Faster Accelerated Permutation Inference for the ACE Model (APACE) with Parallelization

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Introduction

Heritability of a phenotypic trait accounts for the proportion of phenotypic variance that is due to the additive genetic variation, which disentangles the genetic influences on this trait from the environmental effects. Given that monozygotic (MZ) twins are genetically identical while dizygotic (DZ) twins share 50% genes on average, the classical twin study provides an important method to measure heritability without genetic data.

Although there are a few existing software tools (e.g. OpenMx and SOLAR) for analysing heritability, they employ iterative estimation methods that are time-consuming and prone to convergence failure. We developed a freely available Matlab-based tool, called Accelerated Permutation Inference for the ACE model (APACE) for imaging or non-imaging data, implementing a non-iterative heritability method that is so fast to enable permutation inference (Chen et al., 2013; Chen et al., 2014). Importantly, with permutation we can make inference on spatial statistics, like cluster size and mass, and arbitrary but useful summary statistics, like unweighted mean heritability, variance-weighted mean heritability, median (Q2) of heritabilities, third quartile (Q3) of heritabilities, etc. In this work we evaluate a further speed-up to the APACE code.

Methods

Previous versions of APACE sequentially analysed each voxel/element. The tool now uses vectorization and allows the parallelization. The vectorised APACE tool works by estimating all voxel-wise heritabilities simultaneously using vector operations instead of "for" loops. With parallelization, permutations can be divided into multiple job runs that can be allocated and executed in parallel.

We applied our vectorised APACE tool to a real dataset with a sample of 111 subjects, including 16 MZ twin pairs, 25 DZ twin pairs and 29 unrelated subjects. These participants were all male with an age range of 10–13. During the experiment, subjects performed an IAPS matching task while viewing emotionally salient scenes. Amygdala is our target brain region of this analysis since it is purported to play a critical role in emotional processing. With the use of voxel-wise, cluster-based and summary statistics, we conducted 1000 permutations and 1000 bootstrap replications, with 100 per job, and obtained FWE-corrected permutation-based p-values and bootstrapping confidence intervals (CI's).

Results

The 1000 permutation analysis using vectorised APACE is 13.99% faster than the original code.

Figure 1 shows the significant area within the amygdala (in green) at FWE level $\alpha = 0.05$ using cluster size statistic, where the cluster-forming threshold is specified with $p = 0.05$ for a 50-50 mixture of chi-square distributions $0.5\chi^2_0 + 0.5\chi^2_1$, i.e. $u = 2.71$. With permutation, a cluster of 97 voxels with a p-value of $p = 0.023$ was found to be significant after the FWE correction. Figure 2 shows the estimated heritability map for this significant cluster obtained using the cluster size inference, with a heritability range of 0.44–0.70.

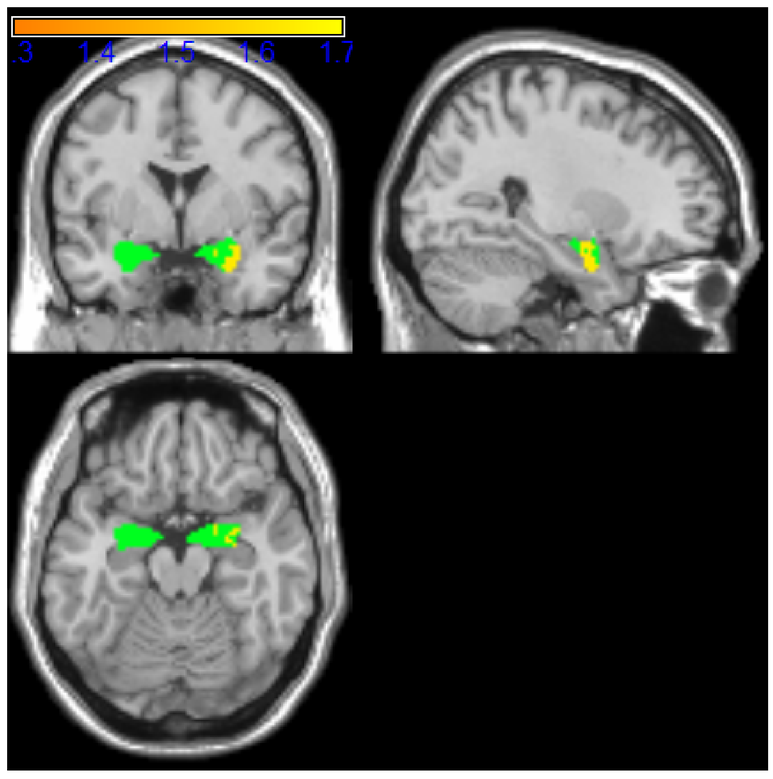

Figure 1: The FWE-corrected p-value image after −log10 transformation of the significant cluster for the amygdala (in green) using cluster size statistic with the cluster-forming threshold of $\mathrm{p} = 0.05$.

