Selective peak inference: Unbiased estimation of raw and standardized effect size at local maxima

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Abstract

The spatial signals in neuroimaging mass univariate analyses can be characterized in a number of ways, but one widely used approach is peak inference: the identification of peaks in the signal. Peak locations and magnitudes provide a useful summary of activation and are routinely reported, however, the magnitudes reflect selection bias as these points have both survived a threshold and are local maxima. In this paper we propose the use of bootstrap methods to estimate and correct this bias in order to estimate both the raw units change as well as standardized effect size measured with Cohen's d and partial R^2. We evaluate our method with a massive open dataset, and discuss how the corrected estimates can be used to perform power analyses.
Keywords: fMRI, selective inference, winner's curse, regression to the mean, bias, bootstrap, local maxima, UK biobank, power analyses, massive linear modelling.

1 Introduction

Any time a set of noisy data is scanned for the largest value, this value will be an overestimate of the true, noise-free maximum. This effect is known as regression to the mean or the winner's curse and occurs because, at random, some of the variables get lucky and take on high values. In neuroimaging, an analysis produces a test statistic at each voxel, and there are then a number of inference methods available to assess the evidence for a true activation. Voxel, peak and cluster level inference are the most common. However, when papers report the effect size at a peak it is biased due to the winner's curse. This bias is caused by two factors, firstly the observed peaks have been chosen such that they lie above a threshold and secondly the value at each peak is the largest value in a local region around the peak. In order to determine the true effect sizes we have to account for this bias.

This issue is well-known in neuroimaging and is called circular inference or double dipping (Kriegeskorte et al., 2010b). Vul et al. (2009) conducted a review and found the

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problem to be widespread in the fMRI literature, to much controversy. In their meta-analysis of 55 articles, where the test-statistic at each voxel was the correlation between %BOLD signal and a personality measure, they found that correlations observed were spuriously high in papers that reported values at peaks, reflecting a bias due to the winner's curse.

The existing solution to this problem in fMRI is data-splitting, where the first half of the data is used to find significant regions and the other half is used to calculate effect sizes; Kriegeskorte et al. (2010a), Kriegeskorte et al. (2010b). While this results in unbiased values, as the estimates are calculated using only half of the data they have larger variance. For the same reason, the locations of local maxima will be less accurate than if they had been calculated using the whole dataset. These problems are especially problematic when the sample sizes are small. Ideally we would like to be able to use all of the data for both purposes, obtaining accurate estimates of the peak locations and unbiased point estimates of the signal magnitude. This type of approach, where you use all of the data, is known as post-model selection or selective inference and has recently generated a lot of interest; see Berk et al. (2013), Lee et al. (2016) and in particular Taylor and Tibshirani (2015) for a good overview.

A similar problem arises in genetics, see Göring et al. (2001), and there has been much recent work on correcting for selection in this setting. Zhong and Prentice (2008), Ghosh et al. (2008) and Xiao and Boehnke (2012) consider pointwise correction by calculating the distribution of the effect statistic conditional on it being significant while Sun and Bull (2005), Wu et al. (2006), Yu et al. (2007), Jeffries (2007) consider resampling based approaches. In the imaging literature, Rosenblatt and Benjamini (2014) propose a selective inference approach to obtain unbiased confidence intervals but not point estimates. Under the assumption of constant variance Benjamini and Meir (2014) propose a method to correct all voxels above a threshold, analogous to the genetics pointwise correction discussed above. However, this doesn't take account of the effect of selecting peaks or the dependence between voxels and has not been designed for estimation of one-sample effect sizes (such as Cohen's d). Esterman et al. (2010) use a leave one out cross validation approach to provide corrected estimates however this approach has the disadvantage that each instance of resampled data has a different estimate of the significant locations meaning that these are not identifiable. We employ a bootstrap resampling method that provides point estimates of local maxima, accounting for both the peak height and the location within the image. We use all of the data to determine significant locations, meaning that these locations are consistent across resamples and relate to the original statistic image used for inference.

The idea of using an estimate other than the sample mean to provide an estimate for the mean is first due to Stein (1956) and James et al. (1961) who introduced the famous James-Stein estimator. More recently there has been work to correct for the bias in estimating the means of the largest observed values of a given distribution. Efron (2011) uses an empirical Bayes technique to correct for this bias, an approach that has been applied in the genetics literature (Ferguson et al. (2013)). In the case of independent random variables that each come from distributions belonging to a known parametric family, Simon and Simon (2013) introduced a frequentist method to correct bias and Reid et al. (2014) details a post-model selection approach which involves calculating the distribution of Gaussian random variables conditional on being selected.

Brain imaging data is more complicated than these other settings as it has complex spatial and temporal dependencies. However, for group analyses we can take advantage of the fact that data from different subjects is independent. This allows us to employ a

bootstrap approach to resample the data while preserving the spatial dependence structure. Our approach is based on an extension of Simon and Simon (2013) to account for dependence proposed by Tan et al. (2014), where a nonparametric bootstrap is used to estimate bias in effect sizes, motivated by a genetics application. We provide a detailed framework for this method and show how it can be applied in the context of neuroimaging. The novel contribution of our work is to develop point estimates which account for selective inference bias due to thresholding and the use of local maxima. We develop these methods to obtain accurate estimates of Cohen's d and R^2, two quantities that are essential for power analyses. See Mumford (2012) for an overview and Appendix E for the mathematical details of how to use power analyses in neuroimaging.

We use functional and structural magnetic resonance images (MRI) from 8,940 subjects from the UK biobank. The size of this dataset allows us to validate our methods in a way that has never been possible before the availability of data of such scale, allowing us to set aside 4,000 subjects to provide an accurate estimate of the truth and divide the remaining subjects into small groups in order to test our methods. The importance of these sort of real data empirical validations is highlighted by recent work on the validity of cluster size inference (Eklund et al., 2016).

The structure of this paper is as follows. Section 2 explains the details behind the bootstrapping method and how it can be applied to one-sample and the more general linear model scenario. In the one-sample case our method provides corrected estimates of the raw effect (e.g. %BOLD mean) and Cohen's d at the locations of peaks of the one-sample t-statistic found to be significant after correction for multiple comparisons. In the case of the general linear model it provides corrected estimates of partial R^2 values. Section 2.4 discusses the methods used for big data evaluation. Section 3.1 illustrates the methods on simulated data and Section 3.2 applies the techniques to one-sample analysis of functional imaging data and GLM analysis of structural gray matter data obtained using voxel based morphometry (VBM). In Section 3.3 we apply our method to a dataset from the Human Connectome Project that involves a contrast for working memory and obtain corrected Cohen's d and %BOLD values at significant peaks.

2 Methods

Let $\mathcal{V}$ be the set of voxel locations corresponding to the brain or some subset under study and define an **image** to be a map which takes voxel locations to intensities. Given an image Z and a connectivity criterion that determines the neighbours of each voxel (we use the connectivity criterion of 18 in our 3D analyses), define a **local maxima** or **peak** of Z to be a voxel such that the value that Z takes at that location is larger than the value Z takes at neighbouring voxels; see Appendix D for a rigorous definition of this.

2.1 One-Sample

Suppose that we have N subjects and for each $n = 1, \ldots, N$ a corresponding random image Y_n on $\mathcal{V}$ such that for every voxel $v \in \mathcal{V}$,

$$Y_n(v) = \mu(v) + \epsilon_n(v) \tag{1}$$

where $\mu(v)$ is the common mean intensity, and the noise terms $\epsilon_1, \ldots, \epsilon_n$ are iid mean zero random images from some unknown multivariate distribution on $\mathcal{V}$. Let $\hat{\mu} = \frac{1}{N}\sum_{n=1}^{N} Y_n$ be the sample mean image and let $\hat{v}_k$ be the location of the kth largest local maximum

of $\hat{\mu}$ above a screening threshold u. For each k, we are interested in inferring on $\mu(\hat{v}_k)$, the value of μ at the location $\hat{v}_k$, improving on the biased circular estimate $\hat{\mu}(\hat{v}_k)$.

2.1.1 Peak Estimation

The noise distribution in model (1) is unknown so in order to estimate the bias of $\hat{\mu}(\hat{v}_k)$ we use the data to generate bootstrap samples without making any distributional assumptions. This allows us to obtain an estimate of the bias for each bootstrap iteration as in Tan et al. (2014). For each maxima $\hat{v}_k$ we estimate the bias-corrected value as $\tilde{\mu}(\hat{v}_k) = \hat{\mu}(\hat{v}_k) - \delta_k$, where δ_k are bias correction terms found as described in Algorithm 1 below.

