Doubly Robust Targeted Minimum Loss Based Estimation to Address Sampling Bias in Functional Connectivity Studies

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Motion quality control exclusion

- Motion in the scanner produces artifacts (Power et al., 2012).
- Lenient criteria: < 5 min data after removing frames with > 3 mm or $3°$ from previous frame (Fassbender et al., 2017).
- Strict criteria: mean framewise displacement $> .2$ mm or < 5 min data after excluding FD $> .25$ mm (Ciric et al., 2017).

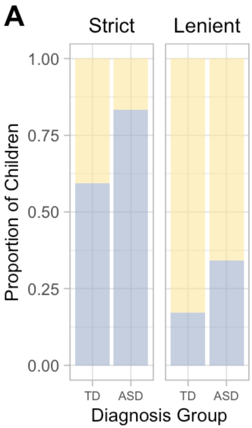


Figure: Quality control removes 30-83% of children with ASD and 12-60% of typically developing.

The problem: motion exclusion criteria in functional MRI causes sampling bias

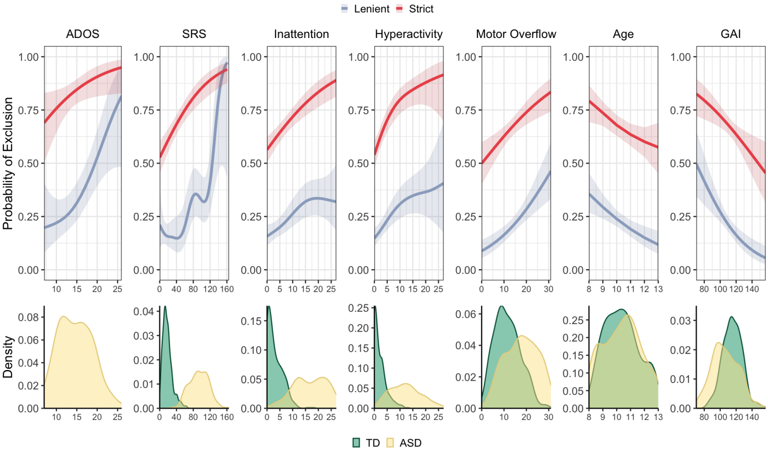


Figure: During quality control, **more severe cases of autism are excluded.**

The solution: Deconfounded group difference via doubly robust targeted mimimum loss based estimation

- $Y(1)$ is the counterfactual that a participant's scan is usable. Define a novel parameter of interest:

$$\psi^* = E^*\left\{E^*\left(Y(1)|A=1,W\right)\right|A=1\} \\ - E^*\left\{E^*\left(Y(1)|A=0,W\right)|A=0\right\}$$

- Define our target parameter:

$$\psi = E\{E(Y \mid \Delta=1, A=1, W) \mid A=1\} \\ - E\{E(Y \mid \Delta=1, A=0, W) \mid A=0\}.$$

- $\psi^* = \psi$ under assumptions:
  - (A1.1) *Conditional Randomization*: for $a = 0, 1$, $E^*\{Y(1) \mid A=a, W\} = E\{Y \mid \Delta=1, A=a, W\}$.
  - (A1.2) *Positivity*: for $a = 0,\ 1$ and all possible w, $P(\Delta=1 \mid A=a, W=w) > 0$.
  - (A1.3) *Consistency*: for all i such that $\Delta_i = 1$, $Y_i(1) = Y_i$,

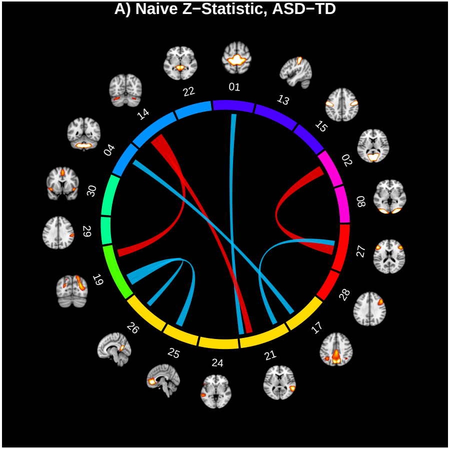
DRTMLE

- We call the target parameter ψ the **deconfounded group difference**.
- Estimate using doubly robust targeted minimum loss based estimation:
  - Propensity model predicting probability of inclusion to upweight usable data with small probabilities of inclusion.
  - Outcome model fit to usable data to predict functional connectivity in usable and unusable data.
  - Use ensemble of machine learning methods to fit the propensity and outcome models (Van Der Laan et al., 2007).
  - DRTMLE combines estimates in a manner such that mean and SEs robust to mis-specification of one of these models (Benkeser et al., 2017).

Data Analysis

- Resting-state fMRI scans from Kennedy Krieger Institute (either 5:20 or 6:45 seconds in length).
- 153 ASD children and 359 typically developing.
- Use the lenient criteria and residuals from a regression of motion and sex covariates.
- 108 ASD and 300 TD pass lenient criteria.
- SuperLearner with 10-fold CV for propensity and outcome models: `SL.earth`, `SL.glmnet`, `SL.gam`, `SL.glm`, `SL.ranger`, `SL.ridge`, `SL.step`, `SL.step.interaction`, `SL.svm`, `SL.xgboost`.
- Predictors: `Primary diagnosis`, `Head coil`, `ADHD secondary`, `Age at scan`, `Sex`, `Handedness`, `Stimulants`, `Motor overflow`, `General ability index`, `Inattention`, `Hyperactivity`, `Social responsiveness`, `Autism diagnostic observation schedule`.

Results and discussion



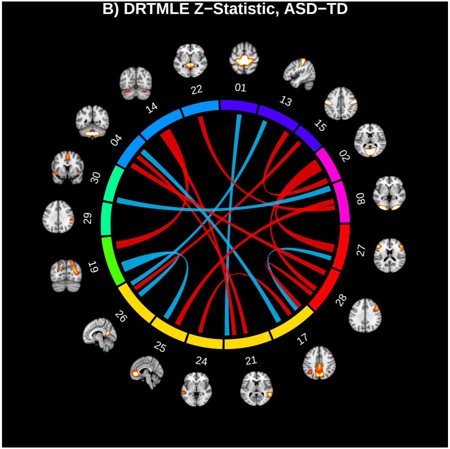


Figure: **The deconfounded group difference via DRTMLE reveals more extensive differences** between ASD and TD. Z-stats from partial correlations from the group ICA parcellation. Thresholded at $|Z| > 1.96$. Blue: ASD>TD. FDR 0.20: Naive: 2 edges, DTRMLE: 8 edges.

Discussion

- Participant exclusion due to motion quality control creates large sampling biases.
- We use DRTMLE to estimate the deconfounded group difference in a large study of autism spectrum disorder.
- More extensive differences between ASD and TD when accounting for sampling biases via DRTMLE.
- Future directions: more work on inference. Develop permutation tests.
- Examine sensitivity to model assumptions: randomization (no unmeasured confounders) and e-values (Van Der Weele and Ding, 2017).
- Thank you for watching!
- Additional info: `github.com/thebrisklab`

References I

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