Functional Mediation Analysis with an Application to Functional Magnetic Resonance Imaging Data

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Acknowledgements

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Motivation

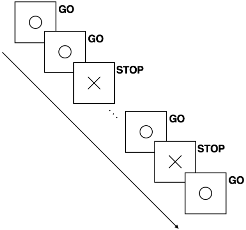
Credit: NSF

Task-related functional MRI (fMRI)

- fMRI: measures brain activities
- task fMRI: perform task under fMRI scanner
- response conflict task
    - “GO” trial: push the button
    - “STOP” trial: withhold the pushing

Motivation

Credit: NSF



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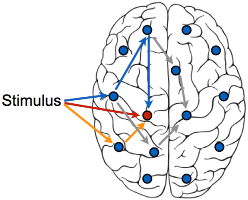
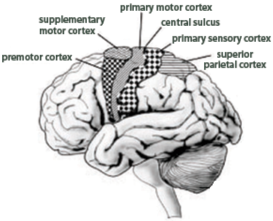


Objective

- identify causal effects of task stimulus on brain activity
- infer brain connectivity (effective connectivity)

Response conflict task

- Brain regions of interest
  - **primary motor cortex (M1)**: responsible for movement
  - **presupplementary motor area (preSMA)**: primary region for motor response prohibition



- Objective
  - Quantify the causal effects
    - stimulus $\rightarrow$ preSMA, stimulus $\rightarrow$ M1
    - preSMA $\rightarrow$ M1[1]

[1] Obeso et al., *Brain Stimulation*, 2013

Response conflict task

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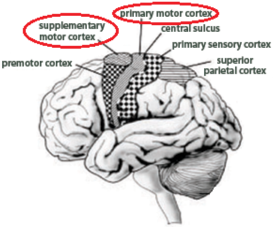

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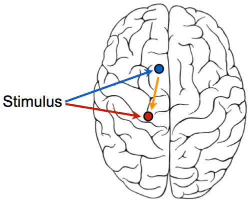
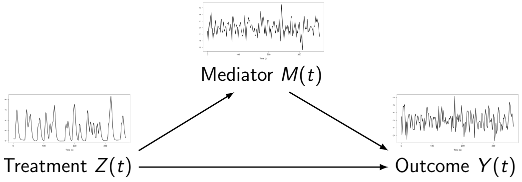
Mediation analysis





- conflict response task: STOP/GO
- mediator region: preSMA, outcome region: M1
- mediation model on functional measures
- dynamic causal effects

Mediation analysis (structural equation modeling)

$$
\begin{aligned}
M &= Z\alpha + \epsilon_1 \\
Y &= Z\gamma + M\beta + \epsilon_2
\end{aligned}
$$

$$
\begin{tikzcd}
 & M \arrow[dr, "\beta"] & \\
Z \arrow[ur, "\alpha"] \arrow[rr, "\gamma"'] & & Y
\end{tikzcd}
$$

- Z, M, Y: scalar measures
- causal estimands

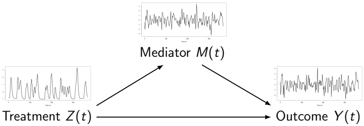
$$
\begin{aligned}
\mathrm{DE} &= (z - z')\gamma \\
\mathrm{IE} &= (z - z')\alpha\beta
\end{aligned}
$$

  - DE: direct effect; IE: indirect effect

Existing methods

- Mediation analysis in neuroimaging studies
  - Two-stage (e.g., Wager et al. (2008, 2009), Atlas et al. (2010, 2014), Zhao and Luo (2014), Chen et al. (2015))
    - Stage I: extract single trial activation
    - Stage II: mediation analysis
  - Functional mediator (Lindquist (2012))
  - Time series data mediation analysis (Zhao and Luo (2018+))
    - SEM + Granger causality
- Time dependent treatment and mediator
  - sparse longitudinal data (Avin et al. (2005), VanderWeele (2009), Goldsmith et al. (2016), Bind et al. (2016), Zheng and van der Laan (2017), VanderWeele and Tchetgen Tchetgen (2017))
- Dynamic brain connectivity
  - dynamic functional connectivity (e.g., Chang and Glover (2010), Calhoun et al. (2013, 2014), Lindquist et al. (2014), Warnick et al. (2017), Gonzalez-Castillo and Bandettini (2017))
  - dynamic effective connectivity (e.g., Samdin et al. (2015))

