Voxel-wise and Cluster-based Heritability Inference for fMRI Data

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Voxel-wise Heritability Estimation

- Existing Methods
  - Falconer's Method: $\hat{h}^2_F = 2 \times (r_{MZ} - r_{DZ})$

    `Pros` Simple, fast and easy to use

    `Cons` Poor estimation accuracy
  - SEM Method Implemented in Mx/OpenMx

    `Pros` Has better estimation properties

    `Cons` Time-consuming, can have convergence problems, and requires R $\longleftrightarrow$ Nifti conversion
- Our LR-SD Method
  - Based on squared differences of paired observations (Grimes and Harvey, 1980)
  - Fast, no iterations, no convergence issues

Outline

- Previous work
  - Demonstrated validity and excellent bias-variance properties
  - As good as or better than OpenMx
- Current work
  - Power comparison of voxel-wise and cluster-based heritability inference methods
  - We demonstrate our method on a real dataset
    - Spatial statistics: cluster size, cluster mass
    - Non-parametric p-values: uncorrected, corrected

Brief Method Description

- Linear Regression with Squared Differences (LR-SD)
  - Relate squared differences of data pairs to variance components A,C,E:

$$\begin{aligned}
\mathbb{E}\left[(MZ_1 - MZ_2)^2\right] &= 2E \\
\mathbb{E}\left[(DZ_1 - DZ_2)^2\right] &= A + 2E \\
\mathbb{E}\left[(I_1 - I_2)^2\right] &= 2A + 2C + 2E
\end{aligned}$$

  - Modification of Grimes and Harvey's method: $n(n-1)/2$ obs. $\rightarrow (n_{MZ} + n_{DZ})/2$ obs. (50,721 vs. 141)
- Permutation Inference
  - Under H0: $h^2 = 0$, MZ and DZ twin pairs are exchangeable
  - $\binom{(n_{MZ}+n_{DZ})/2}{n_{MZ}/2}$ possible permutations
  - Calculate FWE-corrected P-values from maximum distributions

Simulation Setting

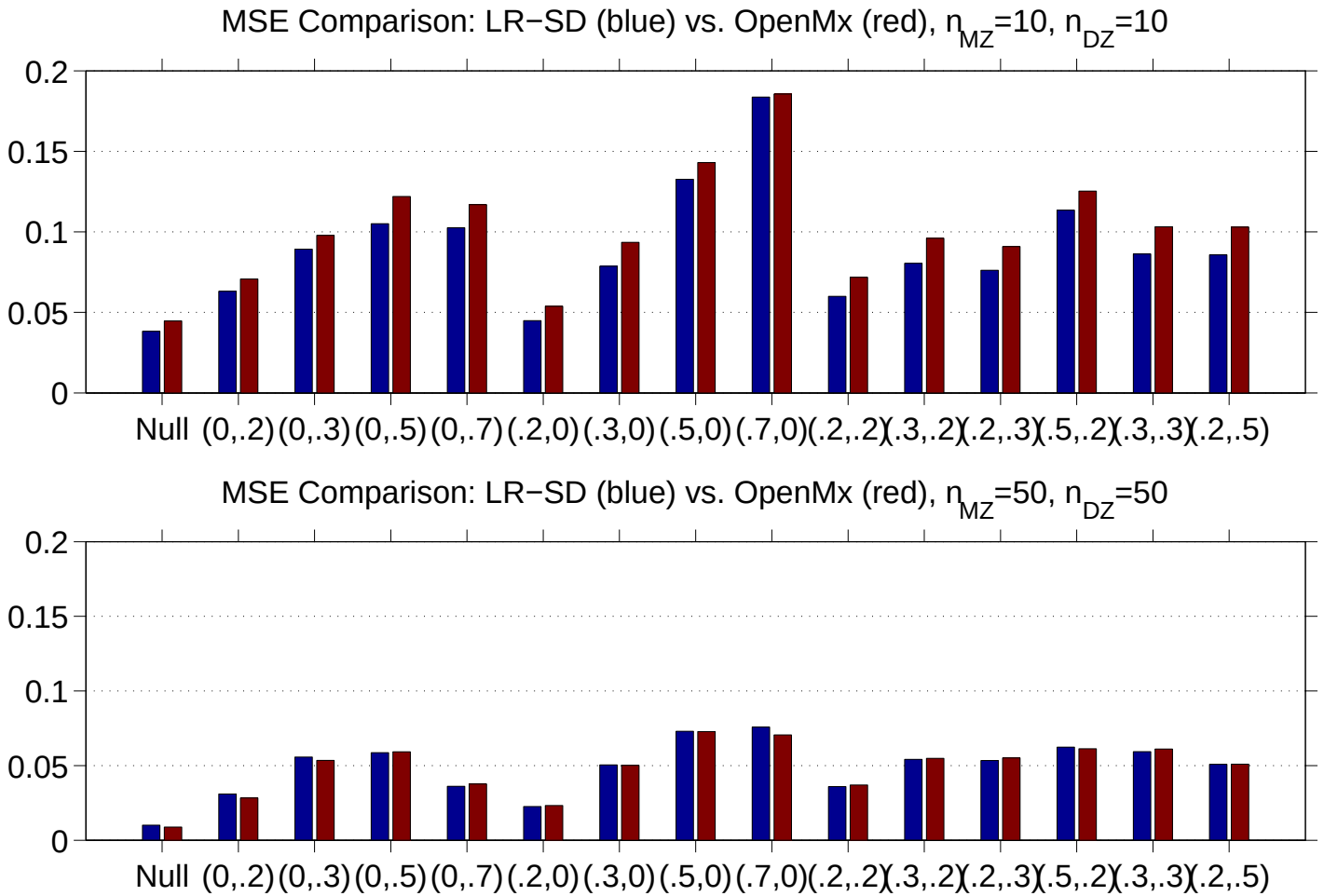
- 10,000 simulations
- Sample sizes: 10+10, 50+50
- 15 ACE parameter settings:

	E	CE				AE			
A	0	0	0	0	0	0.2	0.3	0.5	0.7
C	0	0.2	0.3	0.5	0.7	0	0	0	0
E	1	0.8	0.7	0.5	0.3	0.8	0.7	0.5	0.3

	ACE					
A	0.2	0.3	0.2	0.5	0.3	0.2
C	0.2	0.2	0.3	0.2	0.3	0.5
E	0.6	0.5	0.5	0.3	0.3	0.3

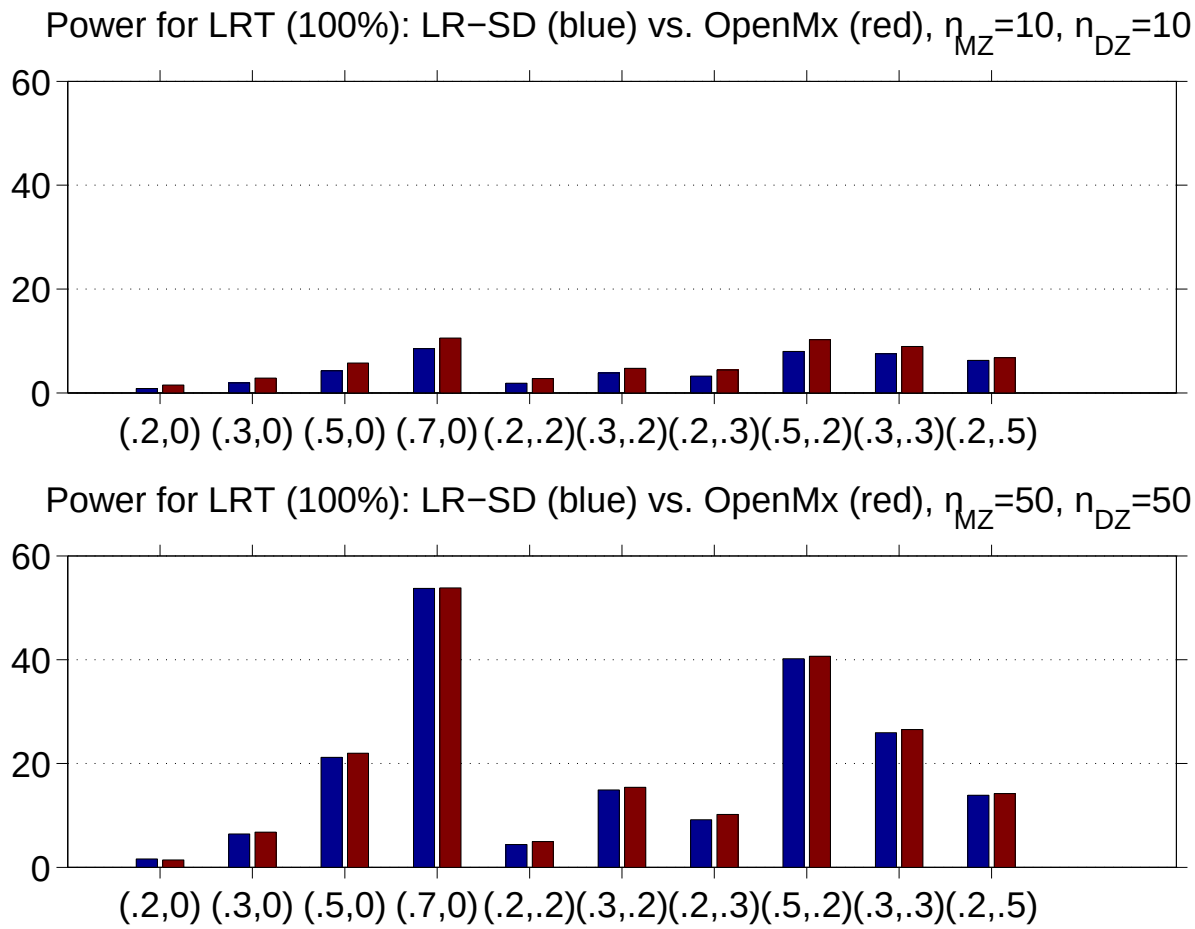