Algorithm 1 Non-Parametric Bootstrap Bias Calculation

Input: Images $Y_1, \ldots, Y_N$, the number of bootstrap samples B and screening threshold u.
Let $\hat{\mu} = \frac{1}{N}\sum_{n=1}^{N} Y_n$ and let K be the number of peaks of $\hat{\mu}$ above u, and for $k = 1, \ldots, K$, let $\hat{v}_k$ be the location of the kth largest maxima of $\hat{\mu}$.
for $b = 1, \ldots, B$ **do**
    Sample $Y^*_{1,b}, \ldots, Y^*_{N,b}$ independently with replacement from $Y_1, \ldots, Y_N$.
    Let $\hat{\mu}_b = \frac{1}{N}\sum_{n=1}^{N} Y^*_{N,b}$ and for $k = 1, \ldots, K$, let $\hat{v}_{k,b}$ be the location of the kth largest local maxima of $\hat{\mu}_b$.
    For $k = 1, \ldots, K$, let $\hat{\delta}_{k,b} = \hat{\mu}_b(\hat{v}_{k,b}) - \hat{\mu}(\hat{v}_{k,b})$ be an estimate of the bias at the kth largest local maxima.
end for
For $k = 1, \ldots, K$, let $\hat{\delta}_k = \frac{1}{B}\sum_{b=1}^{B} \hat{\delta}_{k,b}$.
return $(\hat{\mu}(\hat{v}_1) - \hat{\delta}_1, \ldots, \hat{\mu}(\hat{v}_K) - \hat{\delta}_K)$.

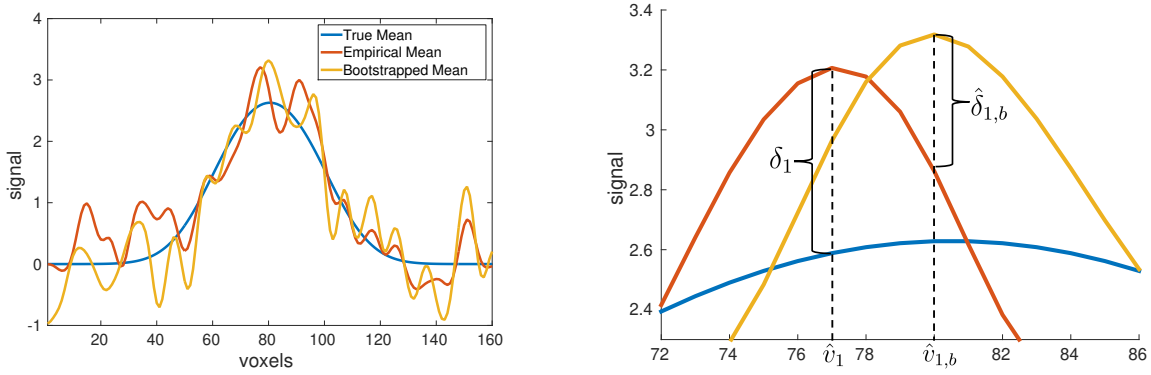
Figure 1 provides an illustrative 1D simulation on a grid of 160 voxels where we consider the case $k = 1$: the global maximum. Here, $N = 20$ and for each $n = 1, \ldots, N$ the error images are created by simulating iid Gaussians at each voxel with variance 4 and then smoothing this with a 6 voxel FWHM Gaussian kernel. The bias above the noise-free signal (δ_1) is evident, and is estimated by comparing a bootstrap sample to the original, yielding an estimate of $\hat{\delta}_{1,b}$. δ_1 is the bias of the empirical mean relative to the true mean.

2.1.2 Peak Estimation for Effect Size

While the above method is based on the sample mean, neuroimaging studies typically base their inferences on statistic images. In the simplest setting, a one-sample analysis of fMRI contrast data, we are testing

$$H_0(v) : \mu(v) = 0 \text{ versus } H_1(v) : \mu(v) \neq 0$$

at each $v \in \mathcal{V}$, using the statistic image, in order to determine whether there is an activation at that voxel. Given the voxels that have been determined to be active we are interested in estimating two different quantities, the effect size (measured in terms of Cohen's d) and the raw unit, i.e. %BOLD change for fMRI.



(a) True vs. sample and bootstrap

(b) Zooming in on the peak

Figure 1: Illustration of our bootstrap peak bias correction method on a simple annotated example. Here our set of voxels is $\mathcal{V} = \{1, \ldots, 160\}$, the true mean μ is shown in blue, the empirical mean $\hat{\mu}$ is shown in red and one sample bootstrap realization (iteration b) is shown in yellow. The figure on the right is a zoomed in version of the figure on the left from voxel 72 to 86. The top peak is biased above the true value by δ_1. Using this realization the height of the bootstrapped peak is compared to the height of the empirical mean at the location of the peak ($\hat{v}_{1,b}$), resulting in an estimate $\hat{\delta}_{1,b}$ of the bias.

We first need to define the test-statistic image. Define σ^2 to be the population variance image, estimated in an unbiased manner using

$$\hat{\sigma}^2(v) = \frac{1}{N-1} \sum_{n=1}^{N} (Y_n(v) - \hat{\mu}(v))^2.$$

In order to perform one-sample hypothesis testing, the t-statistic

$$t(v) = \frac{\hat{\mu}(v)\sqrt{N}}{\hat{\sigma}(v)},$$

is typically used. If the data are Gaussian at each voxel this follows a t-distribution with $N-1$ degrees of freedom.

For a voxel v, $H_0(v)$ is rejected if $t(v)$ lies above a screening threshold u. While a threshold u on a mean image is ultimately arbitrary, on a statistic image we can choose a value of u to control false positives at a desired level while controlling for multiple testing. For example, we can use results from the theory of random fields to find a u such that the familywise error rate, the chance of one or more false positives over the image, is controlled; Worsley (1996), Friston et al. (1994).

While ubiquitously reported, t-statistic values are not interpretable across studies, as they depend on the sample size and grow to infinity with N. Good practice, and in particular to facilitate power analyses (see Appendix E), requires computation of a standardized effect size such as Cohen's d, which at each voxel v is defined as

$$\hat{d}(v) = \frac{\hat{\mu}(v)}{\hat{\sigma}(v)}.$$

As this is just the one-sample t-statistic divided by $\sqrt{N}$, the peaks in the t-statistic image will be at the same locations as those of the one-sample Cohen's d. Algorithm 2 describes how to compute bias-corrected estimates of Cohen's d peaks, which we evaluate

with simulated data (Section 3.1.1) and real task fMRI data (Section 3.2.1). The one-sample Cohen's d is a biased estimator for the population Cohen's d:

$$d(v) = \frac{\mu(v)}{\sigma(v)},$$

with $\mathbb{E}[\hat{d}] = C_N d$ where C_N is a correction factor that depends on the degrees of freedom. $C_N \longrightarrow 1$ as $n \longrightarrow \infty$ but for finite samples we need to account for it; see Appendix E for details.

Algorithm 2 Non-Parametric Bootstrap Bias Calculation

1: **Input**: Images $Y_1, \ldots, Y_N$, the number of bootstraps samples B and threshold u.
2: Compute mean and standard deviation images, $\hat{\mu} = \frac{1}{N}\sum_{n=1}^{N} Y_n$ and $\hat{\sigma}$ with $\hat{\sigma}^2(v) = \frac{1}{N-1}\sum_{n=1}^{N}(Y_n(v) - \hat{\mu}(v))^2$ for each $v \in \mathcal{V}$.
3: Let K be the number of peaks of t above u and for $k = 1, \ldots, K$, let $\hat{v}_k$ be the location of the kth largest maxima of $\hat{d} = \hat{\mu}/\hat{\sigma}$.
4: **for** $b = 1, \ldots, B$ **do**
5: Sample $Y^*_{1,b}, \ldots, Y^*_{N,b}$ independently with replacement from $Y_1, \ldots, Y_N$.
6: Let $\hat{\mu}_b = \frac{1}{N}\sum_{n=1}^{N} Y^*_{n,b}$ and let $\hat{\sigma}^2_b(v) = \frac{1}{N-1}\sum_{n=1}^{N}(Y^*_{n,b}(v) - \hat{\mu}_b(v))^2$ for each $v \in \mathcal{V}$.
7: For $k = 1, \ldots, K$, let $\hat{v}_{k,b}$ be the location of the kth largest local maxima of $\hat{d}_b = \hat{\mu}_b/\hat{\sigma}_b$.
8: Let $\hat{\delta}_{k,b} = (\hat{d}_b(\hat{v}_{k,b}) - \hat{d}(\hat{v}_{k,b}))/C_N$ be an estimate of the bias.
9: **end for**
10: For $k = 1, \ldots, K$, let $\hat{\delta}_k = \frac{1}{B}\sum_{b=1}^{B} \hat{\delta}_{k,b}$
11: **return** $(\hat{d}(\hat{v}_1)/C_N - \hat{\delta}_1, \ldots, \hat{d}(\hat{v}_K)/C_N - \hat{\delta}_K)$.

