Correcting Sampling Bias in Neuroimaging Studies using Doubly Robust Nonparametric Inference

Benjamin Risk

benjamin.risk@emory.edu

Joint work

Nebel, M.B.[1,2], Lidstone, D.E.[1,2], Wang, L.[4], Benkeser, D.[4], Mostofsky, S.H.[1,2,3], and Risk, B.B.[4] (2022). Accounting for motion in fMRI: What part of the spectrum are we characterizing in autism spectrum disorder? *Neuroimage.*

[1] Center for Neurodevelopmental and Imaging Research, Kennedy Krieger Institute
[2] Department of Neurology, Johns Hopkins University School of Medicine
[3] Department of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine
[4] Department of Biostatistics & Bioinformatics, Rollins School of Public Health, Emory University

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).

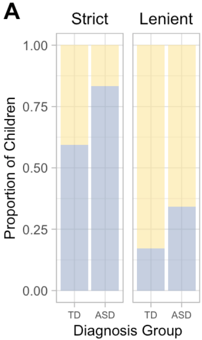


Figure: QC removes 60% and 83% of TD and ASD, respectively, under strict and 16% and 30% under lenient.

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

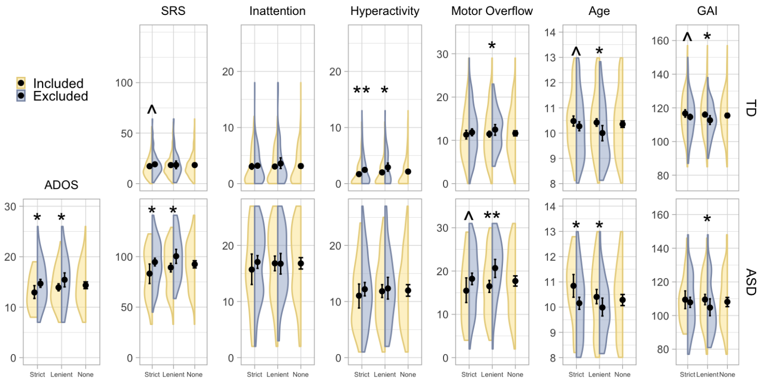


Figure: During quality control, **more severe cases of autism are excluded.** FDR-adjusted p value: ** <0.05; *<0.1; ^<0.2.

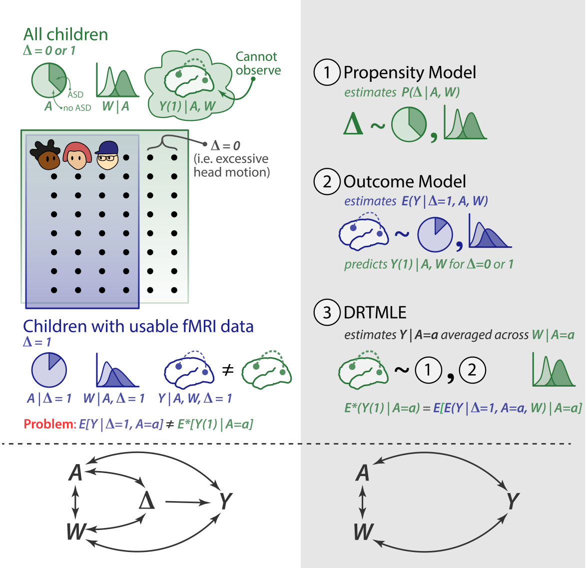
Selection bias

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

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

- $\psi_{naive} = E[Y|\Delta=1, A=1] - E[Y|\Delta=1, A=0]$.
- 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



Target Parameter and Identifiability Assumptions

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

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

- 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 $\Delta_i = 1$, $Y_i(1) = Y_i$.

IPWE and G-computation

- Inverse probability weighted estimator (IPWE):
  - Fit propensity model: $P(\Delta = 1|A, W) = g(A, W)$.
  - E.g., use an ensemble of machine learning methods (Van Der Laan et al., 2007).
  - 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:

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

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

Doubly robust targeted minimum loss based estimation

- Estimate g and 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.

Data Analysis

- 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.

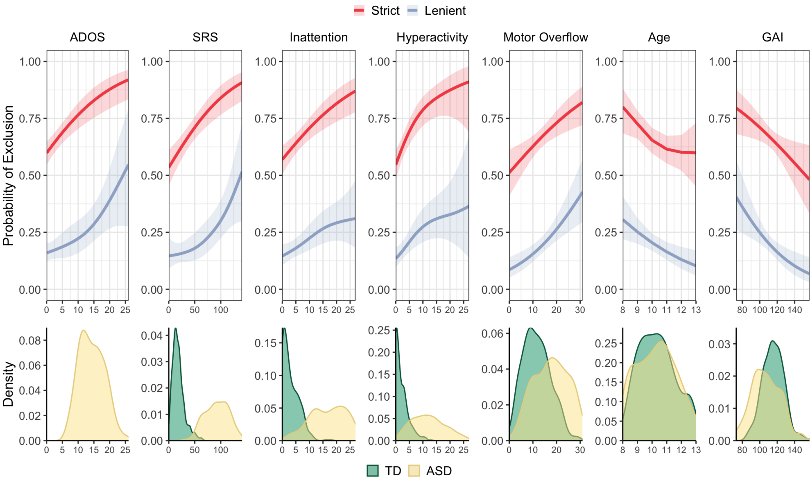


Figure: Behavioral variables are related to the probability that data are excluded.

