A New Approach for Within-Subject Mediation Analysis in AB/BA Crossover Designs

Haeike Josephy[a], Tom Loeys[a] and Stijn Vansteelandt[b]

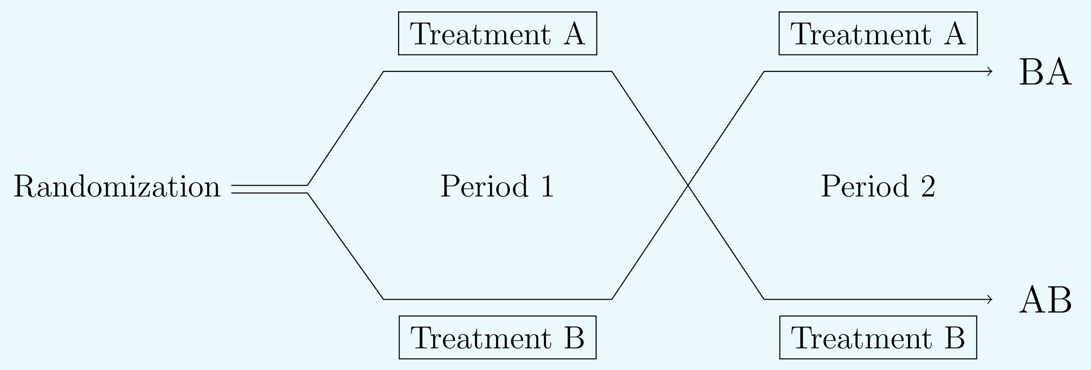
[a] Department of Data Analysis, Ghent University, Belgium

[b] Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Belgium

UNIVERSITEIT GENT

1. Cross-over trials

- Consider a simple **AB/BA crossover trial**.
  - Crossover trials are widely used, to assess the effect of reversible treatments.
  - In such a design, each participant is observed twice: once in each condition (treatment A and B).
  - Moreover, each subject is randomly allocated to a sequence of conditions: first treatment A, then B (**AB**), or the other way round (**BA**).



2. Mediation analysis

- **Mediation analysis** aims to clarify and explain the relation between an exposure X and an outcome Y.
  - Mediation verifies whether the effect of X on Y (partly) runs through an intermediate variable M.
  - This amounts to decomposing the **total** effect of X on Y into a **direct** (not through M) and an **indirect effect** (through M).

- Mediation analysis in crossover studies is relatively unexplored.

3. The counterfactual approach

- A **counterfactual** outcome $Y(x', M_{ij}(x''))$, denotes the outcome that we would observe for a subject, had the exposure X_{ij} been set to the value x', while the mediator is fixed at the level under exposure x''.
- This definition enables model-free definitions for the direct and indirect effect:
  - direct effect $= E(Y_{ij}(X_{ij}=1, M_{ij}(X_{ij}=0) - Y_{ij}(X_{ij}=0, M_{ij}(X_{ij}=0)))$
  - indirect effect $= E(Y_{ij}(X_{ij}=0, M_{ij}(X_{ij}=1) - Y_{ij}(X_{ij}=0, M_{ij}(X_{ij}=0)))$
- Under the following data generating mechanism for M and Y (i = measurement moment, j = individual, binary $X_{ij}=0,1$), where we allow for subject-specific unmeasured confounding of the M-Y relationship (through U_j and $g(U_j)$):

$$\begin{cases} M_{ij} = d_M + aX_{ij} + t_M i + U_j + \epsilon_{Mij} & \text{with } \epsilon_{Mij} \sim N(0, \sigma_M^2) \\ Y_{ij} = d_Y + c'X_{ij} + bM_{ij} + t_Y i + g(U_j) + \epsilon_{Yij} & \text{with } \epsilon_{Yij} \sim N(0, \sigma_Y^2) \end{cases}$$

,the direct effect can be identified as c' and the indirect effect as ab (Pearl, 2012).