2.1.3 Estimation of the Mean at the Location of Effect Size Peaks

Some authors, Chen et al. (2017) most recently, have argued that the attention given to statistic images is misguided, and more focus should be given to results with interpretable units, i.e. %BOLD for fMRI. In order to estimate the mean while still controlling for false positives one needs to use the t-statistic image to identify significant peaks and then estimate the raw unit (e.g. %BOLD) change at these locations. This is easily accomplished with a small modification to Algorithm 2, computing in Step 8 instead a bias in raw effect units of:

$$\hat{\delta}_{k,b} = \hat{\mu}_b(\hat{v}_{k,b}) - \hat{\mu}(\hat{v}_{k,b})$$

and returning $(\hat{\mu}(\hat{v}_1) - \hat{\delta}_1, \ldots, \hat{\mu}(\hat{v}_K) - \hat{\delta}_K)$ instead. See Section 3.1.2 for simulated evaluations of this approach and Section 3.2.2 for validation of this approach on the estimation of %BOLD mean at local maxima of the t-statistics of task fMRI data.

2.1.4 Existing One-Sample Methods

We compare the bootstrap approach to circular inference (no correction) and data-splitting, the main two approaches used in the literature. After finding the number of peaks above the threshold as in Algorithm 2, the circular inference uncorrected estimates are simply $\hat{d}(\hat{v}_1)/C_N, \ldots, \hat{d}(\hat{v}_K)/C_N$.

Data-splitting proceeds as follows. First we divide the images into two groups: $Y_1, \ldots, Y_{N/2}$ and $Y_{N/2+1}, \ldots, Y_N$. Let $\hat{d}_1$ and $\hat{d}_2$ be the image estimates of Cohen's d

from the first and second half of the subjects respectively. Using a threshold u we find the peaks of the one-sample t-statistic $\hat{d}_1\sqrt{N/2}$ that lie above u, at locations $\hat{w}_1, \ldots, \hat{w}_J$ for some number of peaks J (note that u must be adjusted to account for the fact we are using half the data). The data-splitting estimates of the peak values are $\hat{d}_2(\hat{w}_1)/C_{N/2}, \ldots, \hat{d}_2(\hat{w}_J)/C_{N/2}$. See Figure 4 for an illustration of the different methods applied to a sample consisting of 50 subjects. Note that in general the number of significant peaks found by data-splitting will be lower than the number found using all of the data as with half the number of subjects there is less power to detect activation.

2.2 General Linear Model

Having introduced the method in the simplified setting of a one-sample model, we now turn to the regression setting. Here, we will often have no practical meaningful units; for example, for a covariate of age, the units of the coefficient are clear (expected change in response per year) but awkward, and more typically users will want to reference the partial coefficient of determination, partial R^2: the proportion of variance explained by one (or more) predictors not already explained by other terms in the model. Hence we now generalize our method to obtain corrected estimates of the peak partial R^2.

Let Y be an N-dimensional random image such that for each $v \in \mathcal{V}$, we assume the following linear model,

$$Y(v) = X\beta(v) + \epsilon(v), \tag{2}$$

for an $N \times p$ design matrix X and a parameter vector $\beta(v) \in \mathbb{R}^p$ where ϵ is the random image of the noise such that $\epsilon(v) = (\epsilon_1(v), \ldots, \epsilon_N(v))^T$ for each $v \in \mathcal{V}$ (where the ϵ_i are iid zero mean zero random images). Then we are interested in testing

$$H_0(v) : C\beta(v) = 0 \text{ versus } H_1(v) : C\beta(v) \neq 0$$

for some contrast matrix $C \in \mathbb{R}^{m\times p}$ where m is the number of contrasts that we simultaneously test. We can test this at each voxel with the usual F-test, which at each voxel v is

$$F(v) = \frac{(C\hat{\beta}(v))^T(C(X^TX)^{-1}C^T)^{-1}(C\hat{\beta}(v))/m}{\hat{\sigma}(v)^2} \tag{3}$$

where $\hat{\beta}(v)$ is the least squares estimate of $\beta(v)$ and $\hat{\sigma}^2(v)$ is the estimate of the error variance at each voxel. Then assuming normality of ϵ, under the null hypothesis $H_0(v)$, $F(v)$ has an $F_{m,N-p}$ distribution and can therefore be used for testing purposes. We will incorporate this into our bootstrap algorithm in order to establish which peaks are significant.

Define R^2 be the image with the estimated partial R^2 values for comparing the null model against the alternative at each voxel; we then seek a bias corrected estimate of the partial R^2 at local maxima. See Appendix A for details on how partial R^2 is formally defined. Bootstrapping in the general linear model scenario is based on the residuals; see Davison et al. (2003) Chapter 6. This leads to Algorithm 3.

Algorithm 3 Non-Parametric Bootstrap Bias Calculation

Input: Images $Y_1, \ldots, Y_N$, the number of bootstrap samples B and threshold u.
Let K be the number of peaks of F above the threshold u and for $k = 1, \ldots, K$, let $\hat{v}_k$ be the location of the kth largest maxima of F.
Let $\hat{\beta} = \hat{\beta}(X, Y) = (X^T X)^{-1} X^T Y$ and let $\hat{\epsilon} = Y - X\hat{\beta}$ be the residuals.
For each $n = 1, \ldots, N$, let $r_n = \hat{\epsilon}_n / \sqrt{1 - p_n}$ be the modified residuals, where $p_n = (X(X^T X)^{-1} X^T)_{nn}$. Let $\overline{r} = \frac{1}{N} \sum_{n=1}^{N} r_i$ be their mean.
for $b = 1, \ldots, B$ **do**
    Sample $\epsilon^*_{1,b}, \ldots, \epsilon^*_{N,b}$ independently with replacement from $r_1 - \overline{r}, \ldots, r_N - \overline{r}$ and let $\epsilon^*_b = (\epsilon^*_{1,b}, \ldots, \epsilon^*_{N,b})^T$ and set $Y^*_b = X\hat{\beta} + \epsilon^*$.
    Let F^*_b be the bootstrapped F-statistic image computed using Y^*_b and $\hat{\beta}(X, Y^*_b)$ (in both numerator and denominator of equation 3). For $k = 1, \ldots, K$, let $\hat{v}_{k,b}$ be the location of the kth largest local maxima of F^*_b. Let R^2_b be the bootstrapped partial R^2 image and set $\hat{\delta}_{k,b} = R^2_b(\hat{v}_{k,b}) - R^2(\hat{v}_{k,b})$ to be the estimate of the bias.
end for
For $k = 1, \ldots, K$, let $\hat{\delta}_k = \frac{1}{B} \sum_{b=1}^{B} \hat{\delta}_{k,b}$.
return $(R^2(\hat{v}_1) - \hat{\delta}_1, \ldots, R^2(\hat{v}_K) - \hat{\delta}_K)$.

In fMRI we are often interested in the case where $C^T = c \in \mathbb{R}^p$ is a contrast vector in which case we can also test using the $t-$statistic

$$t(v) = \frac{c^T \hat{\beta}(v)}{\sqrt{\hat{\sigma}(v)^2 c^T (X^T X)^{-1} c}} \sim t_{N-p}.$$

which allows us to perform either one or two sided tests in order to determine significance before bootstrapping.

As in the Section 2.1.4 we can define circular inference and data-splitting estimates. See Section 3.2.3 for validation of the use of the bootstrap and comparisons between the methods in a GLM scenario where gray matter images are regressed against the age of the participants and an intercept. Note that there is no analogous correction factor C_N for R^2 and so even the data-splitting estimates will not be completely unbiased as estimates for the population R^2. However as can be seen from implementation of the algorithms in simulations (see Supplementary Material) and on real data this bias is comparatively small.

