Testing Mediation Effects using Logic of Boolean Matrices

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Outline

- talk outline:
  - general overview & scientific motivation
  - problem formulation & literature review
  - hypotheses $\rightarrow$ test statistics $\rightarrow$ testing procedure
  - theoretical guarantees
  - extension to sequential mediation analysis
  - numerical results

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General overview

- **neuroimaging analysis** is a super exciting area, because
  - scientifically, understanding the inner working of human brains, and their connections with numerous neurological disorders, e.g, Alzheimer's disease, as well as normal aging, is one of the most intriguing questions
  - statistically, an array of **diverse** statistical problems, constantly calling for new models, theory, algorithms
  - large public neuroimaging databases are becoming available
  - this area is not overly crowded, yet

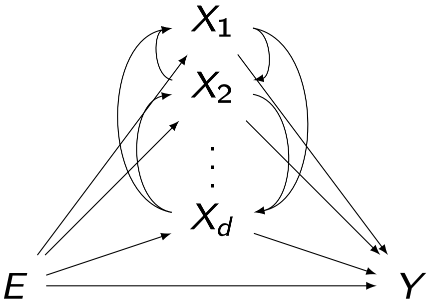
- my group works on a wide variety of neuroimaging problems:
  - imaging tensor analysis
  - brain connectivity network analysis
  - **multimodal neuroimaging analysis**
  - new imaging modalities: functional data analysis; ordinary differential equations; point process modeling

Scientific motivation

- Alzheimer's disease (AD) and normal aging:
  - AD is an irreversible neurodegenerative disorder, characterized by progressive impairment of cognitive and memory functions, then loss of independent living, and ultimately death
  - the leading form of dementia, and currently affecting 5.8 million American adults aged 65 years or older
  - prevalence continues to grow; projected to reach 13.8 million by 2050
  - there is no effective treatment
- **scientific questions of interest**:
  - neurodegeneration measure, often captured as grey matter cortical atrophy, is a well-known biomarker associated with AD
  - amyloid-beta and tau are two hallmark pathological proteins believed to be part of the driving mechanism of AD
  - **question**: how age affects cortical thickness then cognitive outcome
  - **question**: how amyloid-beta affects tau deposition then cortical thickness then cognitive outcome

Mediation analysis

- **mediation analysis**:
  - to identify and explain the mechanism, or pathway, that underlies an observed relationship between an **exposure** and an **outcome** variable, through the inclusion of an intermediary variable, known as a **mediator**
  - facilitate a better understanding of the exposure-outcome mechanism
  - has important intervention consequences, as the intervention may be placed on the mediator instead of the exposure



Inference for mediation analysis

- inference for high-dimensional mediation analysis:
  - question: how to infer the **significance** of individual mediators?
  - challenge: the number of possible paths that go through all combinations of mediators is huge $\rightarrow$ the total number of potential paths that go through any mediator is **super-exponential** in the number of mediators
- mediation estimation through sparse regularization:
  - both can in effect identify important mediators
  - but estimation does not explicitly quantify the significance (p-value), and does not control the false discovery

Inference for mediation analysis

- **mediation inference**:
  - either explicitly impose that the mediators are **conditionally independent** given the exposure, or simply ignore any potential directed paths among the mediators
  - plausible in some applications, but not in others
  - e.g., in neuroimaging, different brain regions influence each other; in genetics, different genes interact with each other

- Chakrabortty et al. (2018):
  - allowed mediator-by-mediator interactions
  - formulated the directed acyclic graph (DAG) structure
  - defined the individual mediation effect of a given mediator as the **summation** of all the effects of the exposure on the outcome that can be attributed to that mediator
  - established the convergence and confidence interval for their estimator

Inference for mediation analysis

- **what we propose** (in a nutshell):
  - propose a new testing procedure to evaluate the individual mediation effect, while allowing directed paths among the mediators
  - construct the test statistic using the **logic of Boolean matrices** $\rightarrow$ establish the proper limiting distribution under the null $\rightarrow$ the asymptotics of the test statistic built on regular matrix operations are difficult to establish
  - can be naturally coupled with a **screening** procedure $\rightarrow$ help scale down the number of potential paths to a moderate level $\rightarrow$ reduce the variance of the test statistic $\rightarrow$ enhance the power of the test
  - use a **data splitting** strategy to ensure a valid type-I error rate control under minimal conditions on the screening
  - devise a **decorrelated estimator** to reduce potential bias induced by high-dimensional mediators
  - employ **multiplier bootstrap** to obtain the critical values
  - couple with a **multiple testing** procedure for FDR control
  - establish the **asymptotic size, power, and FDR control**, while allowing the number of mediators to **diverge** to ∞