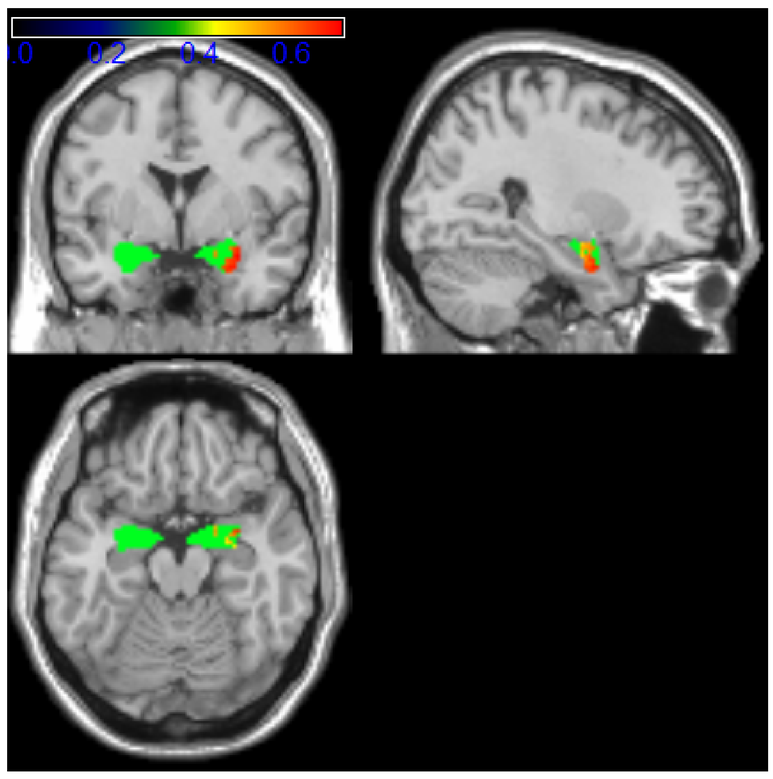

Figure 2: The heritability image of the significant cluster within the amygdala (in green) after the FWE correction, with voxel-wise heritability estimates ranging between 0.44 and 0.70.

Table 1 illustrates the estimates, permutation-based p-values and 95% bootstrapping CI's for heritability h^2 and common environmental component c^2, each assessed with 6 voxel-wise summary statistics. We also found that voxel-wise heritability was not significant ($\min(p_{\mathrm{FWE}}) = 0.138$) but was significant cluster-wise ($\min(p_{\mathrm{FWE}}) = 0.023$ and $\min(p_{\mathrm{FWE}}) = 0.037$ for cluster size and mass respectively). No permutation test is available for c^2 since twins are not exchangeable when $c^2 = 0$, and only 95% bootstrapping CI's were obtained.

(For h^2)	Estimate	P-value	CI
Mean	0.433	0.002	(0.212, 0.593)
wMean	0.417	0.002	(0.206, 0.583)
Q2	0.428	0.002	(0.197, 0.610)
Q3	0.526	0.005	(0.309, 0.703)
Mean(h^2>Q2)	0.534	0.010	(0.313, 0.703)
Mean(h^2>Q3)	0.594	0.010	(0.375, 0.759)
(For c^2)	**Estimate**	**P-value**	**CI**
Mean	0.004	/	(0.000, 0.158)
wMean	0.002	/	(0.000, 0.136)
Q2	0.000	/	(0.000, 0.458)
Q3	0.000	/	(0.000, 0.621)
Mean(c^2>Q2)	0.137	/	(0.011, 0.392)
Mean(c^2>Q3)	0.137	/	(0.011, 0.531)

Table 1: The estimates, permutation-based p-values and 95% bootstrapping CI's for heritability h^2 assessed with unweighted mean (Mean), variance-weighted mean (wMean), median (Q2), third quartile (Q3), mean of h^2 above Q2 (Mean($\mathrm{h}^2 > \mathrm{Q2}$)) and mean of h^2 exceeding Q3 (Mean($\mathrm{h}^2 > \mathrm{Q3}$)) for the amygdala are shown. The p-values derived from significant statistics with level $\alpha = 0.05$ are coloured in red. The estimates and 95% bootstrapping CI's for common environmental component c^2 of Mean, wMean, Q2, Q3, Mean($\mathrm{c}^2 > \mathrm{Q2}$) and Mean($\mathrm{c}^2 > \mathrm{Q3}$) are also shown. CI's and p-values that are not applicable are displayed with a slash symbol.

Conclusions

Our modified vectorised APACE tool further accelerates the calculations, and the parallel execution enables a better job allocation. The current vectorised APACE is freely accessible on the link: https://github.com/nicholst/APACE, where an example script is also provided in the readme document for job parallelization.

References

[1] Chen X, et al. (2013), *OHBM*, Poster.

[2] Chen X, et al. (2014), *OHBM*, Poster.