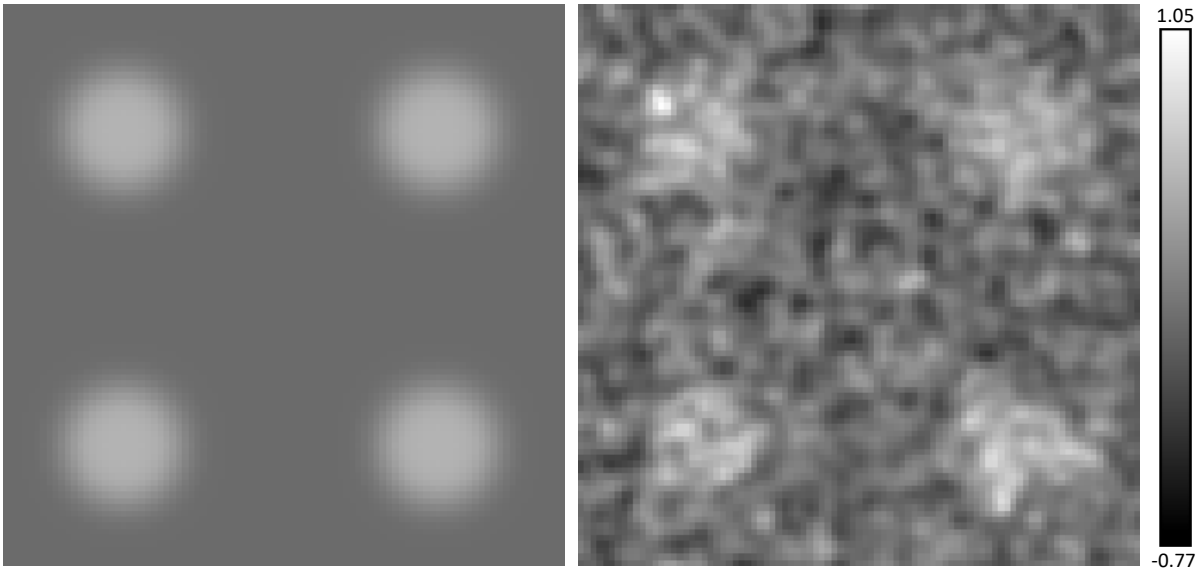
2.3 Simulations

2.3.1 One Sample Mean

In order to test Algorithm 1 we generate 3D simulations on a $91 \times 109 \times 91$ size grid which makes up our set of voxels $\mathcal{V}$. This grid size is that which results from using MNI space and 2mm voxels. We generate data according to model (1) with underlying mean consisting of 3 different peaks with magnitudes of 2, 4, 4 placed at different points of the image. For the ϵ_n we use mean zero Gaussian noise smoothed with an FWHM of 6mm, scaled to have variance 1. In order to evaluate the methods we consider sample sizes of $N = 20, 30, \ldots, 100$ and for each sample size generate 1000 realizations. We use a threshold $u = 2$, this value has been chosen arbitrarily, in practice it could be chosen based on domain knowledge about the underlying signal.

2.3.2 One Sample

In order to test the performance of Algorithm 2 for estimation of Cohen's d and the mean we generate 3D simulations (on the same set of voxels $\mathcal{V}$ as above) according to model (1) with underlying mean consisting of 9 different peaks each with magnitude 1/2, with one located near corner and one at the centre of the image. See Figure 2 for a slice through this signal and one realization. For the ϵ_n we use mean zero Gaussian noise smoothed with an FWHM of 6mm, scaled to have variance 1.



(a) True Signal (b) Sample Cohen's d

Figure 2: Simulation true signal and one realization. Panel (a) illustrates a slice through the true signal corresponding to the plane $y = 20$, with maximum intensity $d = 1/2$. Panel (b) illustrates the same slice through the one sample Cohen's d for 50 subjects. Data for each subject is computed by adding Gaussian noise (with 6mm FWHM) to the signal.

In order to evaluate the methods we consider N random images, $N = \{20, 30, \ldots, 100\}$, generating 1,000 realizations (of the simulations described above) for each N. We use an additional simulation to find the voxelwise threshold that controls the familywise error rate at 5%; for each N we generate 5,000 null t_{N-1} random fields (computed by taking the one-sample t-statistic of N zero mean Gaussian random fields with 6mm FWHM) and take the 95% quantile of the distribution of the maximum.

2.3.3 General Linear Model

In order to test the performance of Algorithm 3 for estimation of partial R^2 we generate 3D simulations (on the same set of voxels $\mathcal{V}$ as above) according to the model

$$Y_n(v) = 1 + \mu(v)x_n + \epsilon_n(v) \tag{4}$$

where $x_n \overset{iid}{\sim} N(0, 1)$, $n = 1, \ldots, N$ and the ϵ_n are iid random images which are mean zero Gaussian, with 6mm FWHM and scaled to have variance 1. μ consists of 9 different peaks each with magnitude 0.5822, with one located near corner and one at the centre of the image. The value 0.5822 has been chosen so that the power matches that of the one-sample simulations, see Supplementary Material Section 2 for details. As for

the one-sample simulations, for $N \in \{20, \ldots, 100\}$ we generate 1,000 realizations of the above model and calculate a voxelwise threshold using additional simulations.

2.3.4 Method Comparison

In order to compare the bootstrap, data-splitting and circular inference, we consider their bias, standard deviation and root mean squared error (RMSE) calculated over the 1,000 realizations for each N. See Appendix C for details of how these quantities are defined. The true parameter is unique to each peak, since the peak locations are random, and as such we need to modify the definitions of the bias, standard deviation and RMSE to take account of this.

2.4 Big Data Validation

In order to test our methods we take advantage of the large sample sizes in the UK Biobank. This enables us to set aside 4,000 (randomly selected) subjects in order to compute a very accurate estimate of the mean, Cohen's d or partial R^2 value. We will refer to this 4,000-subject estimate of the effect as the ground truth. See Appendix B for details on how the ground truth is computed in the different settings. Implementing large linear models with missing data can be computationally burdensome so we outline efficient methods for dealing with this in Appendices B.3 and B.4.

We divide the remaining 4,940 subjects into groups similar in size to those used in typical fMRI/VBM studies. For each such group we apply all three methods and compare the values obtained to the ground truth calculated using the 4000 subjects, allowing the performance of the methods across groups to be evaluated. In each small sample, we consider only complete-data voxels, as is typical in neuroimaging analyses.

2.4.1 Image Acquisition

The UK Biobank is a prospective epidemiological resource combining questionnaires, physical and cognitive measures, and biological samples in a sample of 500,000 subjects in the United Kingdom, aged 40-69 years of age at baseline recruitment. The UK Biobank Imaging Extension provides extensive MRI data of the brain, ultimately on 100,000 subjects. We use the prepared data available from the UK Biobank; full details on imaging acquisition and processing can be found in Miller et al. (2016), Alfaro-Almagro et al. (2018) and from UK Biobank Showcase[1]; a brief description is provided here.

The task fMRI data uses the block-design Hariri faces/shapes task Hariri et al. (2002), where the participants are shown triplets of fearful expressions and, in the control condition, triplets of shapes, and for each event perform a matching task. A total of 332 T2*-weighted blood-oxygen level-dependent (BOLD) echo planar images were acquired in each run [TR=0.735s, TE=39ms, FA=52°, 2.4mm^3 isotropic voxels in $88 \times 88 \times 64$ matrix, $\times 8$ multislice acceleration]. Standard preprocessing and task fMRI modeling was conducted in FEAT (FMRI Expert Analysis Tool); part of the FSL software `http://www.fmrib.ox.ac.uk/fsl`). After head-motion correction and Gaussian kernel of FWHM 5mm, a linear model was fit at each voxel resulting in contrast images for each subject.

Structural T1-weighted images were acquired on each subject [3D MPRAGE, 1mm^3 isotopic voxels in $208 \times 256 \times 256$ matrix]. Images were defaced and nonlinearly warped

[1] `https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf`

to MNI152 space using FNIRT (FMRIBs Nonlinear Image Registration Tool). For VBM, tissue segmentation was performed with FSL's FAST (FMRIBs Automated Segmentation Tool), producing images of gray matter that were subsequently warped to MNI152 space, and modulated by the Jacobian of the warp field. Warped modulated images were written with voxel sizes of 2mm.

Additional processing consisted of transforming intrasubject contrast maps to MNI space with 2mm using nonlinear warping determined by the T1 image and an affine registration of the T2* to the T1 image. We additionally apply a smoothing of 3mm FWHM to the modulated gray matter images.

2.4.2 Task fMRI analysis

We have faces-shapes contrast images from 8,940 subjects and consider the mean and one sample Cohen's d. We compute the 4,000-subject Cohen's d ground truth image for voxels with data for at least 100 subjects (Figure 3). For a given sample size N, let $G_N = \lfloor 4940/N \rfloor$[2] be the number of groups of size N into which we can divide the 4,940 remaining subjects. This division enables a comparison of the performance of the three available methods, circular inference, data-splitting and the bootstrap. As in the simulations, we measure the performance in terms of bias, standard deviation and root mean squared error (RMSE) as defined in Appendix C. We use sample sizes of 20, 50 and 100 to illustrate the performance of the methods, these sizes have been chosen since they are representative of those typically used in fMRI. Sections 3.2.1 and 3.2.2 present the results of applying the methods and Figure 4 illustrates these methods applied to an exemplar sample consisting of 50 subjects.

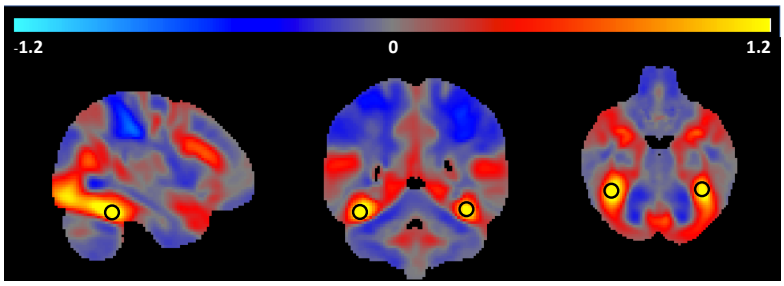
2.4.3 VBM data

We have structural gray matter (VBM) data from the 8,940 subjects to illustrate how our bootstrap method performs in the context of the general linear model. We regress these gray matter images against age, sex and an intercept. Using the 4,000 subjects, we calculate a ground truth estimate of the partial R^2 for age at every voxel for which the mean of the VBM values at that voxel over all 4,000 subjects are greater than 0.1. The maximum of this ground truth is located at voxel (45, 62, 34) and has a partial R^2 of 0.2466. As above we divide the remaining subjects into $G_N = \lfloor 4940/N \rfloor$ groups, for $N = 50, 100$ and 150 to compare the methods by calculating the partial R^2 for age on each subgroup. Here we use larger sample sizes as this setting is more challenging for inference as the effect size is considerably smaller than in the task fMRI data. See Section 3.2.3 for the results of this validation.

