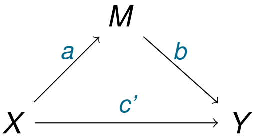
Mediation Analysis in *AB*/*BA* Crossover Studies

Modern Modeling Methods (M3) Conference

Haeike Josephy - Tom Loeys - Stijn Vansteelandt



Department of Data-Analysis, Ghent University - Tuesday 20th May, 2014

Overview

Mediation Analysis - Goal

Goal:
Unravel causal pathways between exposure X and outcome Y:

- What is the effect of X on Y?
  = Total Effect

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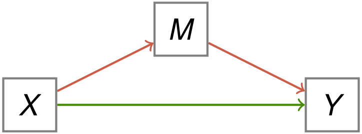
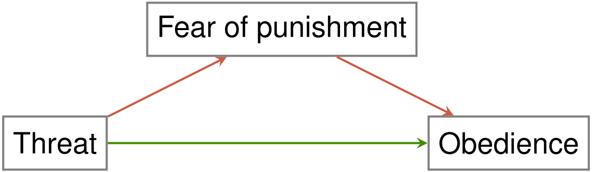


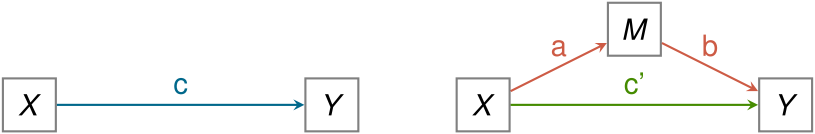
- What part of the effect is mediated by M?
  = Indirect Effect
- What is the remaining causal effect of X on Y?
  = Direct Effect

Mediation Analysis - Example

- Threathening with punishment (X) induces obedience (Y) in children
  - No threat ($X = 0$) versus threatening with punishment ($X = 1$)
- Possible mediator M:
  - Fear of punishment



Traditional Mediation Analysis - How?



The Baron and Kenny (1986) approach:

$$\begin{aligned} E[Y_i \mid X_i] &= i_0 + cX_i \\ E[M_i \mid X_i] &= i_1 + aX_i \\ E[Y_i \mid X_i, M_i] &= i_2 + c'X_i + bM_i \end{aligned}$$

Step 1: $H_0 : c = 0$

Step 2: $H_0 : a = 0$

Step 3: $H_0 : b = 0$

Step 4: $H_0 : c' = 0$

$$\begin{aligned} \textit{Total Effect} &= \textit{Direct Effect} + \textit{Indirect Effect} \\ c &= \qquad c' \qquad + \qquad a \times b \end{aligned}$$

Traditional Mediation Analysis - When?

Modelling assumptions:

(M1) Linear relationships among X, M and Y

(M2) Normally distributed error terms, with constant variance

(M3) Independent error terms

$$M = \iota_1 + \alpha X + \epsilon_M \qquad , \text{ with } \epsilon_M \sim N(0, \sigma_M^2)$$

$$Y = \iota_2 + \zeta' X + \beta M + \epsilon_Y \qquad \epsilon_Y \sim N(0, \sigma_Y^2)$$

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Greek - Data generation

Roman - Estimation

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(A1) No unmeasured confounding of the X-M relationship

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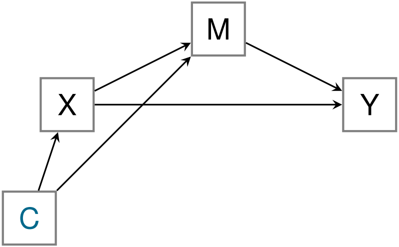
(A4) No confounders of the M-Y relationship, affected by X



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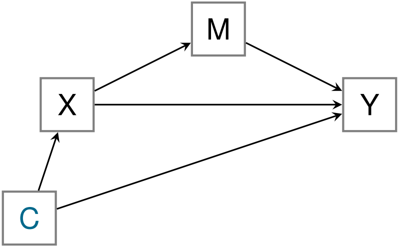

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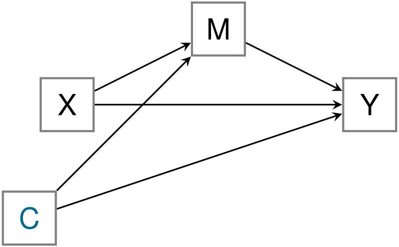