Simulations: MSE Comparison

Mean squared error comparison between LR-SD and OpenMx



Simulations: Power Comparison

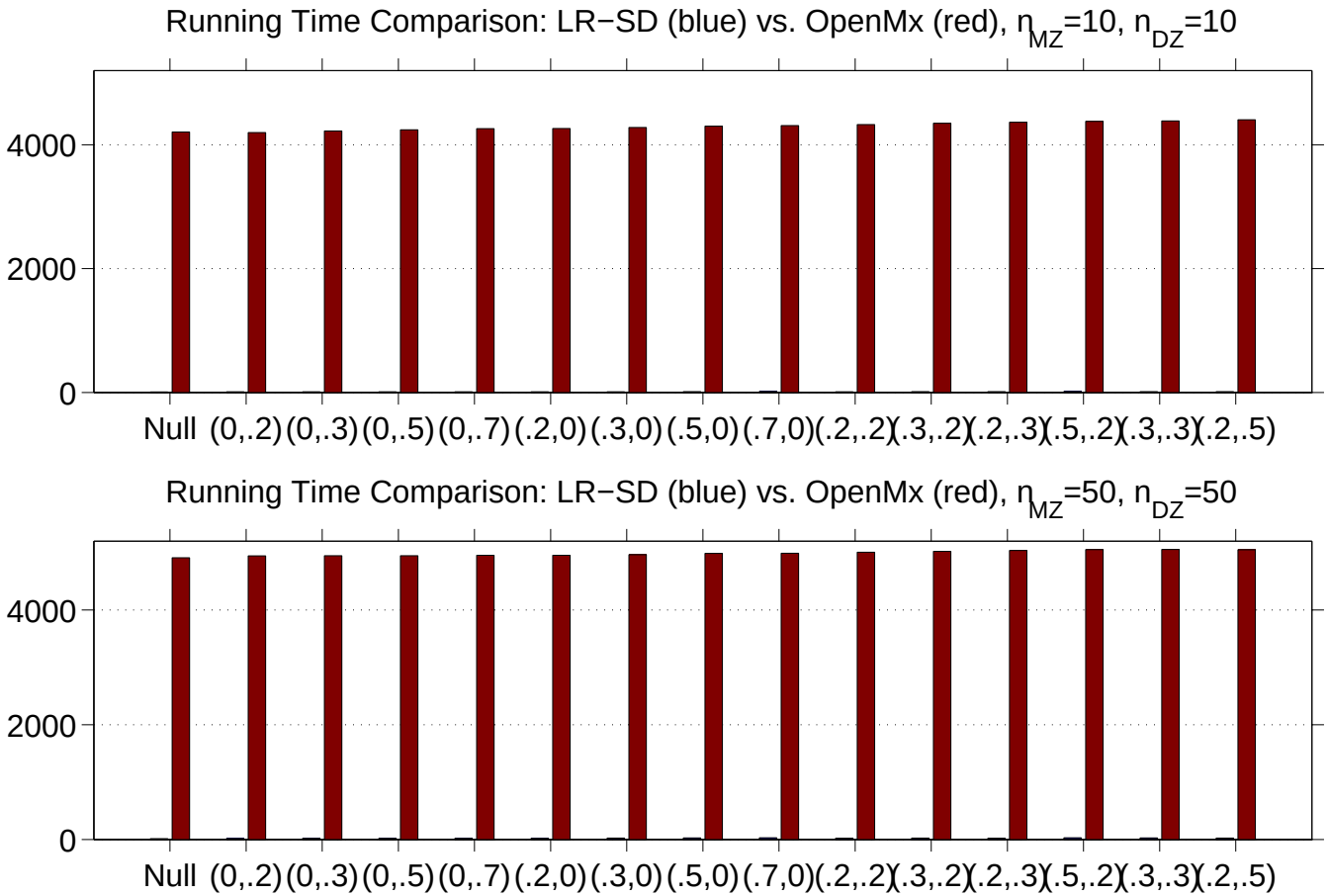
Statistical power comparison between LR-SD and OpenMx