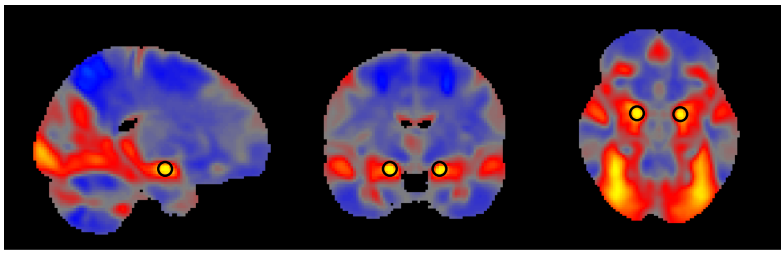
2.4.4 Threshold Computation

For real data analyses, researchers typically either use random field theory (RFT) (Worsley, 1996) or permutation testing (Nichols and Holmes, 2001) to compute screening thresholds. Voxelwise RFT controls the false positive rates but is slightly conservative, (Eklund et al., 2016), primarily because the lattice assumption is not valid for low smoothness levels. On the other hand one-sample permutation can have slightly inflated false positive rates, (Eklund et al., 2018), and has a high computational cost. In our case this cost is very large as we need to perform a big data validation which requires

[2] For $x \in \mathbb{R}$, $\lfloor x \rfloor$ is the largest integer that is less than or equal to x.



(a) Top 2 peaks



(b) 3rd and 4th Highest Peaks

Figure 3: Slices through the top four maxima of the one-sample Cohen's d ground truth. The top two local maxima are located at voxels (42, -46, -22) and (-38, -48, -20) (mm MNI space) which correspond to the left and right temporal occipital fusiform cortices and have Cohen's d values of 1.5756 and 1.4326 respectively. The 3rd and 4th largest local maxima are located at voxels (20,-6,-14) and (-18, -6, -14) which are within the left and right amygdalae and have Cohen's d values of 1.3450 and 1.3041 respectively. The locations of these peaks are indicated using black circles.

many analyses as discussed in Section 2.4. We have thus elected to use voxelwise random field theory for our big data analyses. In practice when running a typical fMRI/VBM analysis, our methods work independently of the method used to choose the threshold.

3 Results

3.1 Results - Simulations

We found that Algorithm 1, bias correction for peak height in a sample mean image alone, had similar performance as for bias correction of statistic peaks (Algorithm 2), detailed below. However, as direct assessment of the mean image provides no way to control false positives, we regard it as a less useful method and have relegated its evaluation (on simulations and real data) to the supplementary material. In this section we illustrate the performance of Algorithm 2. The performance of the methods in the GLM setting (Algorithm 3) is very similar and so this has also been left to the supplementary material.

3.1.1 One Sample Cohen's d

Figure 5 plots the estimates of the bias, standard deviation and root mean squared error from each of the three methods. As expected the circular method has the worst bias, but has low variance, while data splitting is unbiased, but has the highest standard deviation. Bootstrapping has a bias which decreases to 0 as the sample size increases. Summarising mean and standard deviation with RMSE, we find that the bootstrap method has the

lowest RMSE for all sample sizes except $N = 20$. The $N = 20$ exception likely occurs because resampling methods perform better for larger sample sizes.

In our simulations the circular and bootstrap methods find considerably more peaks than data-splitting. This is to be expected as they use double the data (relative to data-splitting) to locate the peaks and are thus more powerful. Indeed in many of our simulations for small sample sizes, data-splitting often found no peaks to be significant at all. In order to compare the peak-detection power of the methods we computed the average number of significant peaks found across all realizations for each sample size (Figure 6). Circular inference and the bootstrap both use the one-sample t-statistic to determine significance so they both find the same number of peaks, which is always more than double the number that data-splitting finds.

3.1.2 Estimating the Mean

As discussed in Section 2.1.3, a bias correction for the mean at locations of peaks in the statistic image can be obtained from a variant of Algorithm 2. Estimates of the bias, standard deviation and RMSE of each of the three methods (see Figure 7), show a very similar performance as for the previous setting, with the bootstrap method having the lowest RMSE across all sample sizes.

3.2 Results - Real Data

In this section we apply the methods to task fMRI and VBM data as described in Section 2.4.

To illustrate the magnitude of the circularity problem we compare maximum peak heights as a function of sample size. We compute the maximum peak height (of Cohen's d) for different N ranging from 10 to 100, (averaged over the G_N groups), and compare to the true max peak height of Cohen's d, see Figure 8. The bias is substantial for small N but is non-negligible even for moderate N. As N increases the bias decreases to zero as expected and the average peak maximum converges to the true maximum value.

3.2.1 Evaluation: Task fMRI Cohen's d peak height estimation

Figure 9 presents the results of applying Algorithm 2 to the one-sample task fMRI data, and is analogous to the simulated data results in Figure 5. (Note that as bias can be measured for each dataset, it can be presented via boxplots; whereas only a single standard deviation and RMSE can be computed per setting.) As in the simulations we find that the circular estimates are highly biased whereas the bootstrap estimates have low bias with the bias decreasing as the sample size increases. The bootstrap has the lowest RMSE for each sample size.

In order to compare the power of the methods, as with the simulations, we have computed the number of peaks found over all G_N groups and the number of peaks per group for each of the methods; see Table 1. From the table we see that, for a given sample size, circular inference and the bootstrap find many more peaks than data-splitting which illustrates the considerable difference in power. We note that for data splitting with $N = 20$ we observe only a total of 7 peaks that were above the threshold over all the $G_{20} = 247$ groups, so the results in Figure 9 could be unstable in this case.

To further understand how the estimates compare we plot their values against the ground truth in Figure 10. For each N, each data point in the corresponding graph shows

N	Circular and Bootstrap		Data-Splitting	
	Total number of peaks found	Number of peaks per group	Total number of peaks found	Number of peaks per group
20	2,005	6.3	7	0.0283
50	5,890	60.1	1950	19.9
100	5,043	102.9	2844	58.0

Table 1: Comparing the power of the three methods as measured by the number of peaks above the screening threshold. For circular and bootstrap (which are based on the same set of peaks) and data splitting, the number of significant peaks found for each N over all G_N groups is reported. Circular inference and the bootstrap find considerably more peaks than data-splitting.

the estimated peak intensity of a significant peak from one of the G_N groups (ordinate), and the ground truth intensity at the location of the peak (abscissa). The $N = 20$ case is the most challenging for estimation. Here the circular estimates are very biased while bootstrap estimates give reasonable estimates and the data-splitting estimates are particularly variable and are fewer in number. As N increases, all of the methods perform better: the circular estimates are biased, and the data-splitting estimates are variable whereas the bootstrap estimates have low bias and variance. The effect of the threshold is particularly evident in the plots for the circular method and, to a lesser extent, for the bootstrap method.

Note that in Figure 10, for large N, the circular method suffers a bias that is relatively constant with respect to the true Cohen's d. The bootstrap method corrects this bias, with the point cloud having roughly the same shape as the circular method's, only shifted downward. In contrast, for the lowest N, there is a greater mismatch in the circular and bootstrap plots. This is because the bootstrap correction is based on the rank order of the peaks, and when SNR is low the sample rank orders is a poor approximation of the noise-free rank order. In practice we observe a random selection of peaks with varying true values meaning that we do not condition on the true values when we observe a peak. As such the bias of the bootstrap estimates is very low (as illustrated in Figure 9) and decreases as N grows.

3.2.2 Evaluation: Task fMRI mean estimation at Cohen's d peak location

Figure 11 illustrates the results of applying Algorithm 2 to the one-sample task fMRI data to estimate the mean at Cohen's d (or t-statistic) peak locations. Here, all the methods perform well and have relatively low little bias, though circular inference is the most biased. Data-splitting has the worst standard deviation and RMSE for $N = 50$ and 100; it has best RMSE for $N = 20$, but we again note that this is based on only 7 peaks.

The selection bias is much less severe in this scenario. This is due to the selection being based on Cohen's d, which is correlated with but not the same as the mean. Notably for $N = 50$ and 100 the circular estimates have a lower RMSE than the data-splitting estimates, but the bootstrap estimates have the lowest RMSE.

Scatter plots comparing the estimates and the ground truth (Figure 12) reflect the observation of a much reduced problem of circularity bias; however, the bias in the circular estimates is still evident.