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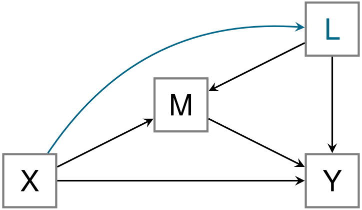

The AB/BA Crossover Design

- Everyone is exposed to an experimental (*A*) and control (*B*) condition in randomised order: order *AB* or *BA*
- This yields two scores for each individual (under *A* and *B*)
- Multilevel design with two levels:
    - Upper level - individual
    - Lower level - measurement moment

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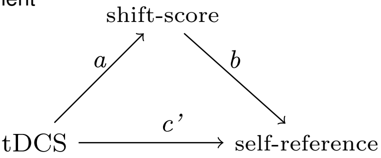

Example:

- **X** $=$ anodal transcranial Direct Current Stimulation (tDCS) over dorsolateral pre-frontal cortex ($X = 0, 1$ for each subject)
- **M** $=$ ability to shift from negative representations in the working memory ($M^{(x=0)}, M^{(x=1)}$ for each subject)
- **Y** $=$ occurrence of self-referent thoughts ($Y^{(x=0)}, Y^{(x=1)}$ for each subject)

The AB/BA Crossover Design - Concerns

Expanding mediation to the AB/BA design proves challenging:

1. Data from AB/BA design shows dependency
    - Modelling assumption of independent observations is violated (M3) in multilevel designs

$$\epsilon_M \overset{\cancel{i.i.d.}}{\sim} N(0, \sigma_M), \qquad \epsilon_Y \overset{\cancel{i.i.d.}}{\sim} N(0, \sigma_Y)$$

    - Traditional analysis underestimates *se*'s
    - Requires methods that incorporate/negate this (Judd et al., 2001; Kenny et al., 2003; Bauer et al., 2006)
2. How will we define the direct and indirect effect in these settings?
    - Define these effects through the Counterfactual Framework
    - Identify these effects through the Mediation formula (Pearl, 2001)

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1. Dependency

Traditionally Judd et al. (2001)'s method is used:

- Removes dependency from AB/BA data by subtracting the two individual scores
- Tests mediation in linear settings using 3 regressions:

$$\begin{aligned} E[Y_i^{Dif}] &= E[Y^{x=1} - Y^{x=0}] \\ &= i_0 + c - i_0 = c \\ E[M_i^{Dif}] &= E[M^{x=1} - M^{x=0}] = a \\ E[Y_i^{Dif} \mid M_i^{Dif}, M_i^{Sum}] &= c' + b_d M_i^{Dif} + b_s M_i^{Sum} \end{aligned}$$

$$\text{with } M_{Sum} = M^{x=1} + M^{x=0}$$

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- There is mediation when H_0's of Step1-3 are rejected
- Test for XM-moderation: $H_0 : b_s = 0$
- Indirect effect: ?

Criticism on traditional approach

1. This method does not yield a clear identification of the indirect effect
2. Adaptation of Causal Steps Approach, also not without criticism:
    - Low power
    - Some steps are obsolete
3. The underlying assumptions w.r.t. causality (about measured and unmeasured confounders) are not explicitly made
4. Limited to continuous *M*- en Y-variables
5. Allows but one type of moderation (*XM*-interaction)
    - Other possibilities: *X*-Covariate, *M*-Covariate
6. Does not take possible period-effects into account, e.g. habituation

2. Inference

2.1 The Counterfactual Approach (for single level data)

Counterfactual outcome $Y_i(x)$ $=$ the outcome that we would (possibly contrary to fact) have observe for individual i, had the exposure X been set to x.

Define counterfactuals $Y_i(x)$ for person i:

- $Y_i(0)$: obedience when no threat is given ($X = 0$)
- $Y_i(1)$: obedience when threats are given ($X = 1$)

$\Rightarrow$ *Individual Total Effect*: $Y_i(1) - Y_i(0)$
BUT $Y_i(1)$ and $Y_i(0)$ never observed jointly! (when exposure is measured between subjects!)