Functional mediation model



For $\forall\ t \in [0, T]$,

- Concurrent model

$$
\begin{aligned}
M(t) &= Z(t)\alpha(t) + \epsilon_1(t) \\
Y(t) &= Z(t)\gamma(t) + M(t)\beta(t) + \epsilon_2(t)
\end{aligned}
$$

- Historical influence model

$$
\begin{aligned}
M(t) &= \int_{\Omega_t^1} Z(s)\alpha(s,t)\,\mathrm{d}s + \epsilon_1(t) \\
Y(t) &= \int_{\Omega_t^2} Z(s)\gamma(s,t)\,\mathrm{d}s + \int_{\Omega_t^3} M(s)\beta(s,t)\,\mathrm{d}s + \epsilon_2(t)
\end{aligned}
$$

  - $\Omega_t^k = [(t-\delta_k) \vee 0, t]$, $\delta_k \in (0, +\infty]$, $k = 1, 2, 3$
  - if $\delta_k \in [T, +\infty]$: whole history

Notations

- $\mathcal{H}_t = [0, t]$
- $\{x(s)\}_{\mathcal{H}_t}$: the history of variable x
- $M(t; \{z(s)\}_{\mathcal{H}_t})$: potential outcome of M at time t if Z has the history $\{z(s)\}_{\mathcal{H}_t}$
- $Y(t; \{z(s), m(s)\}_{\mathcal{H}_t})$: potential outcome of Y at time t when the history of Z and M at level $\{z(s)\}_{\mathcal{H}_t}$ and $\{m(s)\}_{\mathcal{H}_t}$

Causal estimands

- Concurrent model

$$
\begin{aligned}
M(t) &= Z(t)\alpha(t) + \epsilon_1(t) \\
Y(t) &= Z(t)\gamma(t) + M(t)\beta(t) + \epsilon_2(t)
\end{aligned}
$$

$$
\begin{aligned}
\mathrm{DE}(t) &= \mathbb{E}\left[Y(t;\{z(s),m(s)\}_{\mathcal{H}_t}) - Y(t;\{z'(s),m(s)\}_{\mathcal{H}_t})\right] \\
&= \left(z(t) - z'(t)\right)\gamma(t)
\end{aligned}
$$

$$
\begin{aligned}
\mathrm{IE}(t) &= \mathbb{E}\left[Y(t;\{z(s),m(s;\{z(u)\}_{\mathcal{H}_s})\}_{\mathcal{H}_t}) - Y(t;\{z(s),m(s;\{z'(u)\}_{\mathcal{H}_s})\}_{\mathcal{H}_t})\right] \\
&= \left(z(t) - z'(t)\right)\alpha(t)\beta(t)
\end{aligned}
$$

- DE: controlled direct effect

- Historical influence model

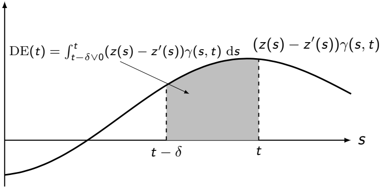
$$
\begin{aligned}
M(t) &= \int_{\Omega_t^1} Z(s)\alpha(s,t)\,\mathrm{d}s + \epsilon_1(t) \\
Y(t) &= \int_{\Omega_t^2} Z(s)\gamma(s,t)\,\mathrm{d}s + \int_{\Omega_t^3} M(s)\beta(s,t)\,\mathrm{d}s + \epsilon_2(t)
\end{aligned}
$$

$$
\begin{aligned}
\mathrm{DE}(t) &= \mathbb{E}\left[Y(t;\{z(s),m(s)\}_{\mathcal{H}_t}) - Y(t;\{z'(s),m(s)\}_{\mathcal{H}_t})\right] \\
&= \int_{\Omega_t^2} \left(z(s)-z'(s)\right)\gamma(s,t)\,\mathrm{d}s
\end{aligned}
$$