3.2.3 Evaluation: Gray matter VBM R^2 peak height estimation

Figure 13 illustrates the results for estimating the partial R^2 of age with the VBM data. The performance here resembles that of Cohen's d peak estimation: there is little bias for data-splitting and the bootstrap, the circular and bootstrap methods have lower standard deviation, and the bootstrap consistently has the lowest RMSE.

While the boxplot and bar plot summaries (Figure 13) are consistent, the analogous Cohen's d scatter plots (Figure 14) have a very different character. As the circular results (left column) make clear, most of the R^2 estimates are close to the threshold, indicating a severe selection effect. As discussed above, when SNR is low the observed rank order can differ substantially from the noise-free rank order, reducing the accuracy of the bootstrap method. However, as the sample size increases the bootstrap estimates fall closer to the identity line more closely and in terms of RMSE, the bootstrap still outperforms circular inference and data-splitting.

3.3 Demonstration on HCP Task fMRI dataset

In order to illustrate the bootstrap method in action we apply it to a sample of 80 unrelated subjects from the Human Connectome project and look at one of the working memory contrasts. Subjects performed an N-back task using alternating blocks of 0-back and 2-back conditions with faces, non-living man-made objects, animals, body parts, house and words. We examine the average (2-back − 0-back) contrast, identifying brain regions supporting working memory in general.

We use a group level model and compute a one-sample t-statistic at each voxel in order to test for activation. Voxelwise permutation testing is used to control the familywise error rate to 5% resulting in a threshold of 5.10 for the t-statistic. The largest peak above this threshold has a t-statistic value of 13.58 and lies within the Medial Frontal Gyrus an area commonly associated with working memory. At the largest peak the circular Cohen's d is $13.58/\sqrt{80} = 1.52$; the bootstrap corrected Cohen's d estimate is 1.161. In total 234 peaks lie above the threshold, with 25 peaks falling within the Medial Frontal Gyrus region (Harvard-Oxford Atlas). Table 2 reports the circular and bootstrapped Cohen's d as well as the bootstrap estimate of the mean for the top 10 of these 25 (Cohen's d/t-statistic) peaks. Slices through the one-sample t-statistic at the voxel corresponding to the largest peak are shown in Figure 15.

Figure 16 shows the effect that these corrections have on power, where we have plotted a graph of sample size against power for a whole brain analysis using a p-value threshold, corresponding to taking $T = 5.10$, of 1.39×10^{-6}. Using the raw value would suggest that only 24 subjects are need to attain 80% power, when in fact the corrected estimate shows that 34 subjects are needed to provide this level of power. See Appendix E.2 for details on how the power is calculated.

4 Discussion

Unbiased estimation of effect size is essential yet absent from most neuroimaging studies. We have evaluated three methods for assessing the signal magnitude at peaks in neuroimaging analyses. The bootstrap method that we have introduced provides circularity-corrected estimates from an analysis using all of the data. Compared to uncorrected,

Circular Cohen's d	Corrected Cohen's d	Circular Mean (%BOLD)	Corrected Mean (%BOLD)	Peak Location
1.519	1.161	0.450	0.433	(28, 8, 56)
1.137	0.922	0.347	0.321	(-48, 6, 42)
1.096	0.889	0.561	0.533	(-34, 0, 64)
1.091	0.888	0.279	0.257	(28, 14, 48)
1.079	0.883	0.461	0.434	(44, 34, 32)
1.078	0.883	0.351	0.328	(-32, 2, 62)
1.078	0.882	0.378	0.356	(40, 34, 36)
1.067	0.876	0.378	0.356	(-48, 8, 38)
0.994	0.817	0.339	0.318	(-44, 26, 36)
0.979	0.807	0.280	0.260	(-40, 6, 56)

Table 2: The circular and corrected estimates of Cohen's d and the mean at the top ten significant peaks of Cohen's d in the Medial Frontal Gyrus. There is appreciable bias for the largest Cohen's d peaks, while the %BOLD values at the Cohen's d peaks have relatively little bias.

circular inference our method has dramatically less bias and lower RMSE. While data-splitting is unbiased by construction, our method has lower standard deviation and RMSE in most settings. Given the small size of many studies, using data-splitting, and thereby having to divide the data in half, may produce unacceptable reductions in power.

Even for small sample sizes the bootstrap has similar or better RMSE relative to data-splitting. However, we note that in neuroimaging it is very important to have an accurate estimate of the location of the effect. For this reason we assert, that even in this scenario, the bootstrap is to be preferred over data-splitting since it uses all data to compute the peak locations. It thus identifies a greater number of significant peaks and its estimates of their locations are more accurate.

The dramatic difference in the plots comparing the estimates with the ground truth for Cohen's d and R^2 (Figures 10 & 14, respectively) should be viewed in terms of the dramatic difference in power between these two settings. Consider that, in these evaluations, we have a typical Cohen's d of 1.0 and R^2 of 0.1. If we consider a power analysis with a whole brain $\alpha = 1.39 \times 10^{-6}$ and a target power of $1 - \beta = 80\%$, a one-sample t-test with this Cohen's d would require 42 subjects; in contrast, a simple linear regression with this R^2 would require 306 subjects. In this light, we find the R^2 results even more impressive, providing adequate performance even with negligible power.

Large scale repositories of neuroimaging data have enabled us to validate our methods in a way that has (to our knowledge) not been done before in the neuroimaging setting. This involves setting aside a large number of subjects to compute an accurate version of the truth and dividing the remaining subjects into small groups on which to test the performance of methods relative to the ground truth. This approach enables methods to be rigorously tested and ensures that they work on real data rather than just on simplified simulations. We recommend this sort of evaluation for all new statistical imaging methods, as well as for existing methods that have not been rigorously tested on real data.

One option for an extension of this work would be to provide an estimate of the global maximum. Our method currently corrects locally; at the location of the empirical sample maximum. This is appropriate because when someone comes to replicate the

results they should be able to test the effect at a given location. However using the bootstrap it would also be possible to compare the maximum bootstrapped peak value to that of the maximum of the empirical mean, thereby allow an estimate of the true maximum of the process across the whole brain, something that cannot be estimated using data-splitting. Alternatively, bootstrapped peaks could be matched to the nearest large empirical peak within a certain radius in order to obtain an estimate of the bias, though the difficulty here would be to obtain a good criteria for matching the peaks. This type of approach would not account for the selection bias over the whole image but could allow for an improved estimate of the local bias.

There is much ongoing research in the field of selective inference and there is much potential for other methods to be modified for use in the fMRI setting. It would particularly desirable to derive theoretical corrections using random field theory, however it is at the moment difficult to estimate the peak height distribution of a non mean zero random process (Cheng and Schwartzman (2015)), so this is an important area for future research.

We have motivated peak-level inference for its use in power analysis, however it also forms an essential part of how results are presented in SPM. Ever since a revision of SPM5 that introduced FDR inference for peaks, the "voxel-level" column label has been replaced with with "peak-level" in the inference table. (Confusingly, FWE p-values are identical for voxels and peaks, while FDR p-values differ substantially, with peak p-values notably depending on a screening threshold). Chumbley et al. (2010) have stridently argued against voxel-level inference, asserting that only peaks (and clusters) should be objects of inference in neuroimaging, as these are topological characteristics that can be unambiguously identified in a continuous process analogue of the statistic image. While we still see the value of both voxel-level and peak-level inference, the ubiquity of reporting peaks in statistic images in SPM and other packages is an important motivation for this work.

In sum the bootstrap approach provides a method to remove the bias while using all of the data to obtain accurate estimates of the locations. Relative to data-splitting and circular inference this results in estimates which have similar or generally better RMSE.

5 Software Availability and Reproducibility

The analysis in this paper using MATLAB 2017a. Scripts to implement the bootstrap, circular inference and data-splitting methods are available at `https://github.com/BrainStatsSam/SIbootstrap`. Code to perform power analyses and large-scale linear modelling has also been included. For reproducibility scripts to reproduce the figures in the results section is also available there in the Results_Figures folder.

Simulations and thresholding were performed using code from the RFTtoolbox available at `https://github.com/BrainStatsSam/RFTtoolbox`.

6 Acknowledgments

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Appendices

A Computing partial R^2 from an F-statistic

For a general linear model, let RSS_Ω and RSS_ω respectively be the residual sum of squares for the overall model Ω and some sub-model $\omega \subset \Omega$ with p_0 degrees of freedom. Then we can write the F statistic for comparing ω and Ω as

$$F = \frac{(\text{RSS}_\omega - \text{RSS}_\Omega)/m}{\text{RSS}_\Omega/N - p}$$

where $m = p - p_0$ and the partial coefficient of determination is:

$$R^2 = 1 - \frac{\text{RSS}_\Omega}{\text{RSS}_\omega}.$$

Thus, with some algebra F can be expressed in terms of R^2 as

$$F = \frac{N-p}{m}\left(\frac{R^2}{1-R^2}\right)$$

and conversely, R^2 can be expressed in terms of F as,

$$R^2 = \frac{mF}{mF + N - p}.$$

The F-statistic above has a different form to the F-statistic defined in Section 2.2. For every $m \times p$ contrast matrix C taking the sub-model $\omega_C = \{\beta : C\beta = 0\}$ and applying the General Linear Hypothesis establishes their equivalence.