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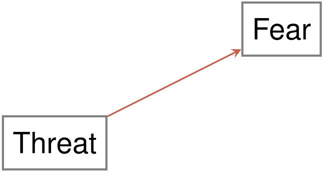
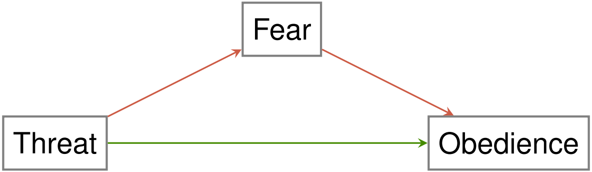
Similarly, define counterfactuals $M_i(x)$



- $M_i(0)$: fear of punishment when no threat is given ($X = 0$)
- $M_i(1)$: fear of punishment when threats are given ($X = 1$)

And nested counterfactuals... $Y(x, M(x^*))$, where x can differ from x^*



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$\Rightarrow$Natural direct effect: $E[Y(1, M(0)) - Y(0, M(0))]$

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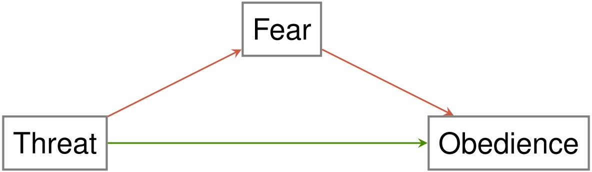

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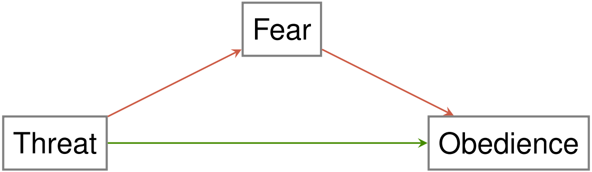

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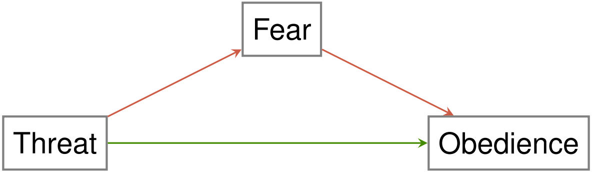

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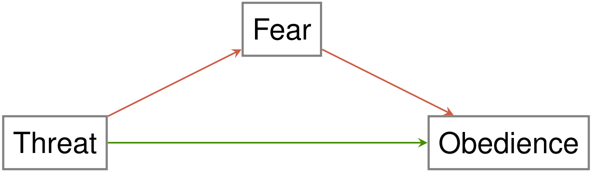

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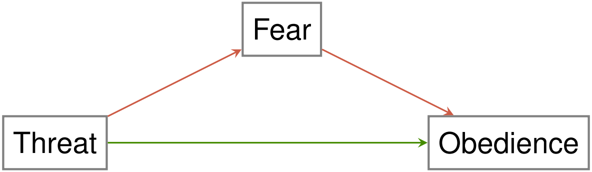

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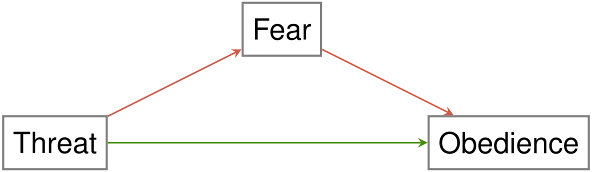

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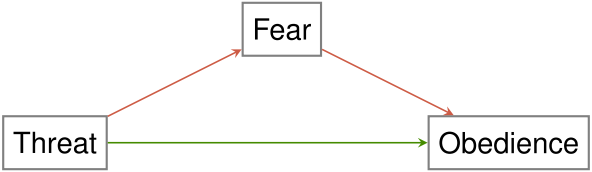

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2. Inference

2.2. The Mediation formula

Under assumptions (A1)-(A4), the above defined natural effects can be identified with the mediation formula (Pearl, 2001):

$$\text{Direct effect} = E[Y(1, M(0)) - Y(0, M(0))] \\ = \sum_m P(M = m|X = 0)(E(Y|X = 1, M = m) - E(Y|X = 0, M = m))$$

$$\text{Indirect effect} = E[Y(1, M(1)) - Y(1, M(0))] \\ = \sum_m E(Y|X = 1, M = m)(P(M = m|X = 1) - P(M = m|X = 0))$$