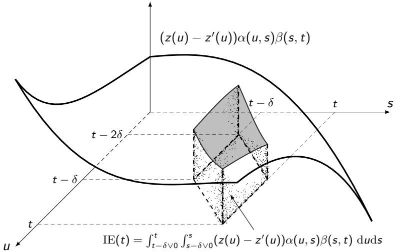
$$
\begin{aligned}
\mathrm{IE}(t) &= \mathbb{E}\left[Y(t;\{z(s),m(s;\{z(u)\}_{\mathcal{H}_s})\}_{\mathcal{H}_t}) - Y(t;\{z(s),m(s;\{z'(u)\}_{\mathcal{H}_s})\}_{\mathcal{H}_t})\right] \\
&= \int_{\Omega_t^3} \left(\int_{\Omega_s^1} (z(u)-z'(u))\alpha(u,s)\,\mathrm{d}u\right)\beta(s,t)\,\mathrm{d}s
\end{aligned}
$$

- DE: controlled direct effect

Direct effect (DE)

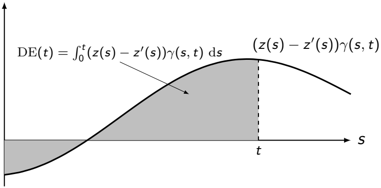


Indirect effect (IE)

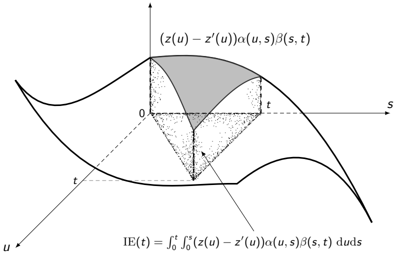


- $\delta_1 = \delta_2 = \delta_3 = \delta$, δ small

Direct effect (DE)



Indirect effect (IE)



- $\delta_1 = \delta_2 = \delta_3 = \delta,\ \delta \in [T, +\infty]$

Causal assumptions

Let $\mathcal{O}_t = \{Z(s), M(s), Y(s)\}_{\mathcal{H}_t \setminus \{t\}}$ ($\mathcal{H}_t = [0, t]$)

- Assumption 1: No (unmeasured) "treatment-outcome confounder"

$$Y(t; \{z(s), m(s)\}_{\mathcal{H}_t}) \perp\!\!\!\perp Z(t) \mid \mathcal{O}_t$$

- Assumption 2: No (unmeasured) "treatment-mediator confounder"

$$M(t; \{z(s)\}_{\mathcal{H}_t}) \perp\!\!\!\perp Z(t) \mid \mathcal{O}_t$$

- Assumption 3: No (unmeasured) "mediator-outcome confounder"

$$Y(t; \{z(s), m(s)\}_{\mathcal{H}_t}) \perp\!\!\!\perp M(t; \{z(s)\}_{\mathcal{H}_t}) \mid Z(t), \mathcal{O}_t$$

Method: Penalized least squares[2]

Concurrent model

$$Y(t) = X(t)\theta(t) + \epsilon(t)$$

$$\mathrm{PLS}(\theta) = \int_0^T \|Y(t) - X(t)\theta(t)\|_2^2 \,\mathrm{d}t + \sum_{j=1}^{q} \lambda_j \int_0^T [\mathcal{L}_j \theta_j(t)]^2 \,\mathrm{d}t$$

- $\mathcal{L}_j$: linear differential operator
  - $\mathcal{L}_j = \mathcal{D}^2$ curvature operator
  - $\mathcal{L}_j = \omega^2\mathcal{D} + \mathcal{D}^3$ harmonic acceleration operator (ω angular frequency)
- λ_j: tuning parameter
- suppose $\theta_j(t) = \sum_k g_{kj}\phi_{kj}(t)$, $\phi_{kj}(t)$ basis function
- estimate g_{jk}