Data Analysis: Functional Connectivity

- 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).

$W \leftrightarrow Y$

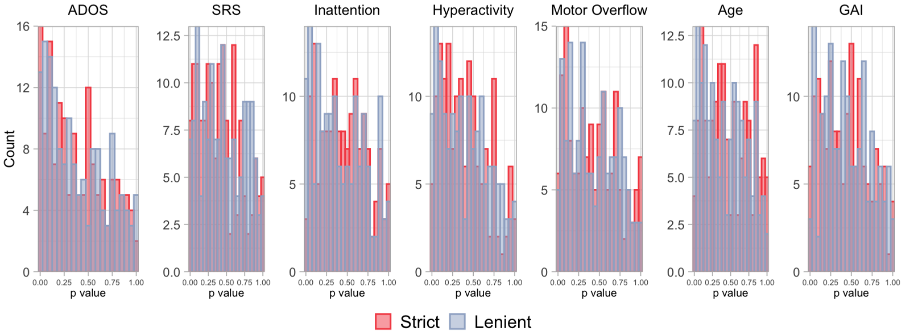


Figure: P values for generalized additive models of the relationship between edgewise functional connectivity (153 edges) in participants with usable rs-fMRI data. Blue: lenient criteria. Red: strict criteria.

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`.

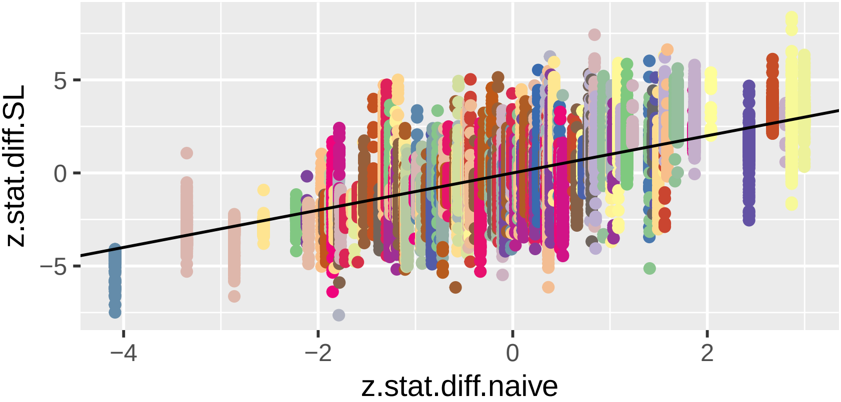
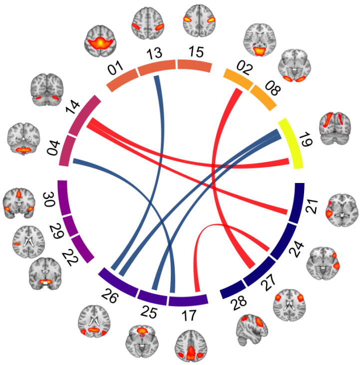
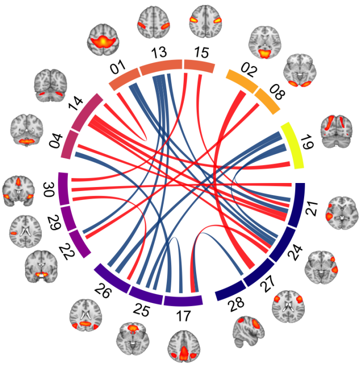


Figure: Used average z-statistic from 400 seeds.

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.

Results, cont.

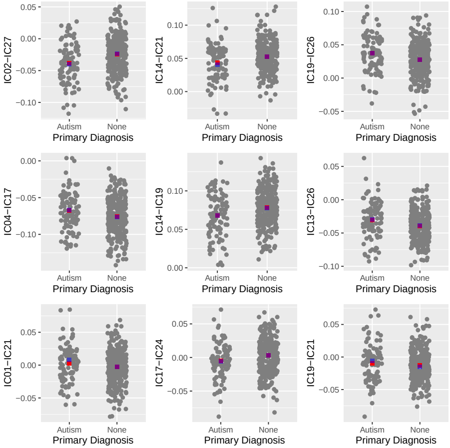


Figure: The changes in the means were small, but this drove the large differences in significance. Red: Naive. Transparent blue: DRTMLE.

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

- Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under award number R01MH129855 to BBR. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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