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APPLICATION 1 - Linear relations in single level data

For models:

$$\begin{aligned} E[M_i \mid X_i] &= \iota_1 + \alpha X_i \\ E[Y_i \mid X_i, M_i] &= \iota_2 + \zeta' X_i + \beta M_i \end{aligned}$$

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Application of the mediation formula yields:

Direct effect $= \zeta'$

Indirect effect $= \alpha \times \beta$

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APPLICATION 2 - Nonlinear relations in single level data

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Application of the mediation formula yields:

Direct effect $= \zeta' + \phi\iota_1$
Indirect effect $= \alpha(\beta + \phi)$

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To identify the direct and indirect effect in *AB*/*BA* data through use of the Mediation formula, the traditional confounding assumptions ((A1)-(A4)) need to be adjusted:

(A1)

(A2)

(A3) No unmeasured lower or upper level confounding of the M-Y relationship

(A4) No upper or lower level confounders of the M-Y relationship, affected by X

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To identify the direct and indirect effect in AB/BA data through use of the Mediation formula, the traditional confounding assumptions ((A1)-(A4)) need to be adjusted:

(A1) ~~No unmeasured upper or lower level confounding of the X-M relationship~~

(A2)

(A3) No unmeasured lower or upper level confounding of the M-Y relationship

(A4) No upper or lower level confounders of the M-Y relationship, affected by X

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Under the adjusted assumptions (A1)-(A4), the above defined natural effects can be identified with the mediation formula (Pearl, 2001):

APPLICATION 3 - Linear relations in *AB*/*BA* data

For models:

$$\begin{aligned} E[M_{it} \mid X_{it}, U_i] &= \iota_1 + \alpha X_{it} + U_i \\ E[Y_{it} \mid X_{it}, M_{it}, V_i] &= \iota_2 + \zeta' X_{it} + \beta M_{it} + V_i \end{aligned}$$

, with $i =$ individual and $t =$ period

, with U_i and V_i uncorrelated subject specific confounders

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, with $i =$ individual and $t =$ period

, with U_i and V_i uncorrelated subject specific confounders

Application of the mediation formula yields: Direct effect $= \zeta'$

Indirect effect $= \alpha \times \beta$

The Difference Approach

= an adaptation of Judd et al. (2001)'s method, that tackles both the challenge of data dependency, as correct inference.

For models:

$$\begin{aligned} E[M_{it} \mid X_{it}, U_i] &= \iota_1 + \alpha X_{it} + U_i \\ E[Y_{it} \mid X_{it}, M_{it}, V_i] &= \iota_2 + \zeta' X_{it} + \beta M_{it} + V_i \end{aligned}$$

, with $i =$ individual and $t =$ period

, U_i and V_i subject specific confounders ($cor(U_i, V_i) = 0$)

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1. Definition - The Difference Approach is defined as:

$$\begin{aligned} E[M_i^{Dif}] &= E[M_i^{x=1} - M_i^{x=0}] \\ &= (\iota_1 + \alpha + U_i) - (\iota_1 + U_i) \\ &= \alpha \\ E[Y_i^{Dif}] &= E[Y_i^{x=1} - Y_i^{x=0}] \\ &= (\iota_2 + \zeta' + \beta M_i^{x=1} + V_i) - (\iota_2 + \beta M_i^{x=0} + V_i) \\ &= \zeta' + \beta M_i^{Dif} \end{aligned}$$

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2. Inference - The average direct and indirect effect are identified as:

Direct effect $= \zeta'$
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Indirect effect $= \alpha \times \beta$

→ Removes dependency by relying on differences scores (and therefore effectively eliminates between-subject effects)

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$$\left.\begin{aligned} \text{Direct effect} &= \zeta' \\ \text{Indirect effect} &= \alpha \times \beta \end{aligned}\right\}$$

→ Correct inference is established through the Counterfactual framework and the Mediation formula.

The Difference Approach

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For models:

$$\begin{aligned} E[M_{it} \mid X_{it}, U_i] &= \iota_1 + \alpha X_{it} + \kappa_M t_i + U_i \\ E[Y_{it} \mid X_{it}, M_{it}, V_i] &= \iota_2 + \zeta' X_{it} + \beta M_{it} + \kappa_Y t_i + V_i \end{aligned}$$

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2. Inference - The average direct and indirect effect are identified as:

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Indirect effect $= \alpha \times \beta$

→ Can incorporate period effects (estimates of DE & IE change!).