[2]Ramsay, *Functional Data Analysis*, 2006

Historical influence model

$$Y(t) = \int_{\Omega_t} X(s)\theta(s,t)\,\mathrm{d}s + \epsilon(t)$$

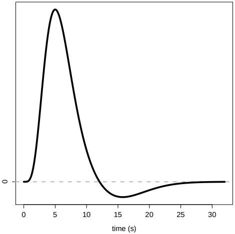
$$\mathrm{PLS}(\theta) = \int_0^T \|Y(t) - \int_{\Omega_t} X(s)\theta(s,t)\,\mathrm{d}s\|_2^2\,\mathrm{d}t + \lambda_s \mathcal{P}_s(\theta) + \lambda_t \mathcal{P}_t(\theta)$$

$$\mathcal{P}_s = \int_0^t \int_0^T [\mathcal{L}_s\theta(s,t)][\mathcal{L}_s\theta^\top(s,t)]\,\mathrm{d}s\mathrm{d}t$$
$$\mathcal{P}_t = \int_0^t \int_0^T [\mathcal{L}_t\theta(s,t)][\mathcal{L}_t\theta^\top(s,t)]\,\mathrm{d}s\mathrm{d}t$$

- suppose $\theta_j(s,t) = \sum_k \sum_l g_{klj}\phi_{kj}(s)\eta_{lj}(t)$
  - $\phi_{kj}(s)$ basis respect to s, $\eta_{lj}(t)$ basis respect to t
- estimate g_{klj}

Simulation study

- simulate BOLD signal using canonical HRF

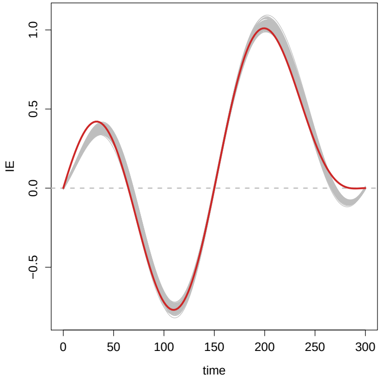


- $N = 50$ subjects, $T = 300$ s, $TR = 2$ s (150 time points)
- Event: $\mathbb{P}(\text{“case”}) = \mathbb{P}(\text{“control”}) = 0.5$ (40 s between trials)
- Method
  - two-stage (**beta-KKB**)
    - stage I: extract single-beta activation
    - stage II: (multilevel[3]) mediation analysis
  - functional mediation (**FMA**)

[3] Kenny, Korchmaros and Bolger, *Psychological methods*, 2003

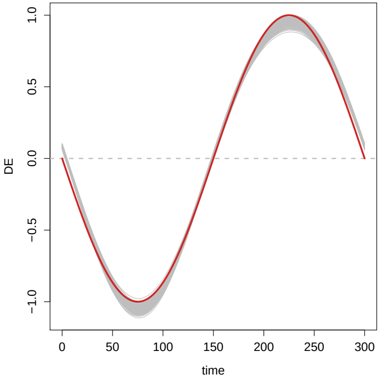
True model: concurrent

IE: $\alpha(t)\beta(t)$



	Estimate (SE)	Power
beta-KKB	-0.009 (0.072)	0.049

DE: $\gamma(t)$

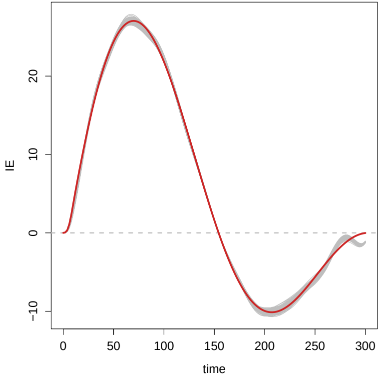


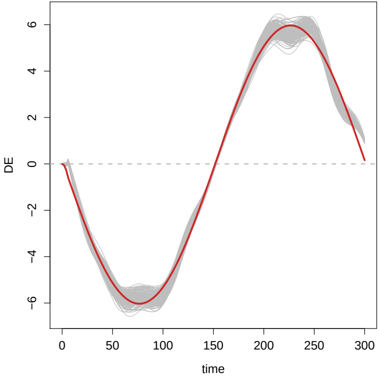
	Estimate (SE)	Power
beta-KKB	-0.000 (0.028)	0.055

