

Correcting Sampling Bias in Neuroimaging Studies using Doubly Robust Nonparametric Inference

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Motion quality control causes massive data loss

- 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).

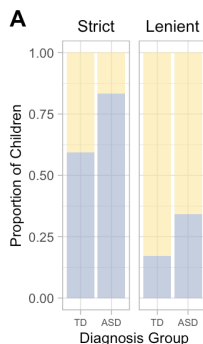


Figure: QC removes 60% and 83% of TD and ASD, respectively, under strict and 16% and 30% under lenient.

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

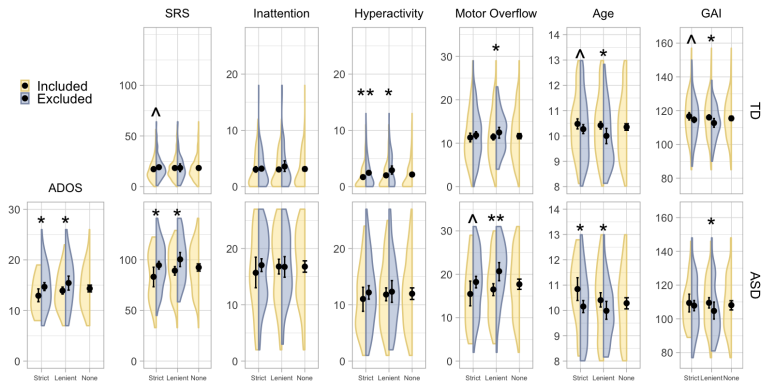


Figure: During quality control, **more severe cases of autism are excluded**. FDR-adjusted p value: ** <0.05; * <0.1; ^ <0.2.

Selection bias

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

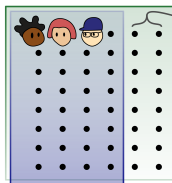
$$\begin{aligned}\psi^* &= E^*[Y(1)|A = 1] - E^*[Y(1)|A = 0] \\ &= E^* \{ E^* (Y(1)|A = 1, W) | A = 1 \} \\ &\quad - E^* \{ E^* (Y(1)|A = 0, W) | A = 0 \}\end{aligned}$$

- $\psi_{naive} = E[Y|\Delta = 1, A = 1] - E[Y|\Delta = 1, A = 0]$.
- Define bias: $\psi_{naive} \neq \psi^*$.
- Confounding bias and selection bias: concepts overlap; see ([Hernan and Robins, 2020](#)) p. 80 for detailed discussion.
- Key: lack of exchangeability between usable and unusable data.
- Bias can arise when $\Delta \leftrightarrow W$, $W \leftrightarrow Y$. Then
 $E^*[Y(1)|A = 1] \neq E[Y|\Delta = 1, A = 1]$

Graphical overview

All children

$\Delta = 0 \text{ or } 1$



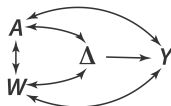
Children with usable fMRI data

$\Delta = 1$



$A | \Delta = 1 \quad W | A, \Delta = 1 \quad Y | A, W, \Delta = 1$

Problem: $E[Y | \Delta = 1, A = a] \neq E^*[Y(1) | A = a]$



① Propensity Model

estimates $P(\Delta | A, W)$



② Outcome Model

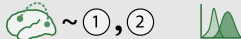
estimates $E(Y | \Delta = 1, A, W)$



predicts $Y(1) | A, W$ for $\Delta = 0$ or 1

③ DRTMLE

estimates $Y | A = a$ averaged across $W | A = a$



$E^*(Y(1) | A = a) = E[E(Y | \Delta = 1, A = a, W) | A = a]$



Target Parameter and Identifiability Assumptions

- Define our target parameter, the **debiased group difference**:

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

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

- Inverse probability weighted estimator (IPWE):
 - Fit propensity model: $P(\Delta = 1|A, W) = g(A, W)$.
 - Propensity model predicting probability of inclusion to upweight usable data with small probabilities of inclusion:

$$\hat{\psi}_{IPWE} = \mathbb{E}_{n, a_i=1} \left(\frac{\Delta_i}{\hat{g}_i} y_i \right) - \mathbb{E}_{n, a_i=0} \left(\frac{\Delta_i}{\hat{g}_i} y_i \right).$$

- G-Computation estimator (G-comp):
 - Fit outcome model:

$$\{Y|(\Delta = 1)\} = Q(A, W) + \epsilon.$$

- Predict values for both $\Delta_i = 0$ and $\Delta_i = 1$:

$$\hat{\psi}_{G-comp} = \mathbb{E}_{n, a_i=1} \hat{Q}_i - \mathbb{E}_{n, a_i=0} \hat{Q}_i.$$

