APACE - Accelerated Permutation Inference for ACE models

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Introduction

- Matlab-based tool, specially designed for heritability analysis of neuroimaging data of twins

- Non-iterative linear regression-based estimation method, a variant of Haseman-Elston regression

- Use permutation test to correct for family-wise error rate

- Allow the use of spatial and summary statistics

Background

- ACE decomposition: $\sigma^2 = A + C + E$

- Heritability: $h^2 = A/(A+C+E)$

- LR-SqD: linear regression with squared twin-pair difference

$$\mathbb{E}\left[(MZ_1 - MZ_2)^2\right] = \qquad\qquad 2E$$

$$\mathbb{E}\left[(DZ_1 - DZ_2)^2\right] = A + \qquad 2E$$

$$\mathbb{E}\left[(I_1 - I_2)^2\right] = 2A + 2C + 2E$$

- Use NNLS to estimate A,C,E and heritability

Optional Inference Approaches

Voxel-wise inference

Cluster-based inference

Summary measure inference

Aggregate heritability inference

Bootstrapping CI's

Permutation-based p-values

Inputs

- Create a structure array **ACEfit_Par** with Required fields:
  - **.Model –** model ACE or AE
  - **.P_nm –** specify input data, allowing different file formats
  - **.InfMx –** kinship information file
  - **.ResDir –** path to result folder
- Can use default values when optional fields are empty
- Save **ACEfit_Par** to a mat file

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- Ca

- Sa

```
1. String, the name of a text file of filepaths to nifti OR cifti
   images, one filepath per row. Each image file consists of all of
   the data for that subject.

2. Cell array, one element per subject, where each element is a
   string, a file path to a nifti OR cifti image. Each image file
   consists of all the data for that subject.

3. Cell array of _length_ _1_, where the single element is a string,
   the filepath to a  multi-subject nifti OR cifti image
   (e.g. {'AllMySubjects.nii'} or {'AllMySubjects.dtseries.nii'). For
   either, the final dimension is equal to the number of sujbects. For
   example, for 120 subjects, it could be a 2D image, 3000 x 120, or a
   3D image, 3000 x 2 x 120, or a 4D image, 91 x 109 x 91 x 120.

4. A real matrix variable, where the final dimension is equal to the
   number of subjects.
```