True model: historical influence ($\delta = 6$ s)

IE: $\int_{\Omega_t^3} \left(\int_{\Omega_t^1} \alpha(u,s)\, \mathrm{d}u \right) \beta(s,t)\, \mathrm{d}s$

DE: $\int_{\Omega_t^2} \gamma(s,t)\, \mathrm{d}s$





	Estimate (SE)	Power
beta-KKB	-0.022 (0.161)	0.049

	Estimate (SE)	Power
beta-KKB	0.001 (0.039)	0.067

Response conflict task fMRI study[4]

- $N = 121$ right-handed healthy participants
- randomized STOP/GO trials: 90 GO trials and 32 STOP trials
  - remove GO trials
- mediator region: preSMA-post (MNI: (-4,-8,60))
- outcome region: M1 (MNI: (-41,-20,62))
- $\mathrm{TR} = 2$ s, 184 time points
- $Z(t)$: convolution of event onsets and canonical HRF
- $M(t)$ and $Y(t)$: BOLD signals after motion correction

[4] OpenfMRI ds000030

- Concurrent model

$$\begin{aligned} M(t) &= Z(t)\alpha(t) + \epsilon_1(t) \\ Y(t) &= Z(t)\gamma(t) + M(t)\beta(t) + \epsilon_2(t) \end{aligned}$$

- Historical influence model

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  - $\Omega_t^k = [(t-\delta_k) \vee 0, t]$, $\delta_k \in (0, +\infty]$, $k = 1, 2, 3$
  - if $\delta_k \in [T, +\infty]$: whole history
  - $\delta = 2, 4, 6, 10, 20, 30, \infty$ (seconds)

Model selection

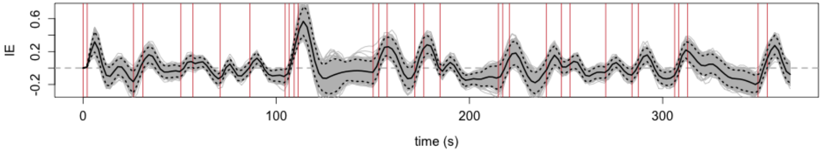
- mean squared error: θ_i observed M_i or Y_i

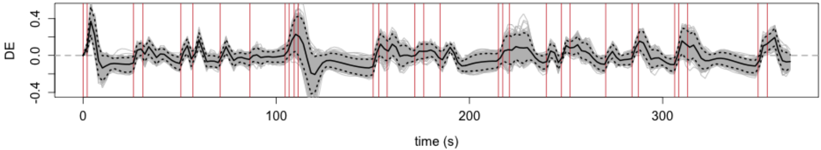
$$\mathrm{MSE}(\hat{\theta}) = \frac{1}{N}\sum_{i=1}^{N}\int_0^T (\hat{\theta}_i(t) - \theta_i(t))^2 \; \mathrm{d}t$$

	Concurrent	Historical ($\sim M$)	Historical ($\sim Z$) $\delta = 2$	$\delta = 4$	$\delta = 6$	$\delta = 10$	$\delta = 20$	$\delta = 30$	$\delta = \infty$
M	353.460		352.645	352.244	351.988	351.652	**351.179**	351.272	357.396
		$\delta = 2$	212.331	212.308	211.960	212.333	212.378	212.130	212.343
		$\delta = 4$	211.324	211.227	**211.062**	211.064	211.124	211.070	211.572
		$\delta = 6$	211.883	211.663	211.541	211.546	211.592	211.575	212.110
Y	220.203	$\delta = 10$	214.277	214.035	213.909	213.953	213.989	213.971	214.510
		$\delta = 20$	218.383	218.098	217.878	217.928	218.312	218.247	218.765
		$\delta = 30$	221.183	220.915	220.666	220.685	221.041	221.266	221.727
		$\delta = \infty$	295.291	294.938	294.904	294.695	294.820	294.742	301.385

Mediator: preSMA-post (MNI: $(-4, -8, 60)$)