4. A new approach

- As each participant is observed twice ($X=0,1$), we obtain two observations for the mediator ($M^{x=0}, M^{x=1}$) and two for the outcome ($Y^{x=0}, Y^{x=1}$).
- Judd et al. (2001) propose analyzing AB/BA data by subtracting the outcomes under treatment 0 from the outcomes under treatment 1:

$$\begin{cases} M^{dif} = M^{x=1} - M^{x=0} \sim 1 \\ Y^{dif} = Y^{x=1} - Y^{x=0} \sim 1 + M^{dif} \end{cases}$$

- We extend this method to allow for period effects and several interactions.
  - We will refer to this a the **difference approach**[1].

5. Alternative multilevel approaches

- **Naive** separate modeling[2]:

$$\begin{cases} M_{ij} \sim X_{ij} \\ Y_{ij} \sim X_{ij} + M_{ij} \end{cases}$$

- **W-only** separate modeling[3]:

$$\begin{cases} M_{ij} \sim X_{ij} \\ Y_{ij} \sim X_{ij} + (M_{ij} - \bar{M}_j) \end{cases}$$

  - Estimates within-subject effect of M on Y

- **W-vs-B** separate modeling[4]:

$$\begin{cases} M_{ij} \sim X_{ij} \\ Y_{ij} \sim X_{ij} + (M_{ij} - \bar{M}_j) + \bar{M}_j \end{cases}$$

  - Estimates between- and within-subject effect of M on Y

- **Joint** modeling[5] (Bauer et al., 2006):

$$\begin{cases} M_{ij} \sim X_{ij} \\ Y_{ij} \sim X_{ij} + M_{ij} \end{cases}$$

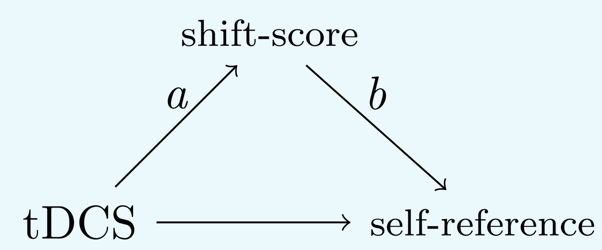
  - Allows for covariance between the random intercepts of M and Y

6. Comparing all methods

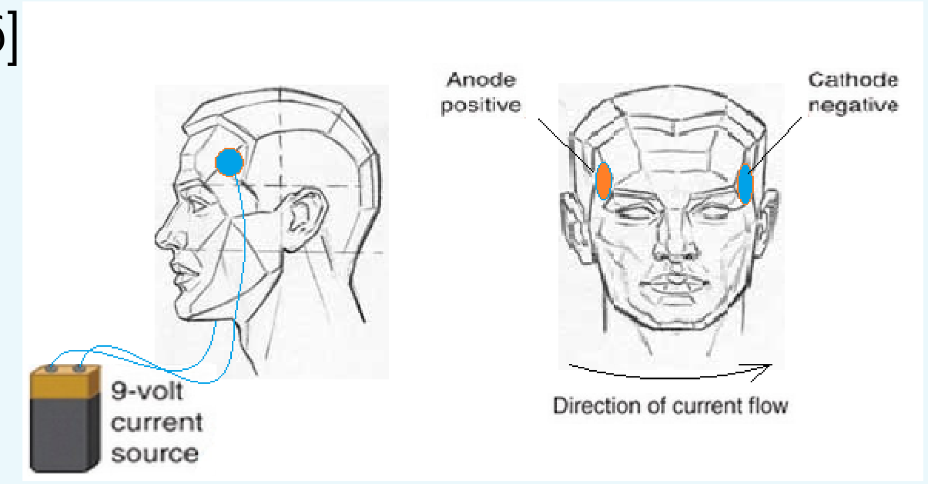
- Presence of M-Y confounding:
  - **No**: all five methods are equivalent.
  - **Yes**: only methods that correct for possible M-Y confounding (models 1, 3-5) yield unbiased estimates of the within-subject effects.
- Presence of non-linearities:
  - **No**: model 1 and models 3-5 yield identical estimates of the within-subject effects.
  - **Yes**: models 1, 3-5 provide slightly different estimates of the within-subject effects, but with similar performance.
- Misspecification or violation of the normality assumption in U_j and/or $g(U_j)$ has no effect.