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```
.../Subj1/con_0001.img
.../Subj2/con_0001.img
.../Subj3/con_0001.img
.../Subj4/con_0001.img
.../Subj5/con_0001.img
.../Subj6/con_0001.img
```

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  -

n	MotherID	FatherID	Zygosity
1	1	1	MZ
2	1	1	MZ
3	2	2	NotMZ
4	2	2	NotMZ
5	3	3	NotTwin
6	4	4	NotTwin

- Ca

- Sa

Inputs ➡ README_APACE_intro.pdf

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  - **.P_nm** **–** specify input data, allowing different file formats

  - **.InfMx** **–** kinship information file

  - **.ResDir –** path to result folder

- Can use default values when optional fields are empty

- Save **ACEfit_Par** to a mat file

Outputs ➡ README_APACE_outputs.pdf

Outputs from the **ACEfit** function of APACE software for the **ACE** model

| Filename	Description	Comments/Caveats
Basic summaries		
Stdev.nii	Phenotypic standard deviation	Computed and saved if image-wise inference is made.
Heritability		
h2_dist.pdf	Cumulative distribution of all in-mask h^2	
h2_hist.pdf	Histogram of positive in-mask h^2	Percentage of positive h^2 is provided.
ACE_A_h2.nii	Narrow sense heritability, h^2	Computed and saved if image-wise inference is made.
ACE_A_LRT.nii	Likelihood ratio test (LRT) statistic for testing H_0: h^2=0	Basis for all thresholding procedures. Computed and saved if image-wise inference is made.
ACE_A_LRT_vox_Pasym.nii	$-\log_{10}$(P-value) for testing H_0: h^2=0 using large sample parametric null distribution	Not trustworthy except for very large samples. Computed and saved if image-wise inference is made.

Outputs

Additional outputs from permutation inference of APACE software for the **ACE** model

Filename	Description	Comments/Caveats
Heritability		
`H0dist_mean.pdf`	Null distribution of mean of all in-mask h^2	Permutation-based p-value is displayed in plot title.
`H0dist_wh2.pdf`	Null distribution of variance-weighted average of all in-mask h^2	Permutation-based p-value is displayed in plot title.