Simulations: Running Time Comparison

Overall running time comparison between LR-SD and OpenMx

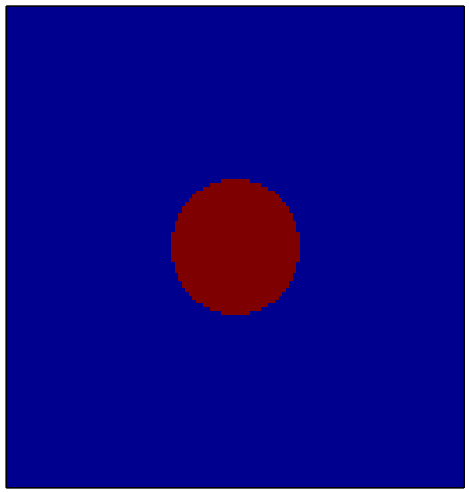
→ On average, our LR-SD is around 300 times faster than OpenMx



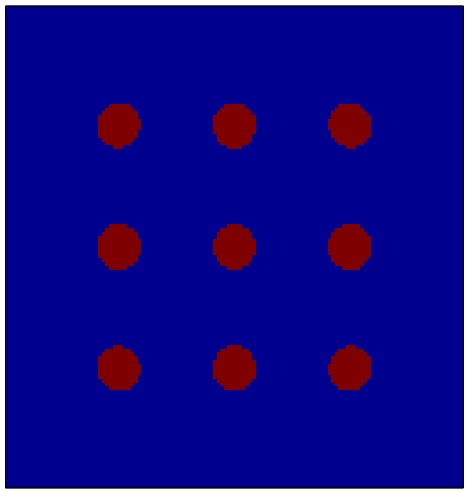
Power Simulations

- 1,000 simulations
- Sample sizes: 10+10, 50+50
- ACE parameter settings: [0.3 0 0.7], [0.5 0.2 0.3], [0.7 0 0.3]
- Signal shapes:

(1) Focal signal

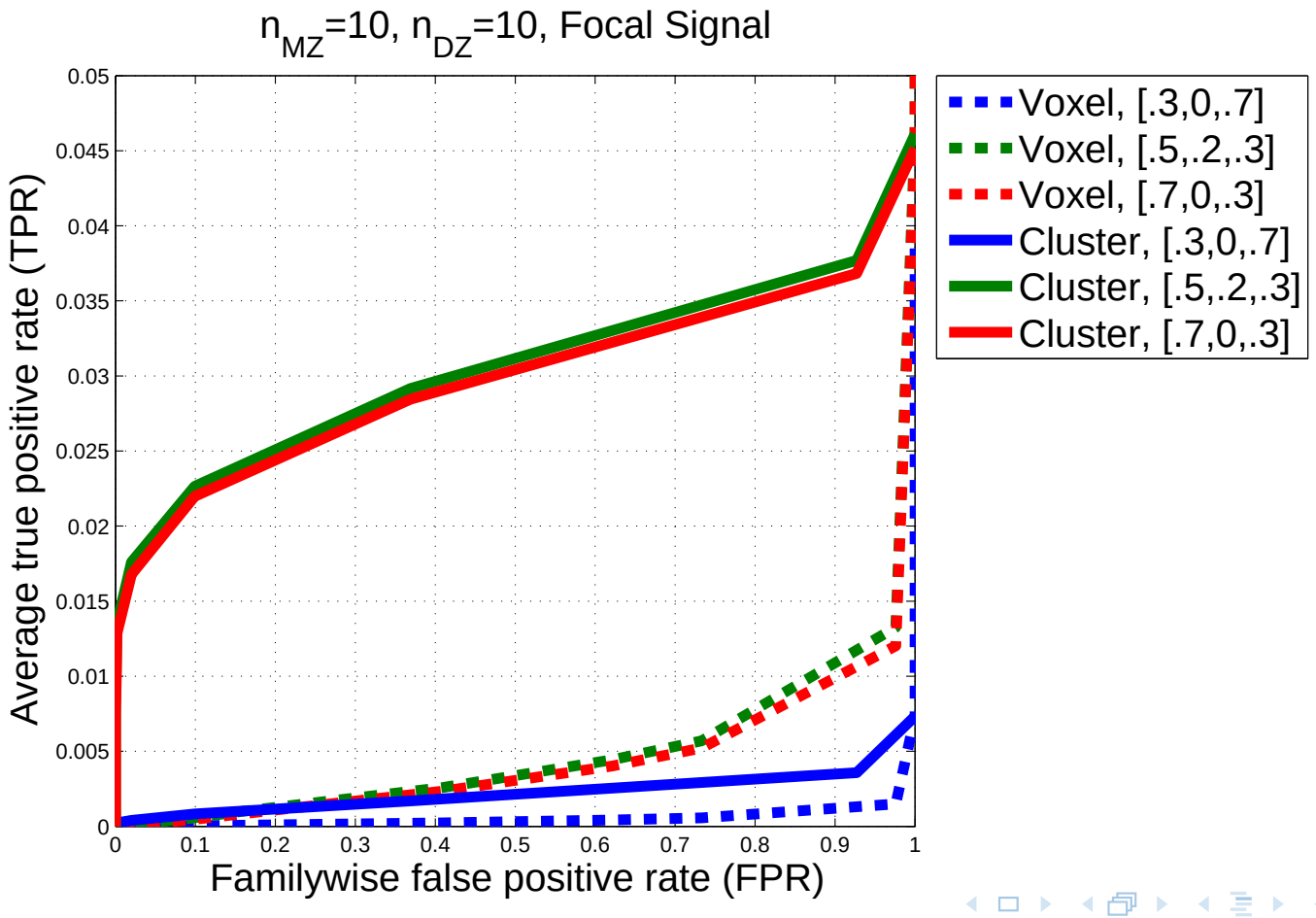


(2) Distributed signal



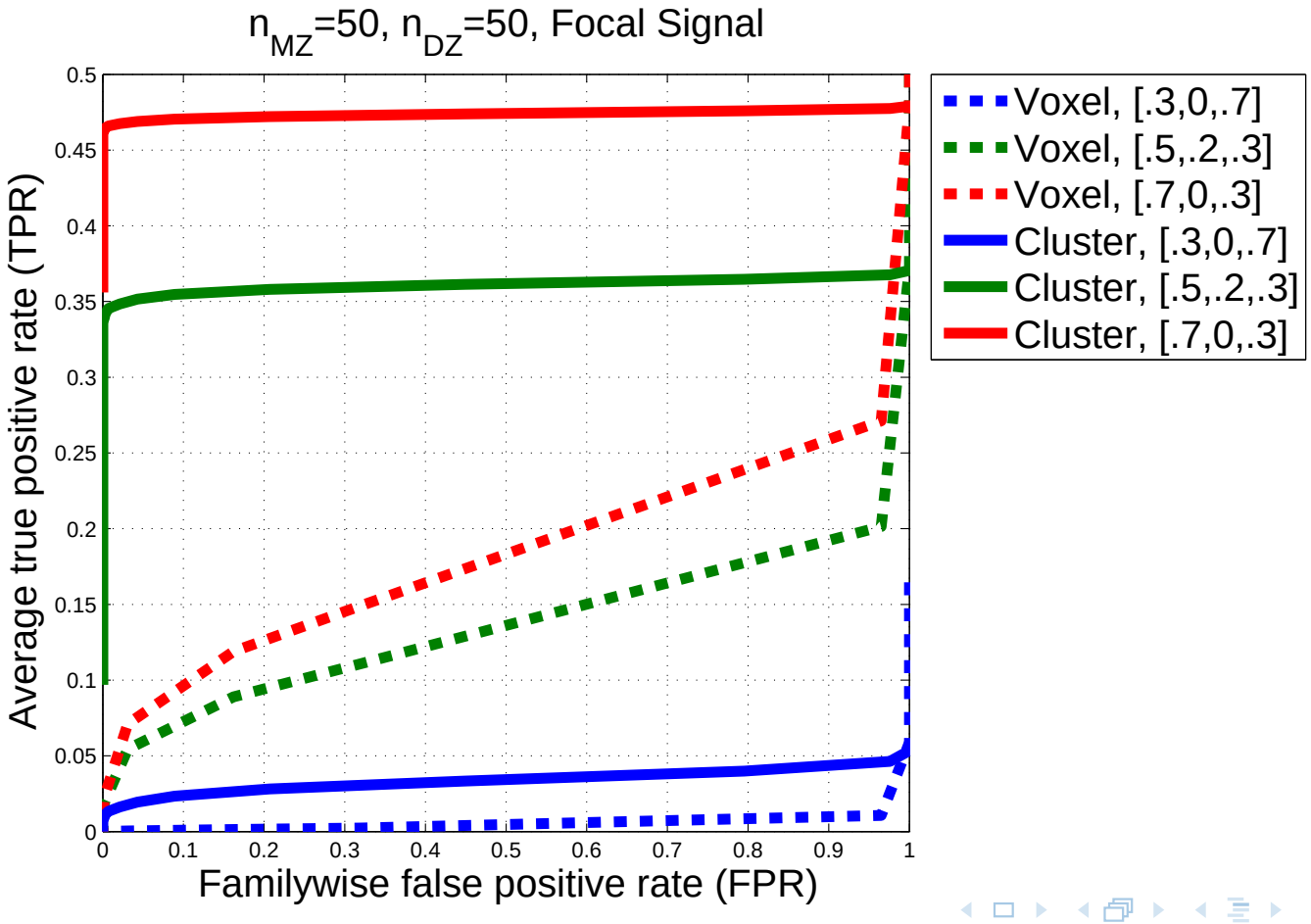
ROC Curve Comparison

ROC curves of voxel-wise and cluster-based methods for different ACE settings