The Difference Approach

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For models:

$$\begin{aligned} E[M_{it} \mid X_{it}, U_i, D_i] &= \iota_1 + \alpha X_{it} + \nu_M X_{it} D_i + U_i \\ E[Y_{it} \mid X_{it}, M_{it}, V_i, D_i] &= \iota_2 + \zeta' X_{it} + \beta M_{it} + \nu_Y X_{it} D_i + \eta_Y M_{it} D_i + V_i \end{aligned}$$

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2. Inference - The average direct and indirect effect are identified as:

$$\begin{aligned} \text{Direct effect} &= \zeta' + \nu_y D \\ \text{Indirect effect} &= (\alpha + \nu_M D)(\beta + \eta_Y D) \end{aligned}$$

→ Is valid with all sorts of interactions (*XM*, *XD*, *MD*, ...).

Other approaches for analyzing AB/BA data

1. The Naive modelling approach models M and Y separately:

$$M_{it} \sim X_{it}$$
$$Y_{it} \sim X_{it} + M_{it}$$
, with i=individual, t=period

2. The Joint modelling approach models M and Y jointly (Bauer et al., 2006):
   - Allows for covariance between the random intercepts of M and Y

$$M_{it} \sim X_{it}$$
$$Y_{it} \sim X_{it} + M_{it}$$
, with i=individual, t=period

3. The Centered approaches model M and Y separately, with centered M-scores:
   - Can estimate between- and within- subject effect of M on Y

$$M_{it} \sim X_{it}$$
$$Y_{it} \sim X_{it} + (M_{it} - \bar{M}_i) + \bar{M}_i$$
, with i=individual, t=period

   - Or the within-subject effect of M on Y only

$$M_{it} \sim X_{it}$$
$$Y_{it} \sim X_{it} + (M_{it} - \bar{M}_i)$$
, with i=individual, t=period

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     $Y_{it} \sim X_{it} + (M_{it} - \bar{M}_i) + \bar{M}_i$, *with i=individual, t=period*
   - Or the within-subject effect of M on Y only
     $M_{it} \sim X_{it}$
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     $$M_{it} \sim X_{it}$$
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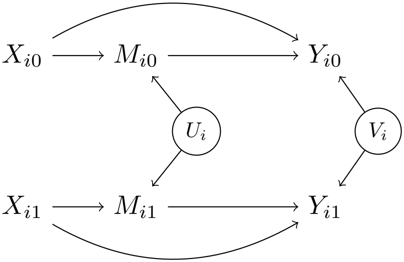
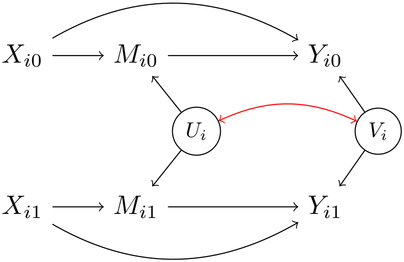
Simulation studies



1. **Simulation 1**
   - Adjusted assumptions (A1) to (A4) are met.
   - Direct and indirect effect estimates are:

Naive	unbiased	
Joint	unbiased	
Centered	unbiased	identical
Difference	unbiased	

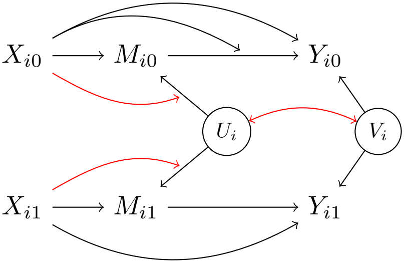
Simulation studies



1. **Simulation 2**
   - Violation of adjusted assumption (A3) - upper level *M*-*Y* confounding
   - Direct and indirect effect estimates are:

Naive	**biased** (14-24.5%)	
Joint	unbiased	
Centrered	unbiased	identical
Difference	unbiased	