`H0dist_median.pdf`	Null distribution of median (Q2) of all in-mask h^2	Permutation-based p-value is displayed in plot title.
`H0dist_q3.pdf`	Null distribution of the third quartile (Q3) of all in-mask h^2	Permutation-based p-value is displayed in plot title.
`H0dist_mGTmedian.pdf`	Null distribution of mean of in-mask $h^2 \geq Q2(h^2)$	Permutation-based p-value is displayed in plot title.
`H0dist_mGTq3.pdf`	Null distribution of mean of in-mask $h^2 \geq Q3(h^2)$	Permutation-based p-value is displayed in plot title.
`Pvals_h2.mat`	Permutation-based p-values for summary statistics	Heritability summary measures include mean, variance-weighted average, Q2, Q3, mean of $h^2 \geq Q2(h^2)$, and mean of $h^2 \geq Q3(h^2)$.
`H0dist_test_statistic.pdf`	Null distribution of maximum LRT statistic	Permutation-based p-value is displayed in plot title. Only produced if

FWE-corrected P-value Image
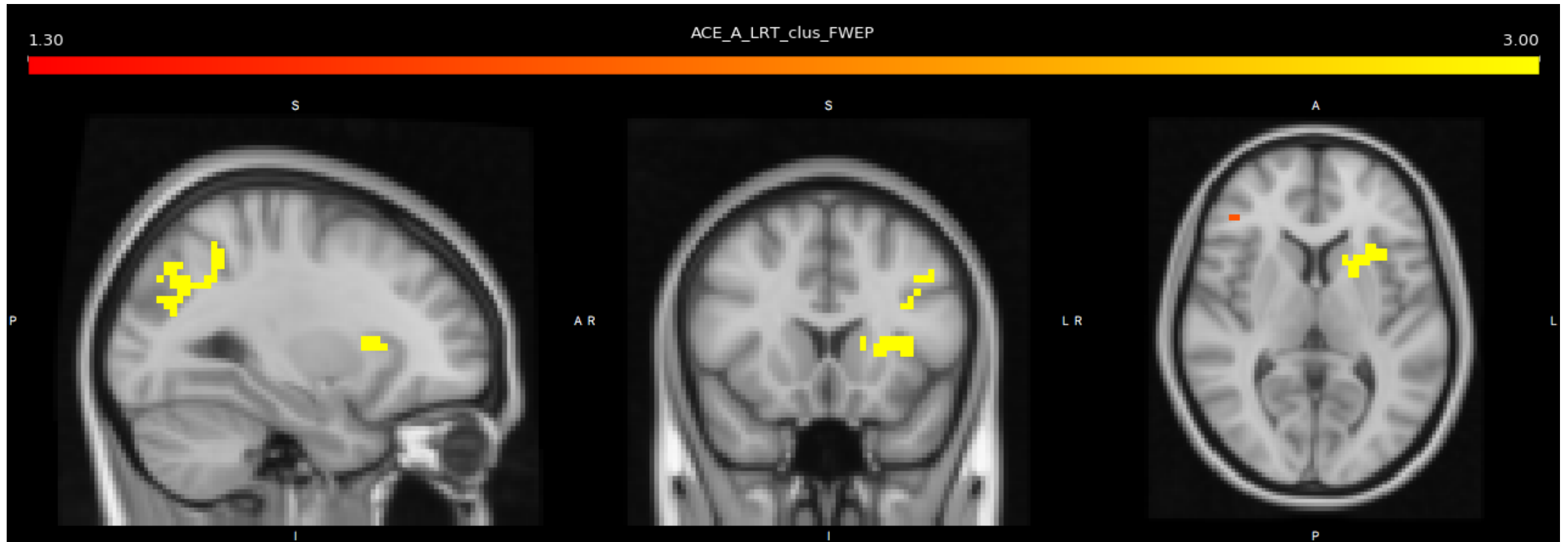
Heritability Estimates
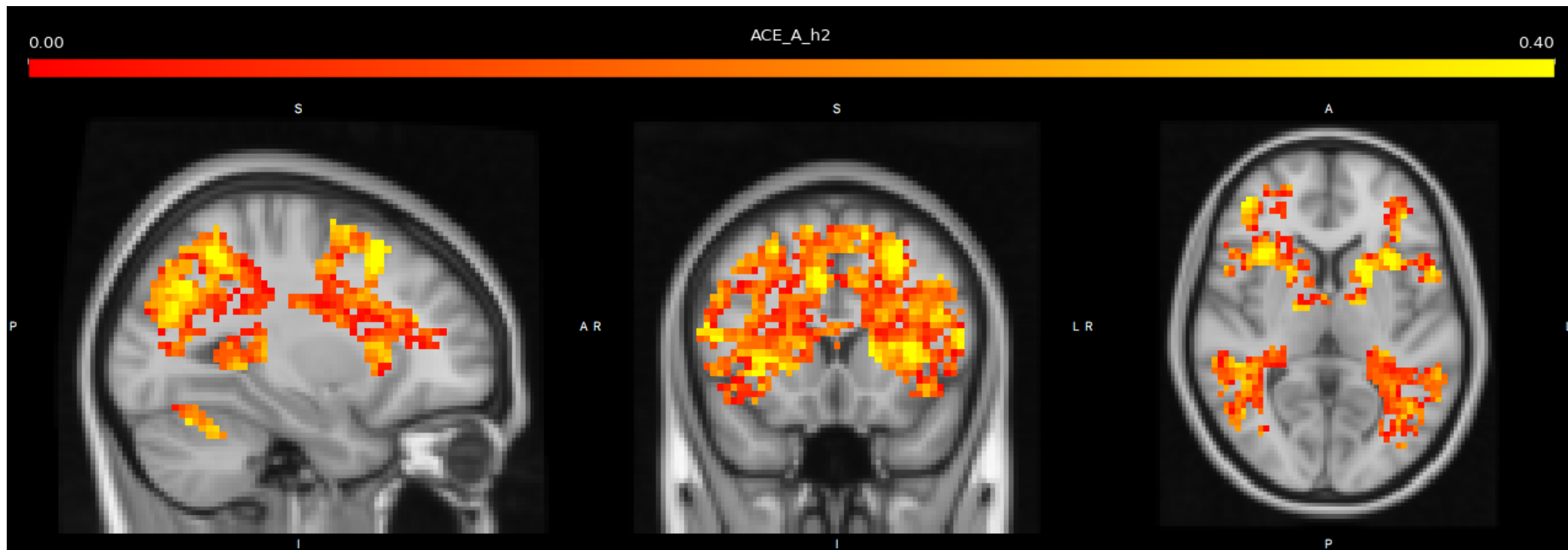
Result Summary

	Heritability h^2 (aka a^2)			Common Env. c^2		
	Estimate	95%CI	P-val	Estimate	95%CI	P-val
Mean	0.433	(0.207 , 0.607)	0.003	0.004	(0.000 , 0.160)	.
VarWtMean	0.417	(0.199 , 0.618)	0.003	0.002	(0.000 , 0.145)	.
AgHe	0.250	(−0.202 , 0.666)	0.114	.	(. , .)	.
Median Q2	0.428	(0.192 , 0.605)	0.002	0.000	(0.000 , 0.311)	.
Q3	0.526	(0.315 , 0.698)	0.006	0.000	(0.000 , 0.503)	.
Mean(>=Q2)	0.534	(0.317 , 0.699)	0.009	0.137	(0.000 , 0.385)	.
Mean(>=Q3)	0.594	(0.366 , 0.756)	0.023	0.137	(0.000 , 0.538)	.
MaxLRT	6.336	(. , .)	0.128	.	(. , .)	.
MaxSize	97.000	(. , .)	0.018	.	(. , .)	.
MaxMass	360.264	(. , .)	0.029	.	(. , .)	.

- The APACE tool can be downloaded at
  http://www.nisox.org/Software/APACE/
  https://github.com/NISOx-BDI/APACE
- For more information, please refer to
  Chen, et al. (2019). Accelerated estimation and permutation
  inference for ACE modeling. *Human Brain Mapping* (Epub ahead of
  print). https://doi.org/10.1002/hbm.24611

Thank you!