Gaussian graphical model

- setup: exposure E/X_0; multivariate mediators $X_1, \ldots, X_d$; outcome Y/X_{d+1}; write $\boldsymbol{X} = (E, X_1, \ldots, X_d, Y)^\top \in \mathbb{R}^{d+2}$
- Gaussian graphical model:

$$\boldsymbol{X} - \boldsymbol{\mu} = \boldsymbol{W}(\boldsymbol{X} - \boldsymbol{\mu}) + \boldsymbol{\varepsilon},$$

  - $\boldsymbol{\mu} = E(\boldsymbol{X})$; $\boldsymbol{W} \in \mathbb{R}^{(d+2)\times(d+2)}$; $\boldsymbol{\varepsilon} = (\varepsilon_0, \ldots, \varepsilon_{d+1})^\top$
  - $\boldsymbol{W}$ specifies the directional relationships among the variables in $\boldsymbol{X}$, which can be encoded by a **DAG**
  - $X_i \to X_j$: X_i is called a parent of X_j, and X_j a child of X_i
  - $X_i \to X_{i_1} \to \ldots \to X_{i_{k-1}} \to X_j$ for some $\{i_k\}_{1\le l<k}$: X_i is called an ancestor of X_j, and X_j a descendant of X_i.
  - X_0 is not the child of any mediator $X_1, \ldots, X_d$; X_{d+1} is not the parent of X_0 nor any mediator $X_1, \ldots, X_d$
  - the errors ε_i, $i = 0, \ldots, d+1$, are jointly normally distributed and independent, and the error variances $\sigma_i^2 = \mathrm{Var}(\varepsilon_i)$, $i = 0, \ldots, d+1$, are **constant** (Peters and Bühlmann, 2014, Yuan et al., 2019)

Hypotheses

- **total effect**: for a directed **path** $\zeta : X_0 \to X_{i_1} \to \ldots \to X_{i_k} \to X_{d+1}$ for some $\{i_t\}_{1 \le t \le k} \subseteq \{1, \ldots, d\}$, define the total effect of X_0 on X_{d+1} attributed to this path as

$$\omega_\zeta = W_{i_1,0} \left(\prod_{t=0}^{k-1} W_{i_{t+1},i_t} \right) W_{d+1,i_k},$$

where $W_{i,j}$ is the (i,j)th entry of $\boldsymbol{W}$. If such a path does not exist, we have $\omega_\zeta = 0$.

- **hypotheses**: for an individual **mediator** X_q, $q = 1, \ldots, d$,

$$\begin{aligned} H_0(q) &: \omega_\zeta = 0, \quad \text{for all } \zeta \text{ that passes through } X_q, \\ H_1(q) &: \omega_\zeta \neq 0, \quad \text{for some } \zeta \text{ that passes through } X_q. \end{aligned}$$

when $H_1(q)$ holds, we say X_q is a **significant mediator**

Hypotheses

- equivalent hypotheses:

$$H_0(q) : 0 \notin \mathrm{ACT}(q, \boldsymbol{W}) \quad \text{or} \quad q \notin \mathrm{ACT}(d+1, \boldsymbol{W}),$$
$$H_1(q) : 0 \in \mathrm{ACT}(q, \boldsymbol{W}) \quad \text{and} \quad q \in \mathrm{ACT}(d+1, \boldsymbol{W}).$$

where $\mathrm{ACT}(j, \boldsymbol{W})$ denotes the set of true ancestors of X_j

- hypotheses we target: for $q_1 = 0, \ldots, d$, $q_2 = 1, \ldots, d+1$,

$$H_0(q_1, q_2) : q_1 \notin \mathrm{ACT}(q_2, \boldsymbol{W}),$$
$$H_1(q_1, q_2) : q_1 \in \mathrm{ACT}(q_2, \boldsymbol{W}).$$

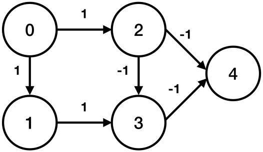
  - the null hypothesis $H_0(q)$ can be **decomposed** into a **union** of the two null hypotheses $H_0(0, q)$ and $H_0(q, d+1)$
  - by the union-intersection principle, $\max\{p(0, q), p(q, d+1)\}$ is a valid p-value for testing $H_0(q)$

