacher&Hayes 08; Imai et al, 10; VanderWeele, 15;...]

- Parametric [Wager et al, 09] and functional [Lindquist, 12] mediation, under (approx.) independent errors
  - Stimulus $\rightarrow$ brain $\rightarrow$ **user reported ratings**, one brain mediator
  - Assuming $U = 0$ between ratings and brain

- Multiple mediator and multiple pathways
  - Dimension reduction by arXiv1511.09354 [Chen, Crainiceanu, Ogburn, Caffo, Wager, Lindquist, 15]
  - Pathway Lasso penalization [Zhao, Luo, 16]

- **This talk**: integrating Granger causality and mediation analysis

# Model & Method

# Our Mediation Model

$$M_t = Z_t a + E_{1t}, \quad R_t = Z_t c + M_t b + E_{2t}$$

- **Temporal** VAR errors

$$E_{1t} = \sum_{j=1}^{p} \left(\omega_{11_j} E_{1,t-j} + \omega_{21_j} E_{2,t-j}\right) + \epsilon_{1t}$$

$$E_{2t} = \sum_{j=1}^{p} \left(\omega_{12_j} E_{1,t-j} + \omega_{22_j} E_{2,t-j}\right) + \epsilon_{2t}$$

- **Spatial** errors: $\epsilon_{1t}, \epsilon_{2t}$

$$\begin{pmatrix} \epsilon_{1t} \\ \epsilon_{2t} \end{pmatrix} \sim \mathcal{N}\left(\mathbf{0}, \mathbf{\Sigma}\right), \quad \mathbf{\Sigma} = \begin{pmatrix} \sigma_1^2 & \delta\sigma_1\sigma_2 \\ \delta\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

# Equivalent Form

$$M_t = Z_t A + \sum_{j=1}^{p} \left( \phi_{1j} Z_{t-j} + \psi_{11_j} M_{t-j} + \psi_{21_j} R_{t-j} \right) + \epsilon_{1t}$$

$$R_t = Z_t C + M_t B + \sum_{j=1}^{p} \left( \phi_{2j} Z_{t-j} + \psi_{12_j} M_{t-j} + \psi_{22_j} R_{t-j} \right) + \epsilon_{2t}$$

- Nonzero $\phi$'s and $\psi$'s denote the temporal influence from stimulus to mediator/outcome and etc
- $A$, $B$, $C$ are causal following a similar proof in

[Sobel, Lindquist, 04]

# Estimation: Conditional Likelihood

- The full likelihood for our model is too complex
- Given the initial $p$ time points, the conditional likelihood is

$$\ell\left(\boldsymbol{\Theta}, \delta \mid \mathbf{Z}, \mathcal{I}_p\right) = \sum_{t=p+1}^{T} \log f\left(\left(M_t\,, R_t\right) \mid \mathbf{X}_t\right)$$

$$= -\frac{T-p}{2} \log \sigma_1^2 \sigma_2^2 (1-\delta^2) - \frac{1}{2\sigma_1^2} \|\mathbf{M} - \mathbf{X}\boldsymbol{\theta}_1\|_2^2$$

$$-\frac{1}{2\sigma_2^2(1-\delta^2)} \|(\mathbf{R} - \mathbf{M}B - \mathbf{X}\boldsymbol{\theta}_2) - \kappa(\mathbf{M} - \mathbf{X}\boldsymbol{\theta}_1)\|_2^2$$

# Multilevel Data: Two-level Likelihood

- Second level model, for each subject $i$
  $$(A_i, B_i, C_i) = (A, B, C) + (\eta_i^A, \eta_i^B, \eta_i^C)$$
  where errors $\eta$ are normally distributed
- The two level likelihood is conditional convex
- Two-stage fitting: plug-in estimates from the first level
- Block coordinate fitting: jointly optimize first level likelihood + second level likelihood

***Theorem***: *Assume assumptions (A1)-(A6) are satisfied. Assume* $\mathbb{E}(Z_{i_t}^2) = q < \infty$, *for* $i = 1, \dots, N$. *Let* $T = min_i T_i$.