B Masking and Calculating the Ground Truth

The UK Biobank enables us to set aside a large number of subjects in order to get a very accurate estimate of the true effect size, be it the mean, Cohen's d or a regression coefficient or partial R^2 in a linear model. This appendix describes the details of how we use such a large sample to create ground truth and how we deal with practical challenges, including masking and the inability to load all images into memory at once.

B.1 Masking

Any neuroimaging analysis requires a mask to define voxels that are to be included in the modeling process. In practice, the mask for each subject is unique. Let $\mathcal{D}$ be the set of all possible voxels in the image, then given a subject: n, define its **mask** to be the image: $M_n : \mathcal{D} \longrightarrow \mathbb{R}$ such that $M_n(v)$ is 1 if subject n has data at voxel v, 0 otherwise. Given this definition, define the **intersection mask** of a subset $\mathcal{S}$ of subjects to be the image $M_\mathcal{S}$ such that

$$M_\mathcal{S}(v) = \begin{cases} 1 & M_n(v) = 1 \text{ for all } n \in \mathcal{S} \\ 0 & \text{otherwise} \end{cases}$$

The mask used for each small sample analysis on the subset $\mathcal{S}$ is the product of the intersection mask $M_\mathcal{S}$ with the 2mm MNI brain mask, the image MNI152_T1_2mm_brain_mask in FSL. We refer to this as the **analysis mask**.

B.2 One-Sample Ground Truth Mean and Cohen's d

We choose a random subset $\mathcal{S}$ of $\{1, \ldots, 8940\}$ of size 4,000 to estimate a ground truth mean and Cohen's d using the the available data at each voxel. Note that 99.99% of voxels had data from from at least 100 subjects, while 98% had data from at least 3,000 subjects. In order that each voxel be a reliable estimate we require that at least 100 subjects have data at that voxel in order that it be included. Given subject images $Y_n, n \in \mathcal{S}$, define the **ground truth mean** to be

$$\mu(v) = \frac{\sum_{n \in S} Y_n(v) M_n(v)}{\sum_{n \in S} M_n(v)} \times \mathbb{1}(M_n(v) = 1 \text{ for at least } 100\ n \in S),$$

where $\mathbb{1}(\cdot)$ is the indicator function. Define the **ground truth variance** to be:

$$\sigma^2(v) = \frac{\sum_{n \in S} (Y_n - \mu(v))^2 M_n(v)}{\sum_{n \in S} M_n(v) - 1} \times \mathbb{1}(M_n(v) = 1 \text{ for at least } 100\ n \in S),$$

and the **ground truth Cohen's** d estimate as

$$d(v) = \frac{\mu(v)}{\sigma(v)}.$$

Finally each of these are additionally masked with the 2mm MNI brain mask.

B.3 Linear Model for Big Data - No Missingness

The full unmasked images comprise $902,629 = 91 \times 109 \times 91$ voxels and for 4,000 subjects this data would occupy 27GB RAM at double precision, presenting serious computational challenges. Here we outline a method for computing linear models when the data cannot be loaded into RAM all at once. Fitting separate linear models at each voxel sequentially is slow as it requires access to all of the images for each of the voxels (in the subset of the brain that is of interest) in turn. Loading all of the images at once is generally not feasible due to memory constraints. An improvement would be to divide the brain image into blocks that can fit in memory, however this still requires each image be accessed multiple times. Instead it is possible to write the estimates of the linear model in terms of individual contributions of each subject, allowing arbitrarily large datasets by only reading one subject's data at a time. Suppose that we have N_{all} subjects (when computing the ground truth $N_{\text{all}} = 4{,}000$), that we have an $N_{\text{all}} \times p$ design matrix X and that there is no missing data. Let Y be the $N_{\text{all}} \times V$ matrix of all the subject images where V is the number of voxels in each subject image Y_n. For the mass univariate linear model $Y = X\beta + \epsilon$, we want to compute

$$\hat{\beta} = (X^T X)^{-1} X^T Y,$$

at each voxel. Instead of computing this directly we observe that for each $v \in \mathcal{V}$,

$$X^T Y(v) = \left(x_1, \ldots, x_{N_{\text{all}}}\right) \begin{pmatrix} Y_1(v) \\ \vdots \\ Y_{N_{\text{all}}}(v) \end{pmatrix} = \sum_{n=1}^{N_{all}} Y_n(v) x_n,$$

where x_n^T is the nth row of X, and so $X^T Y$ can computed by loading one image at a time. This $p \times V$ matrix can then be pre-multiplied by $(X^T X)^{-1}$, which only has to

be calculated once, in order to calculate $\hat{\beta}$. The sample variance image can then be computed by a second pass through the data as

$$\hat{\sigma}^2 = (N_{\text{all}} - p)^{-1} \sum_{n=1}^{N_{all}} (Y_n - x_n^T \hat{\beta})^2.$$

The F-statistic can then be computed as usual and this allows calculation of the ground truth partial R^2 using the transformation from Appendix A.

B.4 Linear Model for Big Data - Accounting for Missingness

The previous section assumed identical masks for all subjects, which is not realistic due to susceptibility drop-out in fMRI, variation in field of view in structural MRI, and simply random variation in the exact brain boundary in each subject. For each subject $n = 1, \ldots, N_{\text{all}}$, suppose that we have a binary mask image M_n which denotes the missingness in the response (we will assume that there is no missingness in the predictors). Since there is no missingness in the covariates and they are fixed, we can obtain an unbiased estimator of the regression coefficient at each voxel using the complete data at that voxel, so long as we assume that the missingness mechanism is independent of the image data (White and Carlin, 2010). Assuming this is reasonable, given that the missingness is typically due to acquisition and technical artifacts.

For each voxel v, let $C(v) := \{n : M_n(v) = 1\}$, and let $C(v)$ as a subscript indicate subsetting the corresponding rows of a matrix. Then for each voxel v we need to compute

$$\hat{\beta}(v) = (X_{C(v)}^T X_{C(v)})^{-1} X_{C(v)}^T Y_{C(v)}.$$

The first and second parts of this expression can be computed as

$$(X_{C(v)}^T X_{C(v)})^{-1} = \left(\sum_{n=1}^{N_{\text{all}}} M_n(v) x_n x_n^T \right)^{-1}$$

and

$$X_{C(v)}^T Y_{C(v)} = \sum_{n=1}^{N_{\text{all}}} M_n(v) Y_n(v) x_n$$

so this can also be computed by loading one image at a time. This requires storage of a $p \times p$ matrix at each voxel which, for moderate p, is not problematic. The same masking computation can be used when computing residual variance, which then allows computation of the F-statistic and this allows calculation of the ground truth partial R^2 using the transformation from Appendix A.

C Bias, RMSE and Standard Deviation Computations

We compute bias, standard deviation and RMSE in a non-standard context, in that the true parameter values vary in each instance. Traditionally, one estimates a common θ with estimators $\hat{\theta}_1, ..., \hat{\theta}_K$, giving us the usual MSE decomposition for a sample of size K,

$$\text{MSE} = \frac{1}{K} \sum_{k=1}^{K} (\hat{\theta}_k - \theta)^2 = \frac{1}{K} \sum_{k=1}^{K} \left(\hat{\theta}_k - \frac{1}{K} \sum_{k=1}^{K} \hat{\theta}_k \right)^2 + \left(\frac{1}{K} \sum_{k=1}^{K} \hat{\theta}_k - \theta \right)^2$$

into variance and squared bias. However in our context we have estimators $\hat{\theta}_1, \ldots, \hat{\theta}_K$ of parameters $\theta_1, \ldots, \theta_K$. In our setting, K is the number of significant peaks that are found over all realizations. For $k = 1, \ldots, K$, $\hat{\theta}_k$ is the value of one of these significant peaks, and θ_k is the true value at the voxel corresponding to the peak. The θ_k are different because the locations of the peaks are random. As such we instead define

$$\tilde{\theta}_k = \hat{\theta}_k - \theta_k$$

and use the fact that the noise-free value of $\tilde{\theta}_k$ is 0 for each k. This allows us to define the MSE as

$$\text{MSE} = \frac{1}{K}\sum_{k=1}^{K}(\tilde{\theta}_k - 0)^2 = \frac{1}{K}\sum_{k=1}^{K}(\tilde{\theta}_k - \frac{1}{K}\sum_{k=1}^{K}\tilde{\theta}_k)^2 + \left(\frac{1}{K}\sum_{k=1}^{K}\tilde{\theta}_k\right)^2$$

where the second equality follows by bias-variance decomposition. This leads us to define the bias

$$\frac{1}{K}\sum_{k=1}^{K}\tilde{\theta}_k = \frac{1}{K}\sum_{k=1}^{K}(\hat{\theta}_k - \theta_k)$$

and variance

$$\frac{1}{K}\sum_{k=1}^{K}(\tilde{\theta}_k - \frac{1}{K}\sum_{k=1}^{K}\tilde{\theta}_k)^2 = \frac{1}{K}\sum_{k=1}^{K}\left(\hat{\theta}_k - \theta_k - \frac{1}{K}\sum_{k=1}^{K}(\hat{\theta}_k - \theta_k)\right)^2,$$

in this context. The root mean squared error or RMSE is defined to be the square root of the MSE and the standard deviation to be the square root of the variance.