Hypotheses

- **alternative definition** of a significant mediator (Chakrabortty et al., 2018):

$$H_0^*(q) : \sum \omega_\zeta = 0, \quad \text{versus} \quad H_1^*(q) : \sum \omega_\zeta \neq 0,$$

where the summation is taken for all ζ that pass through X_q



  - the effects along the path ζ may **cancel out** with each other, resulting in a zero sum, even though there are significant positive and negative mediation effects along ζ
  - e.g., for X_2, two paths, $X_0 \to X_2 \to X_4$ and $X_0 \to X_2 \to X_3 \to X_4$, both pass through X_2, while the aggregated total effect is $\sum_\zeta \omega_\zeta = 1 \times \{-1 + (-1) \times (-1)\} = 0$

Test statistics

- (the usual) power of matrices:
  - **key observation**:

$$H_0(q_1, q_2) \text{ holds if and only if } (|\boldsymbol{W}|^k)_{q_2,q_1} = 0, \text{ for any } k = 1, \ldots, d.$$

  - a natural test statistic is $\{(|\widehat{\boldsymbol{W}}|^k)_{q_2,q_1}\}_{1\le k\le d}$, where $\widehat{\boldsymbol{W}}$ is some consistent estimator for $\boldsymbol{W}$
  - however, it is difficult to obtain the limiting distribution of $(|\widehat{\boldsymbol{W}}|^k)_{q_2,q_1}$ under $H_0(q_1, q_2)$

Test statistics

- **logic of Boolean matrices**: for two real-valued matrices $\boldsymbol{A}_1 = \{a_{1,i,j}\}_{ij} \in \mathbb{R}^{q_1 \times q_2}$, $\boldsymbol{A}_2 = \{a_{2,i,j}\}_{ij} \in \mathbb{R}^{q_2 \times q_3}$
  - define a **new matrix multiplication operator** and **a new matrix addition operator** to replace the usual matrix multiplication and addition
  - define $\boldsymbol{A}_1 \otimes \boldsymbol{A}_2$ to be a $q_1 \times q_3$ matrix whose (i,j)th entry equals $\max_{k \in \{1,\cdots,q_2\}} \min(a_{1,i,k}, a_{2,k,j}) \to$ replace the multiplication operation in the usual matrix multiplication with the minimum operator, and replace the addition operation with the maximum operator
  - define $\boldsymbol{A}_1 \oplus \boldsymbol{A}_2$ to be a $q_1 \times q_2$ matrix whose (i,j)th entry equals $\max(a_{1,i,j}, a_{2,i,j})$
  - when $\boldsymbol{A}_1$, $\boldsymbol{A}_2$ are binary matrices, the minimum and maximum operators are equivalent to the logic operators "and" and "or" in Boolean algebra
  - when $\boldsymbol{A}_1$, $\boldsymbol{A}_2$ are binary matrices, "$\otimes$" operator is equivalent to the Boolean matrix multiplication operator
  - when $\boldsymbol{A}_1, \boldsymbol{A}_2$ are binary matrices, "$\oplus$" operator is equivalent to the Boolean matrix addition operator

Test statistics

- logic of Boolean matrices:
  - key observation:

$$H_0(q_1, q_2) \text{ holds if and only if } (|\boldsymbol{W}|^{(k)})_{q_2,q_1} = 0, \text{ for any } k = 1, \ldots, d.$$

  - aggregating $|\boldsymbol{W}|^{(k)}$ for all k-step paths, $k = 1, \ldots, d$,

$$\boldsymbol{W}^* = |\boldsymbol{W}| \oplus |\boldsymbol{W}|^{(2)} \oplus \cdots \oplus |\boldsymbol{W}|^{(d)}.$$

$H_0(q_1, q_2)$ holds if and only if $(\boldsymbol{W}_0^*)_{q_2,q_1} = 0$

  - test statistic: $\widehat{\boldsymbol{W}}^*_{q_2,q_1}$ for $H_0(q_1, q_2)$, where $\widehat{\boldsymbol{W}}$ is some consistent estimator for $\boldsymbol{W}$