for focal signal, sample size: 10+10



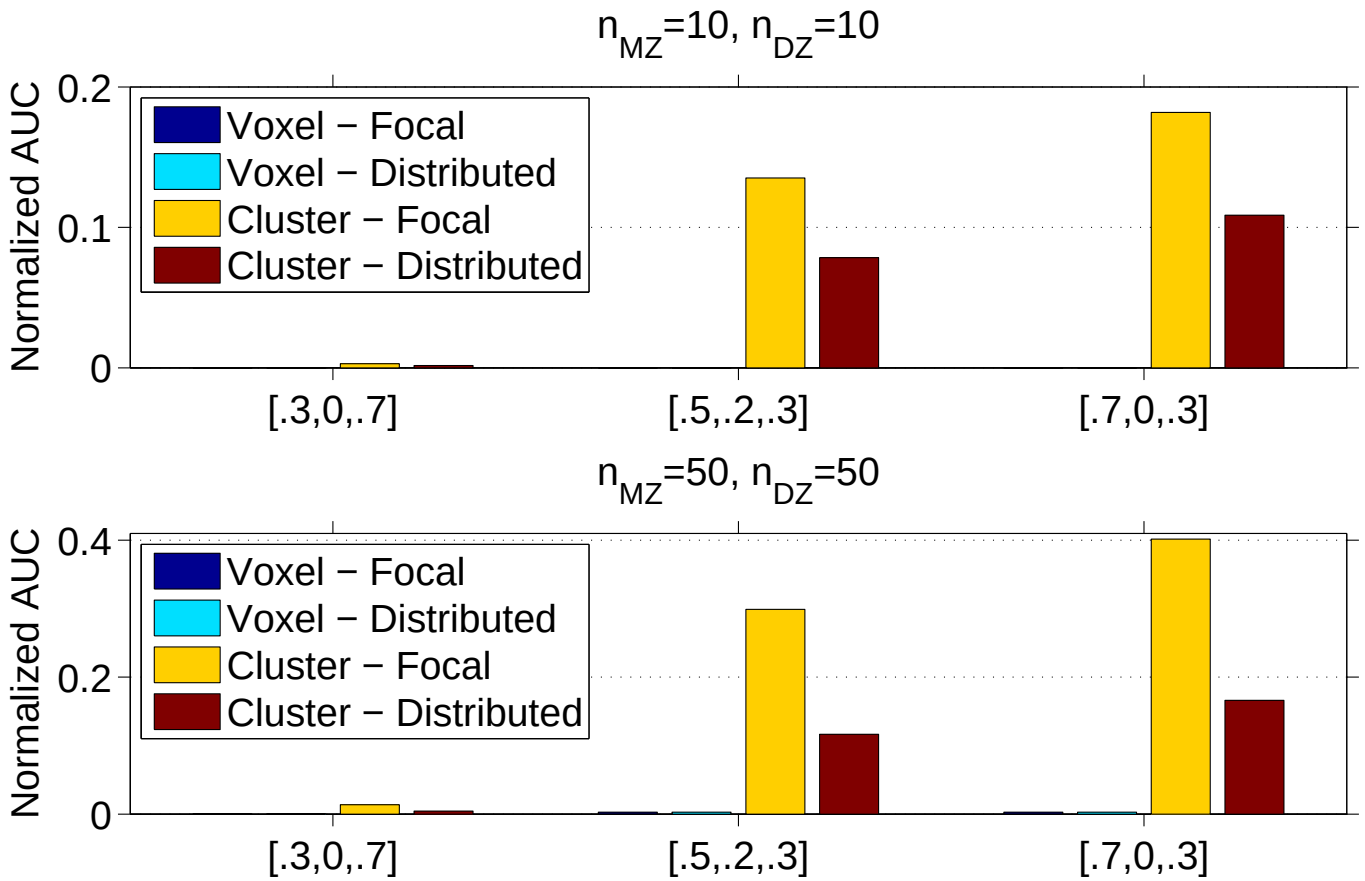
ROC Curve Comparison

ROC curves of voxel-wise and cluster-based methods for different ACE settings for focal signal, sample size: 50+50