Simulation studies



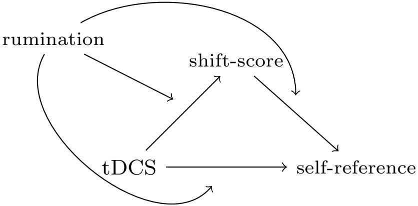
1. **Simulation 3**
   - Further violation of adjusted assumption (A3) - upper level *M*-*Y* confounding, moderated by exposure
   - Direct and indirect effect estimates are:

Naive	**biased** (14-25%)	
Joint	**biased** (1.5-3.5%)	
Centered	unbiased	identical
Difference	unbiased	

A neurostimulation study - Mediation Analysis

Adjusted assumptions (A1)-(A2)-(A4) are met, (A3) is partially met

(no lower level *M*-*Y* confounding)



For models:

$$
\begin{aligned}
E[M_{it} \mid X_{it}, D_i, U_i] &= \iota_1 + \alpha X_{it} + \kappa_M t_i + \omega_M D_i + \nu_M X_{it} D_t + U_i \\
E[Y_{it} \mid X_{it}, M_{it}, D_i, V_i] &= \iota_2 + \zeta' X_{it} + \beta M_{it} + \kappa_Y t_i + \omega_Y D_i + \nu_Y X_{it} D_j + \eta_Y M_{it} D_i + V_i
\end{aligned}
$$

, where $cor(U_i, V_i)$ is unspecified

Application of the mediation formula yields:

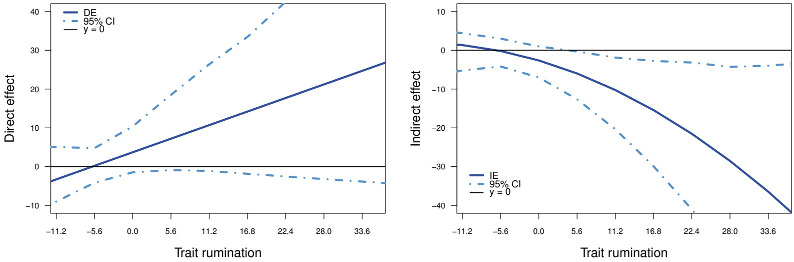
$$
\begin{aligned}
\text{Direct effect} &= \zeta' + \nu_Y D \\
\text{Indirect effect} &= (\alpha + \nu_M D)(\beta + \eta_Y D)
\end{aligned}
$$

A neurostimulation study - Mediation Analysis

Adjusted assumptions (A1)-(A2)-(A4) are met, (A3) is partially met

(no lower level M-Y confounding)

- For trait rumination $= D \in (-11, 35)$ the direct and indirect effect, by means of the Difference approach:



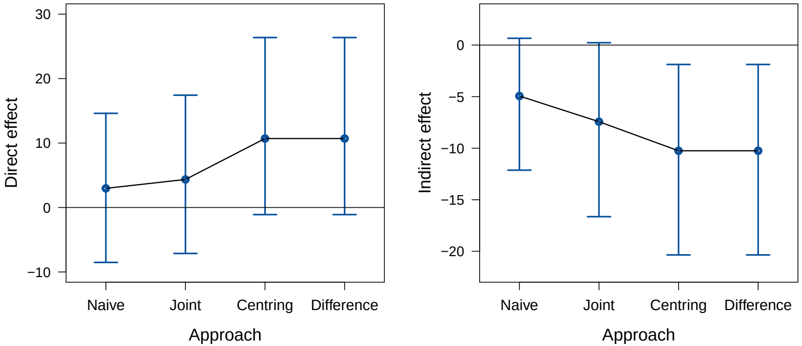
- The effect of tDCS on self-referent thoughts is mediated by the working memory for high levels of trait rumination (D) only.

A neurostimulation study - Mediation Analysis

Adjusted assumptions (A1)-(A2)-(A4) are met, (A3) is partially met

(no lower level *M*-*Y* confounding)

Direct and indirect effect for the four different modelling approaches, at $D = 1\ sd = 11.19$



Conclusions

- We clarified the assumptions under which the direct and indirect effect can be identified in the AB/BA design
- We proposed an elegant method to estimate these effects (the Difference approach)
- Simulations showed that subject level confounding of the M-Y relation can be accounted for by means of
    - The Difference approach
    - The two Centered approaches
    - In a lesser extent by the Joint modelling approach
    - NOT by the Naive modelling approach

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