Testing procedure

- data: let $\boldsymbol{x}_1, \cdots, \boldsymbol{x}_n$ denote i.i.d. copies of $\boldsymbol{X}$
- **step 1: data splitting**
  - split the data into two equal halves $\{\boldsymbol{x}_i\}_{i \in \mathcal{I}_1} \cup \{\boldsymbol{x}_i\}_{i \in \mathcal{I}_2}$, where $\mathcal{I}_\ell$ is the set of indices of subsamples, $\ell = 1, 2$
  - ensure the resulting test achieves a valid type-I error rate under minimal conditions
  - commonly used in statistical testing (Romano and DiCiccio, 2019)
  - construct two test statistics based on both halves of data, then combine them
  - can also do multiple splits, at the cost of heavier computations

Testing procedure

- step 2: initial estimation of W
  - compute an initial estimator $\widetilde{\boldsymbol{W}}^{(\ell)}$ for $\boldsymbol{W}_0$, given each half of the data $\{\boldsymbol{x}_i\}_{i \in \mathcal{I}_\ell}$, $\ell = 1, 2$
  - several choices: Zheng et al. (2018); Yuan et al. (2019)
  - a novel characterization of the acyclic constraint:

$$\widetilde{\boldsymbol{W}}^{(\ell)} = \mathrm{argmin}_{\boldsymbol{W} \in \mathbb{R}^{(d+2)\times(d+2)}} \sum_{i \in \mathcal{I}_\ell} \|\widetilde{\boldsymbol{x}}_i - \boldsymbol{W}\widetilde{\boldsymbol{x}}_i\|_2^2 + \lambda |\mathcal{I}_\ell| \sum_{i,j} |W_{i,j}|$$

$$\text{subject to } \mathrm{trace}\{\exp(\boldsymbol{W} \circ \boldsymbol{W})\} = d + 2.$$

  - only require $\widetilde{\boldsymbol{W}}^{(\ell)}$ to be consistent to $\boldsymbol{W}_0$; considerably weaker than requiring $\widetilde{\boldsymbol{W}}^{(\ell)}$ to be selection consistent; i.e., $\mathbb{I}(\widetilde{W}_{i,j}^{(l)} = 0) = \mathbb{I}(W_{0,i,j} = 0)$ for any $i, j = 0, \ldots, d+1$
  - we establish the consistency of $\widetilde{\boldsymbol{W}}^{(\ell)}$ as a by-product, which is not available in Zheng et al. (2018)

Testing procedure

- step 3: screening
  - compute the binary matrix $\widehat{\boldsymbol{B}}^{(\ell)}$ given the initial estimator $\widetilde{\boldsymbol{W}}^{(\ell)}$
  - use the nonzero entries of $\widehat{\boldsymbol{B}}^{(\ell)}$ to determine the support of the subsequent decorrelated estimation step
  - bring down the number of potential paths to a moderate level $\rightarrow$ reduce the variance of the test statistic $\rightarrow$ enhance the power of the test

- step 4: decorrelated estimation of W using cross-fitting
  - use one set of samples $\mathcal{I}_\ell$ to obtain the initial estimator $\widetilde{\boldsymbol{W}}^{(\ell)}$ and $\widehat{\boldsymbol{B}}^{(\ell)}$, then use the other set of samples $\mathcal{I}_\ell^c$ to compute the entries of the decorrelated estimator $\widehat{\boldsymbol{W}}^{(\ell)}$
  - reduce the bias of $\widetilde{\boldsymbol{W}}^{(\ell)}$ under the setting of high-dimensional mediators
  - guarantee the entry of $\widetilde{\boldsymbol{W}}^{(\ell)}$ is $\sqrt{n}$-consistent and asymptotically normal

Testing procedure

- **step 5: bootstrap to compute the critical values**
  - for the test statistic:

$$\sqrt{|\mathcal{I}_\ell^c|}(\widehat{\boldsymbol{W}}^{*(\ell)})_{q_1,q_2} \leq \max_{(i,j)\in\mathcal{S}(q_1,q_2,\widehat{\boldsymbol{B}}^{(\ell)})} \sqrt{|\mathcal{I}_\ell^c|}\,|\widehat{W}_{i,j}^{(\ell)} - W_{0,i,j}|,$$