***1***. *If* $\boldsymbol{\Lambda}$ *is known, then the two-stage estimator* $\hat{\delta}$ *maximizes the profile likelihood of model asymptotically, and* $\hat{\delta}$ *is* $\sqrt{NT}$*-consistent.*

***2***. *If* $\boldsymbol{\Lambda}$ *is unknown, then the profile likelihood of model has a unique maximizer* $\hat{\delta}$ *asymptotically, and* $\hat{\delta}$ *is* $\sqrt{NT}$*-consistent, provided that* $1/\varpi = \bar{\kappa}^2/\varrho^2 = \mathcal{O}_p(1/\sqrt{NT})$, $\kappa_i = \sigma_{i_2}/\sigma_{i_1}$, $\bar{\kappa} = (1/N)\sum \kappa_i$, *and* $\varrho^2 = (1/N)\sum(\kappa_i - \bar{\kappa})^2$.

*Using the two-stage estimator* $\hat{\delta}$, *the CMLE of our model is consistent, as well as the estimator for* $\boldsymbol{b} = (A, B, C)$.

# Theory: Summary

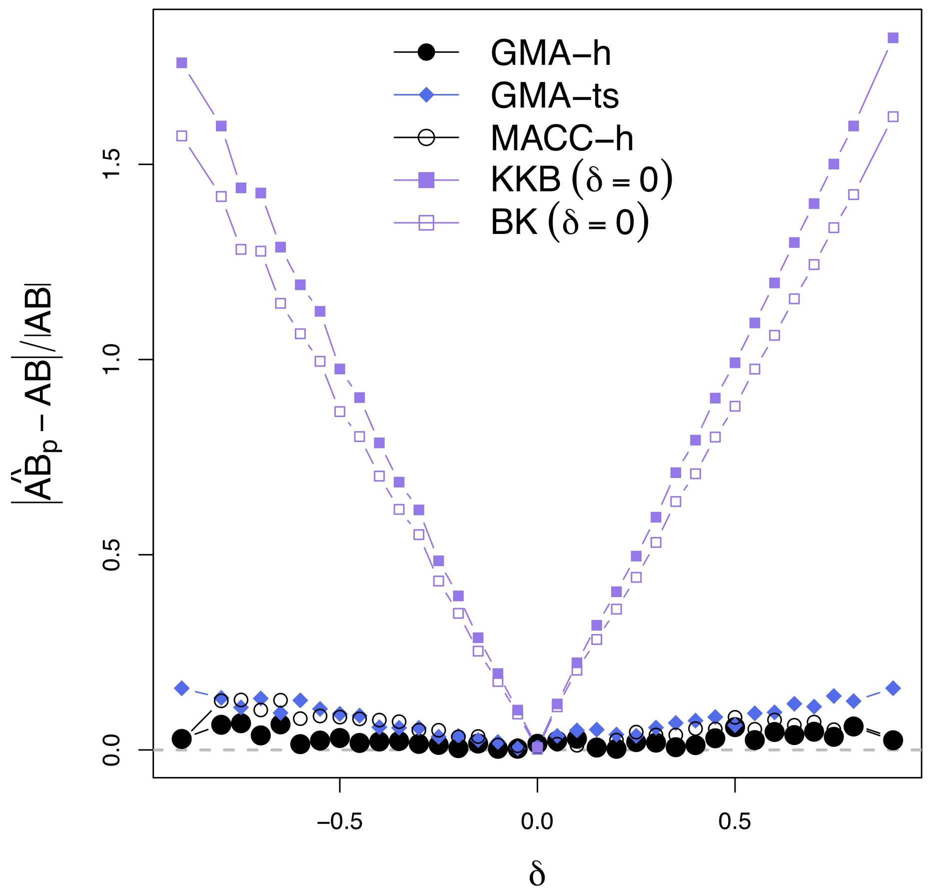
- Under regularity conditions, $N$ subs, $T$ time points
- Our $\hat{\delta}$ is $\sqrt{NT}$-consistent
  - This relaxes the unmeasured confounding assumption in mediation analysis
- Our $(\hat{A}, \hat{B}, \hat{C})$ is also consistent