Doubly robust estimators

- Doubly robust estimators combine both IPWE and G-comp.
- If either the propensity (IPWE) or the outcome (G-comp) is consistent, then the DR estimator is a consistent estimator of ψ .
- Examples include Augmented IPWE:

$$\begin{aligned}\hat{\psi}_{AIPWE} = & \hat{\psi}_{IPWE} + \mathbb{E}_{n,a_i=1} \left\{ 1 - \frac{I(\Delta_i = 1)}{\hat{g}_i} \right\} \hat{Q}_n(a_i = 1, w_i) \\ & - \mathbb{E}_{n,a_i=0} \left\{ 1 - \frac{I(\Delta_i = 1)}{\hat{g}_i} \right\} \hat{Q}_n(a_i = 0, w_i).\end{aligned}$$

- Another estimator: $\hat{\psi}_{TMLE}$: targeted minimum loss based estimation (TMLE), can improve finite sample performance.

Doubly robust targeted minimum loss based estimation

- Use an ensemble of machine learning methods ([Van Der Laan et al., 2007](#)): \hat{g} and \hat{Q} using SuperLearner with 10-fold CV:
SL.earth, SL.glmnet, SL.gam, SL.glm, SL.ranger,
SL.ridge, SL.step, SL.step.interaction, SL.svm,
SL.xgboost.
- Double robustness of AIPWE and TMLE does not extend to their limiting normal distribution if adaptive estimators are used.
- [Benkeser et al. \(2017\)](#); [Van Der Laan \(2014\)](#) developed doubly robust targeted minimum loss-based estimator: if *at least* one of the two regressions is consistently estimated, both $\hat{\psi}$ and its *SE* are consistently estimated.
 - 1 Fit propensity model.
 - 2 Fit outcome model.
 - 3 Apply DRTMLE to propensities and predicted outcomes. Involves a special iterative logistic regression.

- Resting-state fMRI scans from Kennedy Krieger Institute (either 5:20 or 6:45 seconds in length) collected from 2007-2020.
- 137 ASD children without an intellectual disability and 348 typically developing.
- Use the lenient criteria because we don't have enough data left after strict.
- 96 ASD and 292 TD pass lenient criteria.

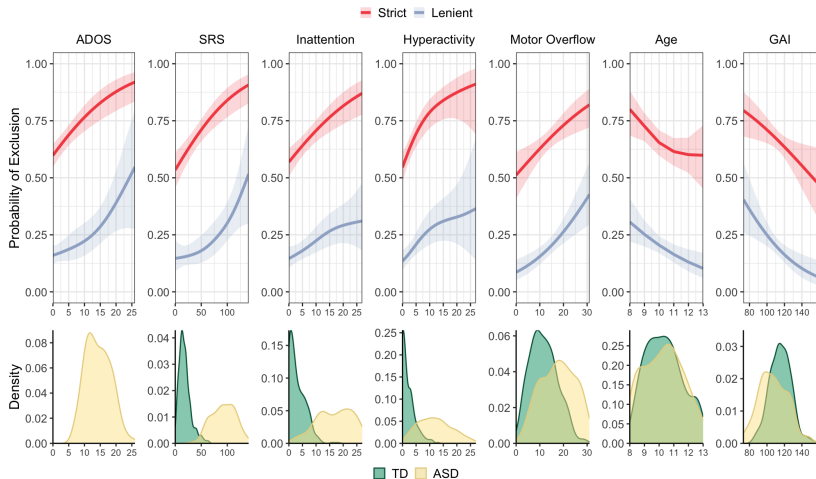


Figure: Behavioral variables are related to the probability that data are excluded.

- Group ICA with 30 components, extract subject-specific time courses, calculate partial correlations reproducing pipeline from [Lombardo et al. \(2019\)](#).
- Retained 18 signal components, resulting in 153 edges.
- For each edge, fit a linear model: Fisher transformed partial correlation \sim diagnosis + motion variables + sex + race + SES).
- Use adjusted residuals: Add diagnosis effect back into residuals.
- Naive approach with t-statistic then corresponds to approach in [Di Martino et al. 2013](#)).