  - use bootstrap to obtain the critical values of

$$\max_{(j_1,j_2)\in\mathcal{S}(0,q,\widehat{\boldsymbol{B}}^{(\ell)})} \sqrt{|\mathcal{I}_\ell^c|}\,|\widehat{W}_{j_1,j_2}^{(\ell)} - W_{0,j_1,j_2}^{(\ell)}|$$

$$\max_{(j_1,j_2)\in\mathcal{S}(q,d+1,\widehat{\boldsymbol{B}}^{(\ell)})} \sqrt{|\mathcal{I}_\ell^c|}\,|\widehat{W}_{j_1,j_2}^{(\ell)} - W_{0,j_1,j_2}^{(\ell)}|,$$

    under the significance level $\alpha/2$; denote the two critical values by $\widehat{c}^{(\ell)}(0,q)$ and $\widehat{c}^{(\ell)}(q,d+1)$

Testing procedure

- **decision making**:
  - reject $H_0(0, q)$ if $\widehat{\boldsymbol{B}}^{*(\ell)}_{q,0}\left\{|\mathcal{I}^c_\ell|^{-1/2}\widehat{c}^{(\ell)}(0, q)\right\} = 1$
  - reject $H_0(q, d+1)$ if $\widehat{\boldsymbol{B}}^{*(\ell)}_{d+1,q}\left\{|\mathcal{I}^c_\ell|^{-1/2}\widehat{c}^{(\ell)}(q, d+1)\right\} = 1$
  - reject the null $H_0(q)$ when $H_0(0, q)$ and $H_0(q, d+1)$ are both rejected
  - for each half of the data $\ell = 1, 2$, we have made a decision $\mathcal{D}^{(\ell)}$ regarding $H_0(q) \rightarrow$ we reject $H_0(q)$ when either $\mathcal{D}^{(1)}$ or $\mathcal{D}^{(2)}$ decides to reject $\rightarrow$ by Bonferroni's inequality, this yields a valid α-level test

- **multiple testing**:
  - adopt the ScreenMin procedure of Djordjilović et al. (2019) for multiple testing and false discovery control

Theoretical guarantees

- **asymptotic size**:

$$\mathbb{P}\{H_0(q) \text{ is rejected} \mid H_0(q) \text{ holds}\} \leq \alpha + o(1).$$

- **asymptotic power**:

$$\mathbb{P}\{H_0(q) \text{ is rejected} \mid H_1(q) \text{ holds}\} \to 1, \quad \text{as } n \to \infty.$$

- **asymptotic FDR control**:

$$\mathrm{FDR}(\mathcal{H}) \leq \alpha + o(1)$$

- **consistency of the initial DAG estimator**:
  - the convergence rate of the initial DAG estimator $\widetilde{\boldsymbol{W}}^{(\ell)}$ obtained from Zheng et al. (2018) is the same as that of the oracle estimator

AD case study 1

- mediation inference:
  - **exposure**: age; **outcome**: PACC score; **mediators**: gray matter cortical thickness of $d = 68$ brain regions-of-interest (ROIs)
  - $n = 389$ subjects
  - set FDR level at 10%

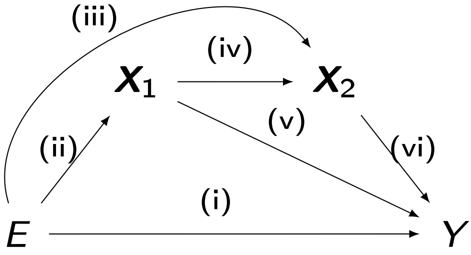
- findings:

amyloid negative group	
l-entorhinal	l-precuneus
l-superiortemporal	r-inferiorparietal
r-superiorfrontal	r-superiortemporal

  - entorhinal cortex functions as a hub in a widespread network for memory, navigation and the perception of time; one of the most heavily damaged cortices in AD
  - precuneus is involved with episodic memory, visuospatial processing, reflections upon self, and aspects of consciousness, and is found to be an AD-signature region

Sequential mediation analysis

- **sequential mediation analysis**:
  - question: how amyloid-beta affects tau deposition then cortical thickness then cognitive outcome
  - challenge: **multiple sets** of mediators are **sequentially** ordered on the potential pathways following certain biological constraints



Sequential mediation analysis

- **setup**: exposure E/X_0; first set of mediators $\boldsymbol{X}_1 = (X_{11} \ldots, X_{1d_1})^\top \in \mathbb{R}^{d_1}$; second set of mediators $\boldsymbol{X}_2 = (X_{21} \ldots, X_{2d_2})^\top \in \mathbb{R}^{d_2}$; outcome $Y/X_{d_1+d_2+1}$
- **Gaussian graphical model**:

$$\boldsymbol{X} - \boldsymbol{\mu} = \boldsymbol{W}(\boldsymbol{X} - \boldsymbol{\mu}) + \varepsilon,$$