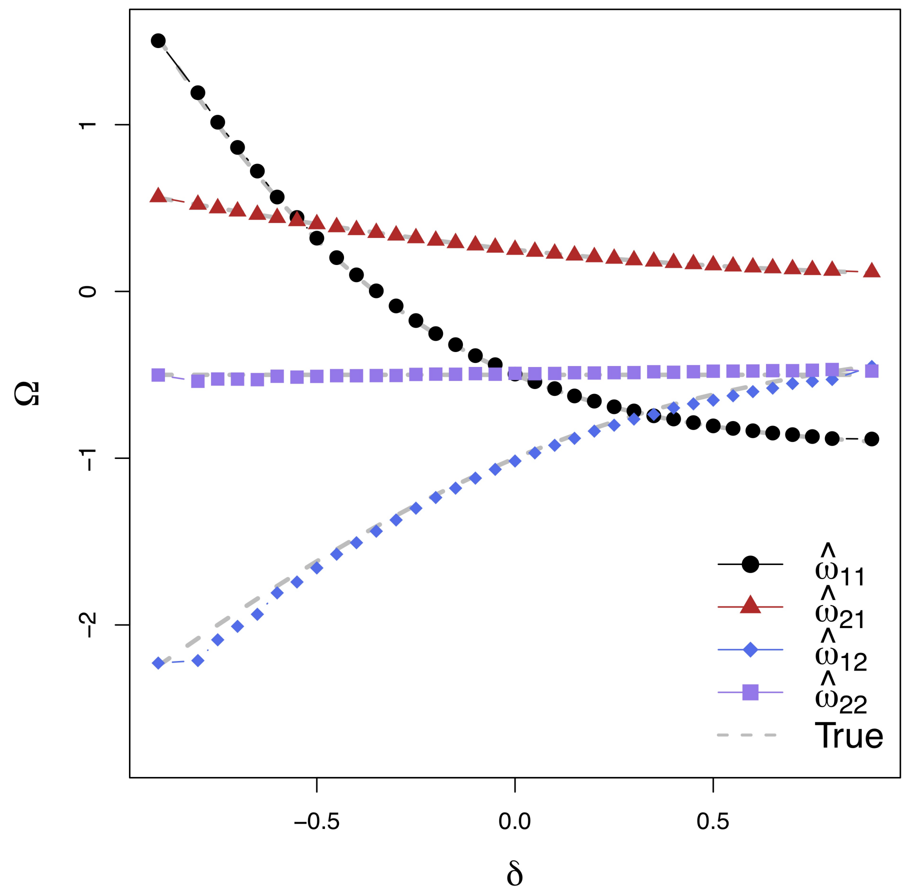
# Simulations & Real Data

# Comparison

- Our methods: **GMA-h** and **GMA-ts**
- Previous methods: BK [Baron & Kenny], MACC [Zhao and Luo], KKB [Kenny et al]
- Other methods do not model the temporal correlations or time series like ours