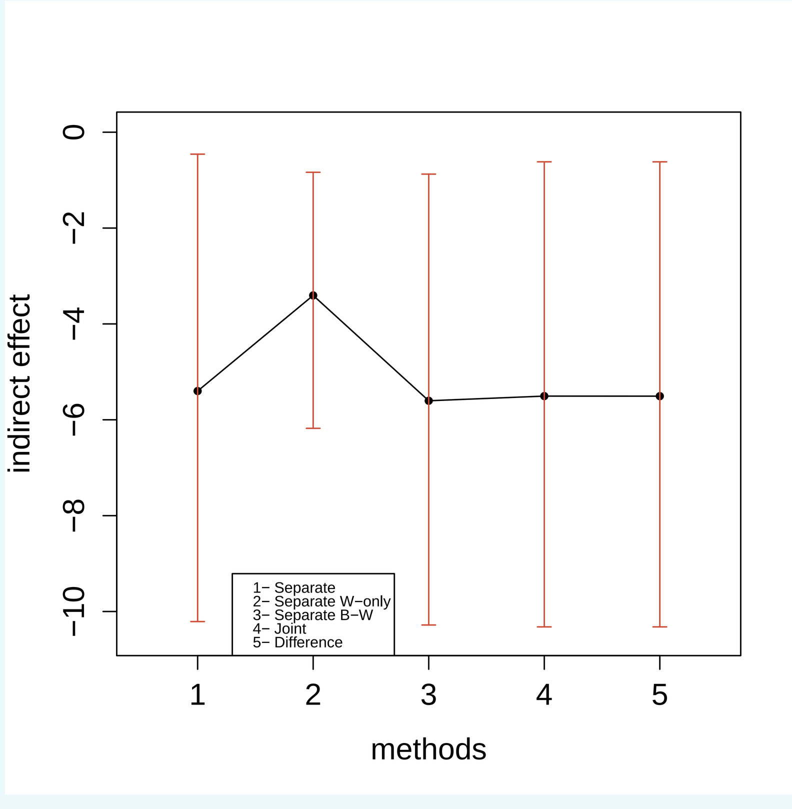
7. Comparing all methods on a crossover study in behavioral neuroscience

- Crossover study in 32 healthy participants.
  - **X**: anodal transcranial Direct Current Simulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC)
  - **M**: ability to shift from negative representations in the working memory
  - **Y**: occurrence of self-referent thoughts



- **Question**: Is the relationship between DLPFC-activity and self-referent thoughts mediated by working memory operations?
  - With the difference approach (assuming a period effect and XM-interaction): $\hat{ab} = -5.40$, with a 95% bias-corrected bootstrap confidence interval of $[-10.21; -0.46]$





8. Conclusions

- In contrast to the parallel group study design, crossover studies allow identification of the direct and indirect effect in the presence of M-Y confounding at the subject-level.
- The difference approach provides a flexible framework to deal with settings that include X-M, X-Covariate, M-Covariate and X-period interactions.

References

Bauer, D. J., Preacher, K. J., and Gil, K. M. (2006). Conceptualizing and testing random indirect effects and moderated mediation in multilevel models: new procedures and recommendations. *Psychological methods*, 11(2):142–63.

Judd, C. M., Kenny, D. a., and McClelland, G. H. (2001). Estimating and testing mediation and moderation in within-subject designs. *Psychological methods*, 6(2):115–34.

Pearl, J. (2012). The causal mediation formula–a guide to the assessment of pathways and mechanisms. *Prevention science : the official journal of the Society for Prevention Research*, 13(4):426–36.