- **decomposition**:

$$\boldsymbol{W}_0 = \begin{pmatrix} 0 & 0_{d_1}^\top & 0_{d_2}^\top & 0 \\ \boldsymbol{W}_{0,1} & \boldsymbol{W}_{1,1} & 0_{d_1 \times d_2} & 0_{d_1} \\ \boldsymbol{W}_{0,2} & \boldsymbol{W}_{1,2} & \boldsymbol{W}_{2,2} & 0_{d_2} \\ W_{0,3} & \boldsymbol{W}_{1,3}^\top & \boldsymbol{W}_{2,3}^\top & 0 \end{pmatrix} \in \mathbb{R}^{(d_1+d_2+2)\times(d_1+d_2+2)},$$

where $\boldsymbol{W}_{0,1} \in \mathbb{R}^{d_1}$, $\boldsymbol{W}_{0,2} \in \mathbb{R}^{d_2}$, $\boldsymbol{W}_{0,3} \in \mathbb{R}$, $\boldsymbol{W}_{1,1} \in \mathbb{R}^{d_1 \times d_1}$, $\boldsymbol{W}_{1,2} \in \mathbb{R}^{d_2 \times d_1}$, $\boldsymbol{W}_{1,3} \in \mathbb{R}^{d_1}$, $\boldsymbol{W}_{2,2} \in \mathbb{R}^{d_2 \times d_2}$, and $\boldsymbol{W}_{2,3} \in \mathbb{R}^{d_2}$

Sequential mediation analysis

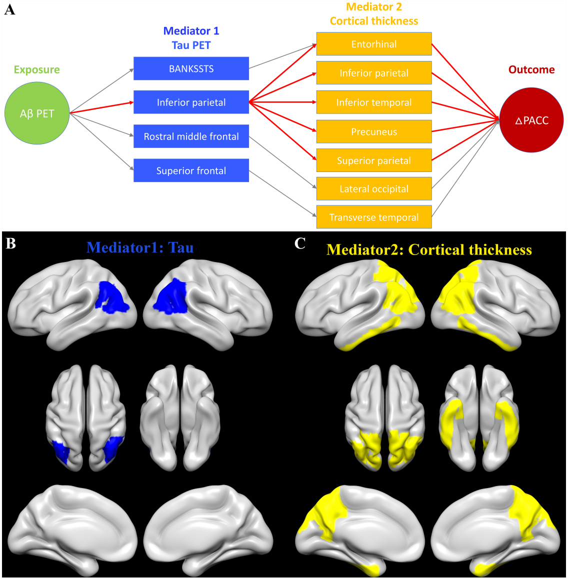
- **hypotheses**: for some $q_1 = 1, \ldots, d_1$, and $q_2 = 1, \ldots, d_2$,
  - $H_0(q_1, q_2)$: There does *not* exist a path from the exposure E to the outcome Y that passes through some mediator X_{1,q_1} in $\boldsymbol{X}_1$ *and* some mediator X_{2,q_2} in $\boldsymbol{X}_2$;
  - $H_1(q_1, q_2)$: There exists a path from the exposure E to the outcome Y that passes through some mediator X_{1,q_1} in $\boldsymbol{X}_1$ *and* some mediator X_{2,q_2} in $\boldsymbol{X}_2$,
  - H_0 means that, at least one potential pathway denoted by (ii), (iv) and (vi) is completely missing in this diagram
  - other forms of null hypothesis are possible too
- equivalent hypotheses in terms of $\boldsymbol{W}_{0,1}$, $\boldsymbol{W}_{1,1}$, $\boldsymbol{W}_{1,2}$, $\boldsymbol{W}_{2,2}$ and $\boldsymbol{W}_{2,3}$
- estimation of $\boldsymbol{W}$ following the decomposition structure
- mediation inference

AD case study 2

- mediation inference:
  - **exposure**: amyloid-beta;
    outcome: change of PACC score of two consecutive visits;
    mediator set 1: tau deposition of $d_1 = 35$ brain ROIs;
    mediator set 2: gray matter cortical thickness of $d_2 = 34$ brain ROIs
  - $n = 184$ subjects
  - set FDR level at 10%

AD case study 2

- findings:



Thank You!