Path Analysis in the Development of New Antidepressants

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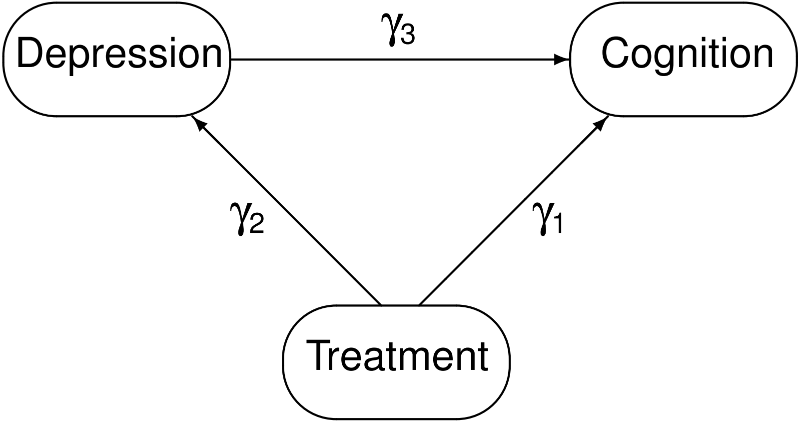
The problem we are trying to solve

- Patients with depression often demonstrate a number of cognitive deficits
- Treatment with an antidepressant reduces the depressive symptoms for most patients
- Treatment with an antidepressant also improves the cognitive functioning

- Is the improvement of cognitive functioning "just"an effect of reducing the depressive symptoms ?
- Can the direct effect of treatment on cognition be estimated ?
- How much of the treatment effect on cognition is explained by depression ?

The problem we are trying to solve



Path analysis methodology

- Treatment (T), depression is the mediator variable (M) and cognition is the outcome variable (Y)
- The standard regression model: $Y = \beta T$
- β: total effect of treatment on outcome
- Effect of treatment on the mediator: $M = \gamma_2 T$
- Effects of treatment and mediator on the outcome: $Y = \gamma_1 T + \gamma_3 M$
- Rearranging the regression model we get: $\beta = \gamma_1 + \gamma_2\gamma_3$
- Decomposition of the total effect β of treatment on outcome into the direct effect γ_1 and the indirect effect $\gamma_2\gamma_3$

Path analysis methodology

- Introducing additional explanatory variables, X, measured or assessed pre-treatment

$$
\begin{aligned}
Y_i &= \alpha_1 + \beta_1 T_i + \xi_1^T X_i + \varepsilon_{i1} \\
M_i &= \alpha_2 + \beta_2 T_i + \xi_2^T X_i + \varepsilon_{i2} \\
Y_i &= \alpha_3 + \beta_3 T_i + \gamma M_i + \xi_3^T X_i + \varepsilon_{i3}
\end{aligned}
$$

- $\hat{\beta}_2\hat{\gamma}$: an estimate of the indirect effect
- $\hat{\beta}_1 - \hat{\beta}_3$ yields a numerically identical estimate by computing in the linear case
- $\hat{\beta}_1 = \hat{\beta}_2\hat{\gamma} + \hat{\beta}_3$ and $\beta_1 = \beta_2\gamma + \beta_3$ always holds $\Longrightarrow$ first equation is redundant given the second and third

Path analysis methodology

- Evidence of an indirect effect is likely if:
  - β_2 is significant, i.e. there is evidence of a linear relationship between treatment and mediator
  - β_1 is significant, i.e. there is a linear relationship between treatment and outcome
  - γ is significant, indicating that the mediator helps predicting the outcome
  - β_3, the effect of treatment directly on outcome, becomes significantly smaller in size relative to β_1

General estimation algorithm

Product of coefficients only applicable when both the mediator and outcome models are linear regressions

Step 1 Fit models for the observed outcome and mediator variables to get estimated model parameters Θ_Y and Θ_M for the outcome and mediator respectively

Step 2 Simulate model parameters by sampling J copies of Θ_Y and Θ_M from their sampling distribution (approximation based on the multivariate normal distribution with mean and variance equal to the estimated parameters and their estimated covariance matrix)

Step 3 For each $j = 1, \cdots, J$ repeat the following three steps: a) simulate the potential values of the mediator, b) simulate the potential outcomes given the simulated values of the mediator, c) compute the direct and indirect effects

Step 4 Compute summary statistics such as point estimates and confidence intervals

Key assumptions

1. Given the observed pre-treatment variables (X), the treatment assignment is independent of outcome (Y) and mediator (M)
2. The mediator is ignorable given treatment (T) and pre-treatment variables (X)

- 1) is satisfied in randomised clinical studies
- 2) means that among patients in the same treatment group and with the same pre-treatment characteristics, the mediator can be regarded as if it was randomised
- 2) is a strong assumption in randomised clinical studies
- Unobserved variables might confound the relationship between the outcome and the mediator variables even after conditioning on treatment and pre-treatment variables

Key assumptions

- Cannot be tested from observed data
- Sensitivity analyses to assess the robustness of the results against violations of the key assumptions
- Sensitive inference $\rightarrow$ slight violation of the key assumptions may lead to substantively different conclusions

Sensitivity analysis

- Based on the correlation ρ between the error for the mediation model and the error for the outcome model
- A correlation can arise if there exist omitted variables that affect both mediator and outcome variables because these omitted variables will be part of the two error terms
- Under key assumptions ρ equals zero, and nonzero values of ρ imply departures from the ignorability assumption