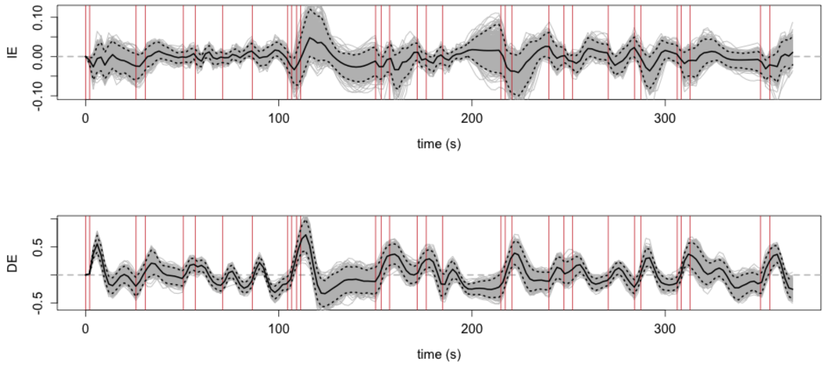
- STOP trial: $\delta_{MZ} = 20$, $\delta_{YZ} = 6$, $\delta_{YM} = 4$





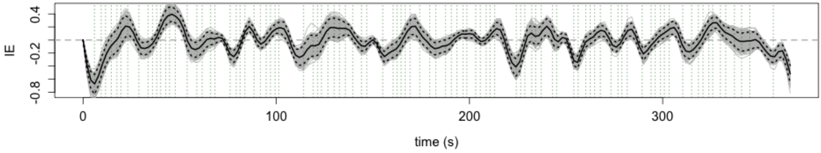
Mediator: preSMA-ant (MNI: $(-4, 36, 56)$)

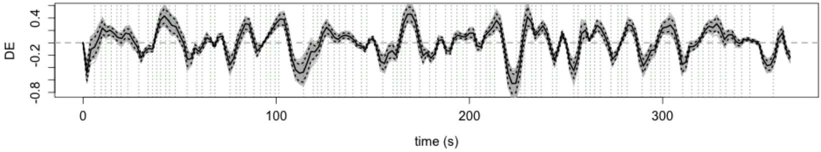
- STOP trial: $\delta_{MZ} = 8$, $\delta_{YZ} = 30$, $\delta_{YM} = 6$



Mediator: preSMA-post (MNI: $(-4, -8, 60)$)

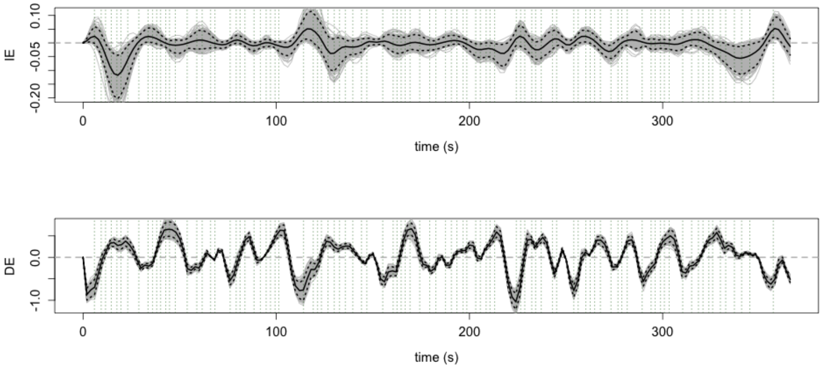
- GO trial: $\delta_{MZ} = 20$, $\delta_{YZ} = 4$, $\delta_{YM} = 4$





Mediator: preSMA-ant (MNI: $(-4, 36, 56)$)

- GO trial: $\delta_{MZ} = 20$, $\delta_{YZ} = 4$, $\delta_{YM} = 6$



Discussion

- Functional mediation analysis: dynamic effective connectivity
- Limitation and future direction
  - application limitation
  - unmeasured confounding, sensitivity analysis
  - covariates: scalar and functional
  - different HRF for different brain regions, i.e., $\{Z(t)\}_t$ different
  - dense/sparse functional data
- R package cfma available

Thank you!