Area under the ROC Curves

Normalized area under the ROC curves ($20 \times$ AUC) for FPR=0:0.05 for different ACE settings



Real Data Acquisition

An fMRI heritability study of working memory brain activation by Blokland et al., 2011

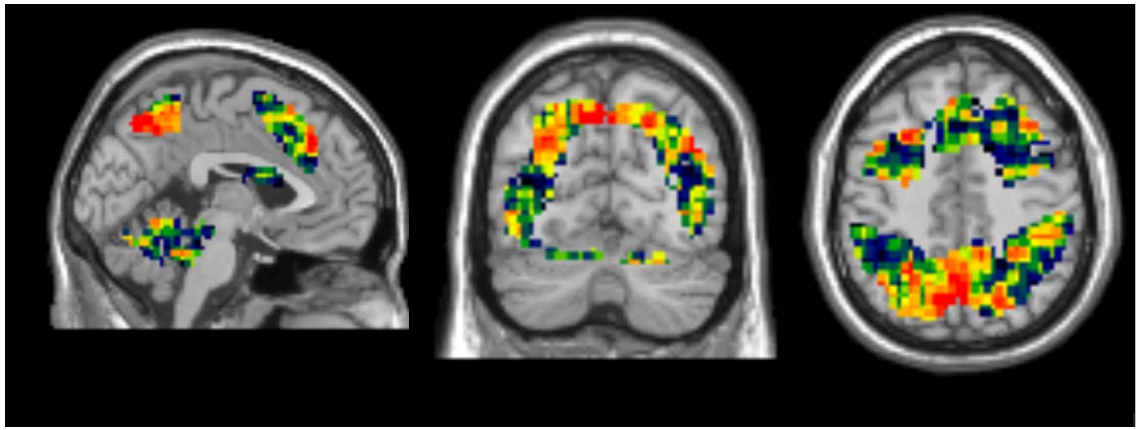
- n = 319 young and healthy participants
- 75 MZ twin pairs, 66 DZ twin pairs and 37 singletons
- Age range: 20 - 28 (mean $\pm$ SD: 23.6 $\pm$ 1.8 years)
- 199 females and 120 males
- Performed an n-back (0- and 2-back) working memory task
- Task-related fMRI BOLD signals were acquired
- Age, gender and 2-back performance accuracy were included as the covariates

Running Time

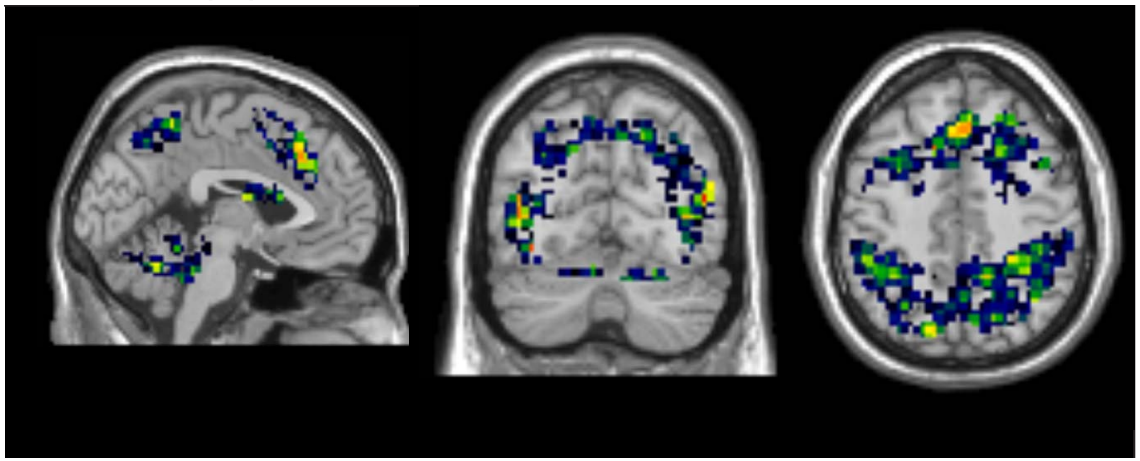
- On a MacPro with 12 physical CPUs (24 logical CPUs), using the system at full capacity
- Only areas of expected activation were included in the mask
- Totally 14,627 in-mask voxels
- 1,000 permutations, 10 parallelized jobs, each with 100 permutations
- Running time for one permutation
  - LR-SD: 6 mins
  - Mx: around 2 days (= 2880 mins)
- Running time for 10 parallelized jobs
  - LR-SD: 15.5 hours

