APACE: Accelerated Permutation Inference for the ACE Model

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Introduction

Heritability studies of imaging phenotypes are becoming more commonplace. Heritability, the proportion of phenotypic variance attributable to genetic sources, is typically estimated with variance components model (e.g. in SOLAR) or structural equation models (e.g. in OpenMx), but these approaches are computationally expensive and cannot exploit the sensitivity of the spatial statistics, like cluster-wise tests. Thus, we developed a non-iterative estimation method for the ACE model; this method is accurate [1] and is so fast that it allows the use of permutation, which provides sensitive family-wise error (FWE) corrected voxel- and cluster-wise inferences [1].

In this work we demonstrate our tool and its ability to consider arbitrary statistics. In particular, we fit the ACE model for twin data (and the HCP extended-twin design) at each voxel and compute summary and aggregate measures of heritability (details in [2]; applications in [3][4]). We call our Matlab-based tool "Accelerated Permutation Inference for the ACE Model (APACE)", and are distributing it freely.

Methods

APACE is partitioned into 4 main parts: the preparation for the analysis, permutation analysis for computing p-values, bootstrapping analysis for generating confidence intervals (CI's) and aggregate heritability analysis. It offers 4 optional inference approaches: voxel-wise inference, cluster-wise inference, summary measure inference, and the aggregate inference. The default is to implement all inferences, but the users can easily select only the desired inferences. The outputs of this tool include image-wise heritability estimates and p-values from voxel-wise and cluster-wise inferences, and the estimates, p-values and CI's of the summary and aggregate heritability measures. APACE is script-based and is designed to be easily parallelized over a computing cluster.

We illustrate the heritability inference for voxels, clusters and whole-image summaries carried out with APACE using an fMRI dataset of 111 subjects including 16 monozygotic twin pairs, 25 dizygotic twin pairs and 29 unrelated individuals. All participants were males and aged 10-12 from the Twins Early Development Study (TEDS) [5], and performed an IAPS emotional pictures matching task during the experiment, where 50 subjects out of 111 were with behavioural problems by the SDQ assessment. Our analysis focused on amygdala, which is a brain area typically implicated in emotional processing tasks. We computed the estimates, p-values (with 1000 permutations) and CI's (with 1000 bootstrap replicates) of the summary measures for the amygdala region, and outputted the image-wise results of estimates and p-values for voxels and clusters.

Results

Table 1 shows that the average heritability in amygdala obtained strong significance. Although the best FWE-corrected p-value for voxels was not significant, cluster statistics were found significant, demonstrating the importance of these spatial statistics. Figure 1 shows the brain area considered, the 555-voxel amygdala mask in green, and the significant clusters ($P_{FWE} \leq 0.05$), 2 clusters comprised of 167 voxels, in red. The cluster-forming threshold is $u = 2.706$, or $p = 0.05$ based on the parametric likelihood ratio null distribution.

	Estimate	95% CI	P-value
mean(h^2)	0.4329	(0.2145, 0.6012)	0.003
mean(c^2)	0.0037	(0.0000, 0.1682)	0.807
mean(e^2)	0.5634	(0.3782, 0.7784)	/
max(T)	6.3357	/	0.125
max(K)	97	/	0.017
max(M)	360.264	/	0.026
max(T) - maximum likelihood ratio statistic			
max(K) - maximum suprathreshold cluster size			
max(M) - maximum suprathreshold cluster mass			

Table 1: Estimates, p-values and 95% CI's of the summary measures and maximum statistics from voxel- and cluster-wise inferences.

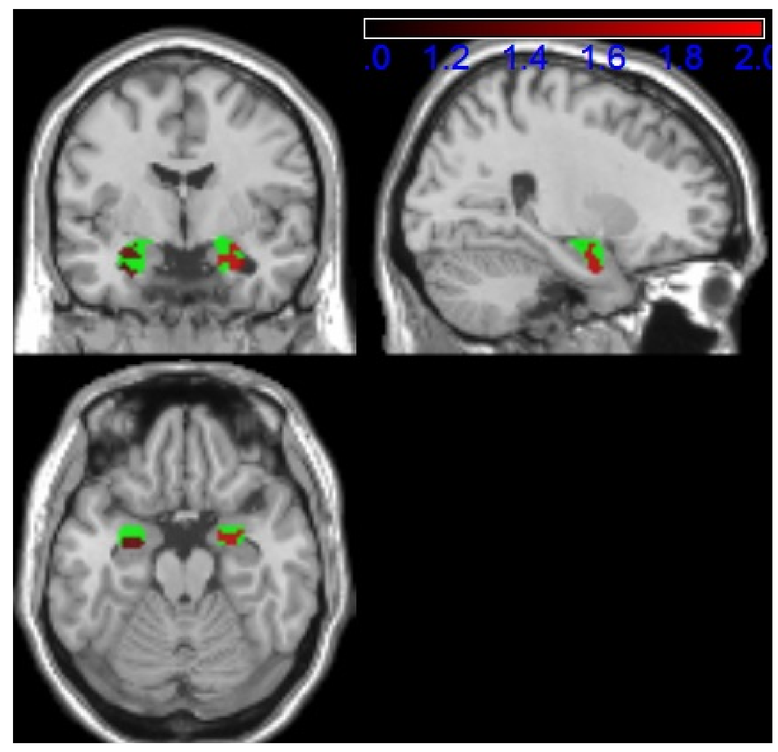

Figure 1: FWE-corrected p-value image (after -log10 transformation) of significant clusters (in red) for the amygdala area (in green).

Conclusions

Our newly developed Matlab-based tool APACE provides different analysis approaches specialized for heritability inference, in which the use of the flexible permutation approach allows any test statistics applied in computing the p-values (e.g. LRT, TFCE, etc), and is freely available at http://warwick.ac.uk/tenichols/apace

References

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