# Simulations




Low bias for $AB$ Low bias for temporal cor

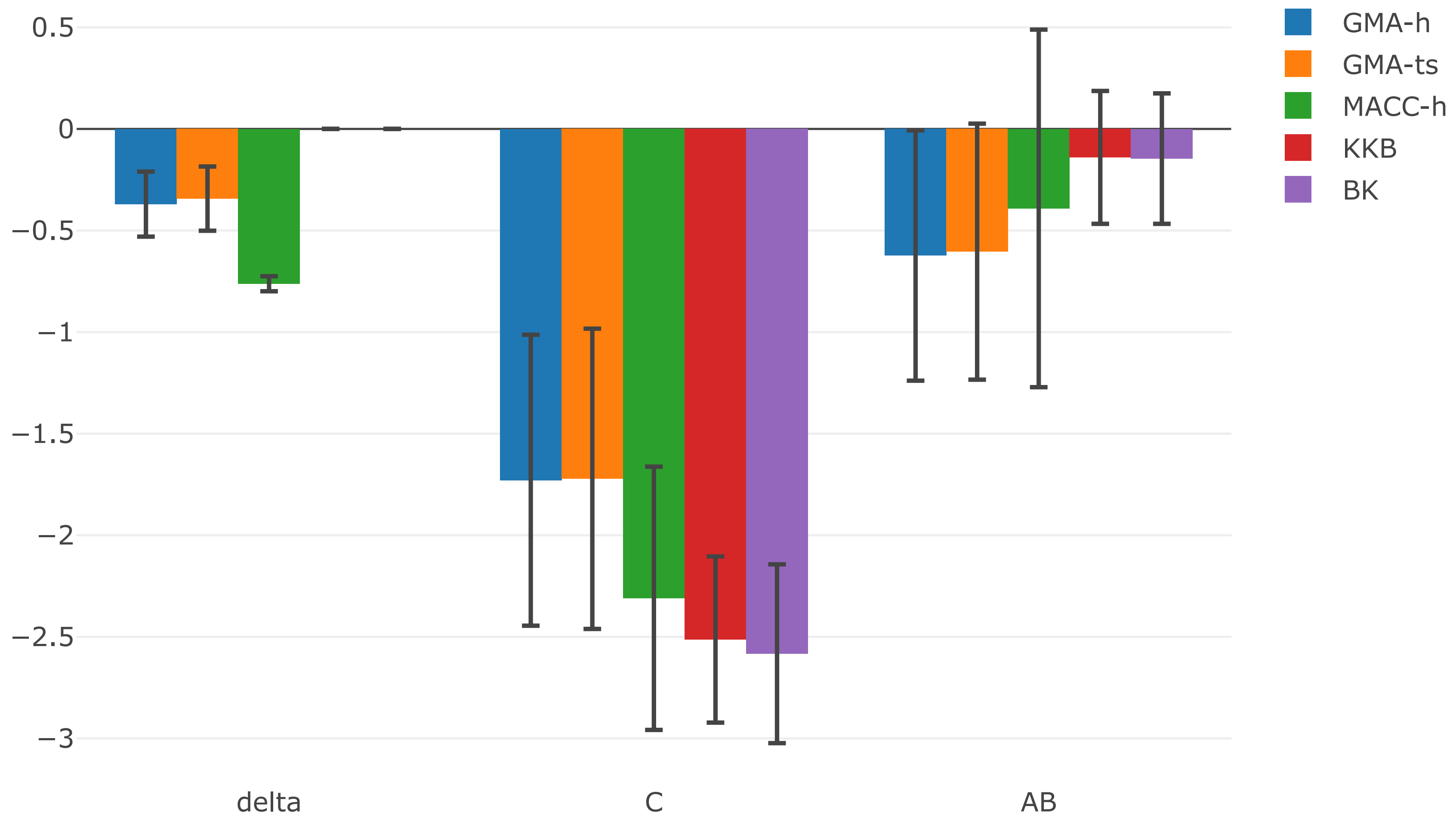
Gray dash lines are the truth

**GMA** performs the best, and recovers the temporal correlations

# Real Data Experiment

- Public data: OpenFMRI ds30
- Stop-go experiment: withhold (STOP) from pressing buttons
- Expect "STOP" stimuli to deactivate brain region M1
- Goal: quantify the role of region preSMA

# Result



# Result

| Method | $\delta$ | $C$ | $A$ | $B$ | $AB_p$ |
|---|---|---|---|---|---|
| GMA-h | -0.370 (-0.530, -0.156) | -1.729 (-2.445, -0.964) | -0.739 (-1.487, 0.035) | 0.838 (0.644, 0.999) | -0.623 (-1.239, 0.033) |
| GMA-ts | -0.343 (-0.501, -0.163) | -1.722 (-2.461, -0.904) | -0.740 (-1.442, 0.080) | 0.810 (0.656, 0.965) | -0.604 (-1.234, 0.055) |
| MACC-h | -0.762 (-0.799, -0.721) | -2.310 (-2.958, -1.641) | -0.259 (-0.810, 0.303) | 1.511 (1.410, 1.619) | -0.391 (-1.271, 0.465) |
| KKB | - | -2.513 (-2.922, -2.073) | -0.225 (-0.772, 0.326) | 0.617 (0.589, 0.647) | -0.140 (-0.467, 0.196) |
| BK | - | -2.583 (-3.023, -2.142) | -0.235 (-0.774, 0.352) | 0.616 (0.588, 0.647) | -0.146 (-0.467, 0.211) |

- STOP deactivates M1 directly ($C$) and indirectly ( $AB$)
- preSMA mediates a good portion of the total effect
  - Help resolve the debates among neuroscientists
- Other methods under-estiamte the effects
- Novel feedback findings: M1 $\rightarrow$ preSMA after lag 1 and 2 (not shown)

# Discussion

- Mediation analysis for multiple time series
- Method: Granger causality + mediation
  - Optimizing complex likelihood
- Theory: identifiability, consistency
- Result: low bias and improved accuracy
- Extension: functional mediation (Zhao, Function 37)
- CRAN pkg: **gma** and references within

# Thank you!

## Comments? Questions?

**BigComplexData.com**

or **BrainDataScience.com**