Twin Correlations

(1) MZ twin correlation

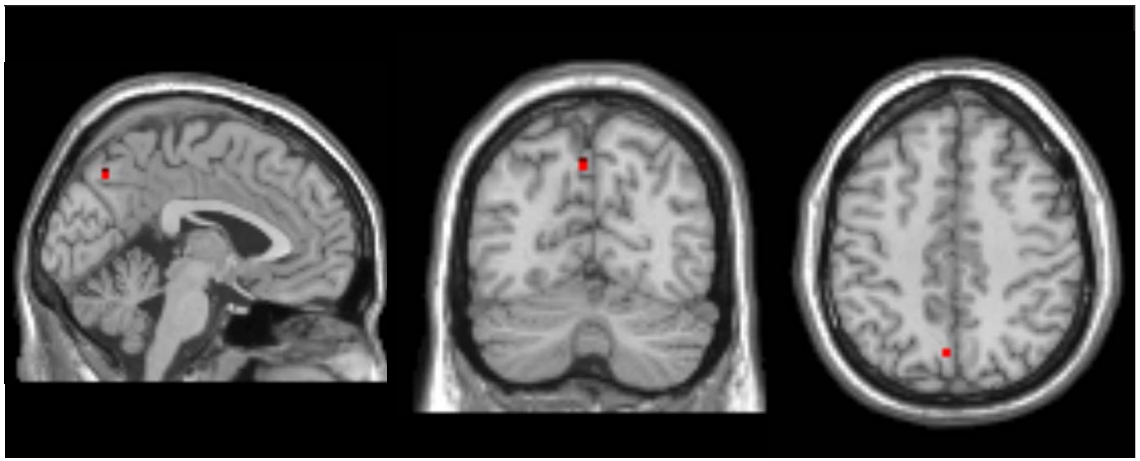


(2) DZ twin correlation

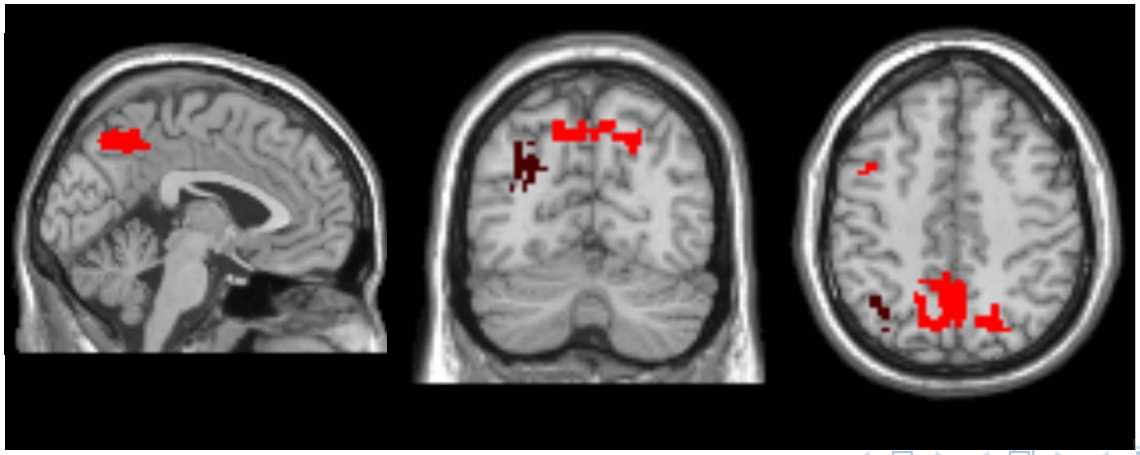


FWE P-value Images of Significance

(1) Voxel-wise significance image



(2) Cluster-based significance image



Voxel-wise vs. Cluster-based Methods

- Voxel-wise Method
  - Construct empirical distribution of maximum test statistic
  - FWE P-value = 0.006 for voxel
  - 3 significant voxels
- Cluster-based Method
  - Construct empirical distributions of maximum suprathreshold cluster size and cluster mass
  - FWE P-value = 0.003 for cluster size
  - FWE P-value = 0.002 for cluster mass
  - 3 significant clusters (127, 201, 210)

Conclusions

1. We have developed a fast, accurate, and non-iterative heritability inference method, which makes permutation feasible
2. Our LR-SD method is faster than SEM method in Mx/OpenMx with comparable power and accuracy
3. For equivalent false positive rates, cluster-based method gives higher sensitivity, and thus more statistical power
4. Demonstrate the need for permutation inference to take advantage of cluster statistics

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