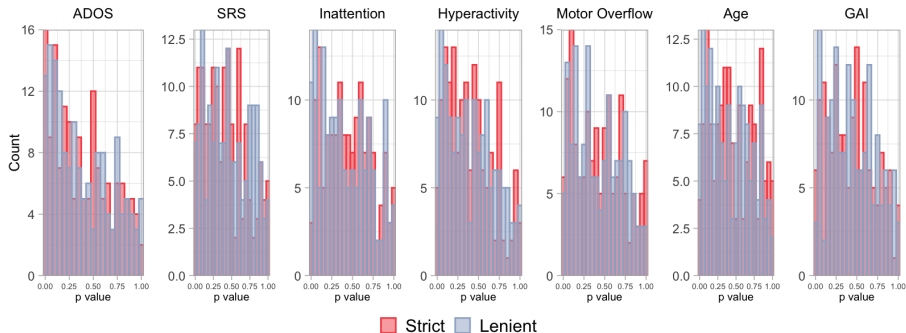


Figure: P values for generalized additive models of the relationship between edgewise functional connectivity (153 edges) in participants with usable rs-fMRI data. Blue: lenient criteria. Red: strict criteria.

Data Analysis

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.

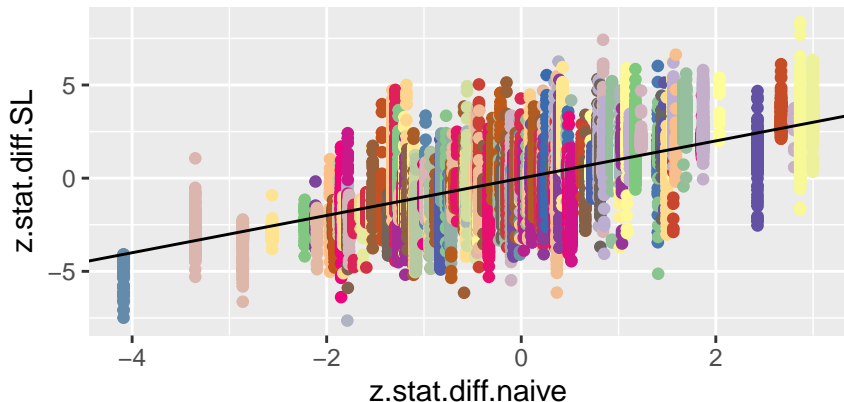
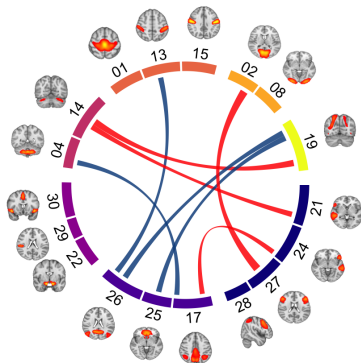
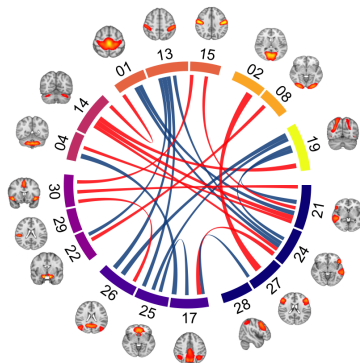


Figure: Used average z-statistic from 400 seeds.

Results



(a) Naïve



(b) DRTMLE

Figure: Z-stats of ASD-TD difference in partial correlations. Thresholded at FDR=0.20. Blue: ASD>TD. Naïve (left): 8 edges, DRTMLE (right): 25 edges. Navy nodes: control. Blue violet: default mode. Purple: salience/ventral attention. Magenta: pontomedullary/cerebellar. Coral: somatomotor. Orange: visual. Yellow: dorsal attention.

Results, cont.

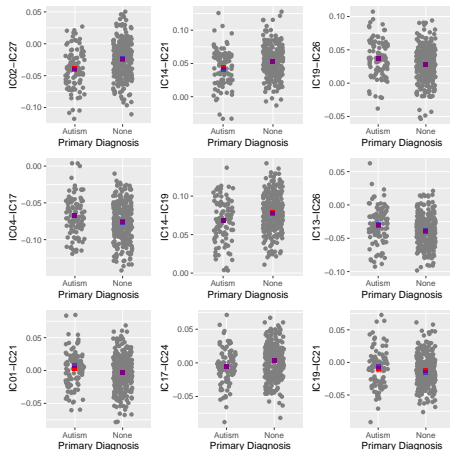


Figure: The changes in the means were small, but this drove the large differences in significance. Red: Naive. Transparent blue: DRTMLE.

Discussion and limitations

- Participant exclusion due to motion quality control creates sampling biases.
- We use DRTMLE to estimate the debiased group difference in a large study of autism spectrum disorder.
- More extensive differences between ASD and TD using DRTMLE.
- Limitations: only addressed missing outcome. Dataset also missing covariate values.
- Limitations: possible issues with smaller sample sizes. Develop permutation tests.
- Additional info: github.com/thebrisklab
- Post doc opportunity available – email me for information.

Acknowledgments

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