In the context of our estimates in Section 3.2, for a given sample size N, K is the number of significant peaks over all the G_N subsets. In the boxplots in Figures 9, 11, 13 for each set of estimates we have made boxplots for the bias $\hat{\theta}_k - \theta_k$ over all K significant peaks. For the bar plots in these figures we have plotted the RMSE and standard deviation as defined above.

D Neighbourhoods and Local Maxima

Suppose that the vertices in $\mathcal{V}$ are connected by a set of edges. Let the collection of these edges be denoted by E. Then we define two vertices u and v to be **neighbours** in the graph $\mathcal{G} = (\mathcal{V}, E)$ if the edge connecting u and v is contained in the set of edges E. Given $v \in \mathcal{V}$, define the **neighbourhood** of v to be the set of voxels that are neighbours to v and denote this by $ne(v)$.

Given an image $Z : \mathcal{V} \longrightarrow \mathbb{R}$, we define a voxel v to be a **local maxima** if $Z(v) \geq Z(v')$ for all $v' \in ne(v)$. In 3D brain images we have a rectilinear grid of voxels and take the edge set to be defined by a connectivity criterion of either 6, 18 or 26, which if our voxels are represented by cubes correspond to those surrounding voxels which share surfaces, edges and corners respectively. As such which voxels are defined to be local maxima is dependent on the connectivity criterion. In this paper we have used a neighbourhood criterion of 18 which is the default in SPM.

E Non-Central Distributions and Power Analyses

E.1 Non-Central Distributions

E.1.1 One-Sample t-statistic

Following the model from Section 2.1, under the assumption of Gaussian noise,

$$\hat{\mu}\sqrt{N} \sim N(\mu\sqrt{N}, \sigma^2)$$

is independent of $\hat{\sigma}$ and so the t-statistic $\hat{\mu}\sqrt{N}/\hat{\sigma}$ has a non-central t-distribution with non-centrality parameter $\mu\sqrt{N}/\sigma$ and $N-1$ degrees of freedom. The mean of the non-central t is not the non-centrality parameter, instead

$$\mathbb{E}\left[\frac{\hat{\mu}\sqrt{N}}{\hat{\sigma}}\right] = \frac{\mu}{\sigma}\sqrt{\frac{N-1}{2}}\frac{\Gamma((N-2)/2)}{\Gamma((N-1)/2)} = C_N\frac{\mu\sqrt{N}}{\sigma}$$

for $N > 2$, where Γ is the gamma function and C_N is a bias correction factor (Hogben et al., 1961). Thus we use

$$\frac{\hat{\mu}}{\hat{\sigma}C_N}$$

as an unbiased of the population Cohen's d. Note that here and henceforth whenever we have two images A and B we write $\frac{A}{B}$ to be the image which takes the values $\frac{A(v)}{B(v)}$ at each voxel v.

E.1.2 Non-Central F and t distributions in the General Linear Model

For the general linear model at a given voxel (note we suppress the voxel v index here), we have $\hat{\beta} \sim N(\beta, \sigma^2(X^TX)^{-1})$ independently of $\hat{\sigma}^2 \sim \frac{\sigma^2}{N-p}\chi^2_{N-p}$ which implies that

$$(C(X^TX)^{-1}C^T)^{-1/2}C\hat{\beta} \sim N\big((C(X^TX)^{-1}C^T)^{-1/2}C\beta, \sigma^2 I_m\big).$$

Thus $(C\hat{\beta})^T(C(X^TX)^{-1}C^T)^{-1}(C\hat{\beta})$ has a non-central chi-squared distribution with m degrees of freedom and non-centrality parameter $(C\beta)^T(C(X^TX)^{-1}C^T)^{-1}(C\beta)$. In particular

$$F = \frac{(C\hat{\beta})^T(C(X^TX)^{-1}C^T)^{-1}(C\hat{\beta})/m}{\hat{\sigma}^2}$$

has a non-central F distribution with non-centrality parameter

$$(C\beta)^T(C(X^TX)^{-1}C^T)^{-1}(C\beta)/\sigma^2$$

and degrees of freedom m and $N-p$ and so

$$\mathbb{E}[F] = \frac{(N-p)(m + (C\beta)^T(C(X^TX)^{-1}C^T)^{-1}(C\beta)/\sigma^2)}{m(N-p-2)},$$

as derived in Patnaik (1949). In the case where $C = c^T$ is just a single contrast vector and we want to perform inference using the t-statistic instead of the F-statistic, the t-statistic

$$\frac{c^T\hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T(X^TX)^{-1}c}}$$

has a non-central t-distribution with $N-p$ degrees of freedom and non-centrality parameter $c^T\beta/\sqrt{\sigma^2 c^T(X^TX)^{-1}c}$.

E.2 Power Analyses

E.2.1 One Sample

In the one sample scenario, for a potential future sample size N' and an estimate of the non-centrality parameter: λ, the power is:

$$\mathbb{P}(T_{N'-1,\lambda} > t_{1-\alpha,N'-1})$$

where $t_{1-\alpha,N'-1}$ is chosen such that $\mathbb{P}(T_{N'-1,0} > t_{1-\alpha,N'-1}) = \alpha$ and $T_{N'-1,\lambda}$ has a non-central T distribution with $N'-1$ degrees of freedom and non-centrality parameter λ.

E.2.2 Multiple Regression - Cohen's f^2

Calculation of power in the general linear model scenario is slightly more complicated as it requires distribution assumptions and approximations. To do so define Cohen's f^2 to be

$$f^2 := \frac{R^2}{1-R^2} = \frac{m}{N-p}F = \frac{(C\hat{\beta})^T(C(\frac{1}{N-p}X^TX)^{-1}C^T)^{-1}(C\hat{\beta})}{\hat{\sigma}^2}.$$

where where R^2 is the partial coefficient of determination and we have used the fact that $\frac{R^2}{1-R^2} = \frac{m}{N-p}F$ as derived in Appendix A. In the framework of the general linear model (2), for $N \in \mathbb{N}$ suppose we observe an N-dimensional image Y_N such that

$$Y_N = X_N\beta + \epsilon^N$$

for some p-dimensional parameter image β and N-dimensional noise image $\epsilon^N = (\epsilon_1, \ldots, \epsilon_N)^T$ where $\{\epsilon_n\}_{n\in N}$ is an iid sequence of noise images which have finite variance. Let $X_N = \left[x_1, \ldots, x_N\right]^T$ be the design matrix, where $\{x_n\}_{n\in\mathbb{N}} \in \mathbb{R}^p$ is a sequence of finite variance, iid random vectors (independent of the noise process) each with multivariate distribution D. For each N, let $\hat{\beta}_N$ be the p-dimensional image linear least squares estimator and let $\hat{\sigma}_N^2$ be the image estimate of variance.

Then $\frac{1}{N}X_N^TX_N \xrightarrow{a.s.} \mathbb{E}\left[x_1x_1^T\right]$, $\hat{\beta}_N \xrightarrow{a.s.} \beta$ and $\hat{\sigma}_N^2 \xrightarrow{a.s.} \sigma$ as $N \longrightarrow \infty$ (where $\xrightarrow{a.s.}$ denotes pointwise almost sure convergence) see the supplementary material Section 4 for proofs. Let f_N^2 be Cohen's f^2 for the Nth model. Then combining the above results,

$$f_N^2 \xrightarrow{a.s.} f_p^2 := \frac{(C\beta)^T(C(\mathbb{E}\left[x_1x_1^T\right])^{-1}C^T)^{-1}(C\beta)}{\sigma^2}$$

as $N \longrightarrow \infty$. This also implies almost sure convergence of R^2.

Given a new sample of N' subjects from model E.2.2 with corresponding design matrix X' (an $N' \times p$ matrix whose rows are iid with distribution D), then as long as N' is sufficiently large, we can obtain reasonable estimates of the power. To do so note that the (new) F-statistic has a non-central F distribution with non-centrality parameter:

$$\frac{(C\beta)^T(C(X'^TX')^{-1}C^T)^{-1}(C\beta)}{\sigma^2} = N'\frac{(C\beta)^T(C(\frac{1}{N'}X'^TX')^{-1}C^T)^{-1}(C\beta)}{\sigma^2} \approx N'f_p^2 \approx N'f^2.$$

Let $\lambda = N'f^2$ be the estimate of the non-centrality parameter. Then the power is:

$$\mathbb{P}(F_{m,N'-p,\lambda} > f_{1-\alpha,m,N'-p})$$

where $f_{1-\alpha,m,N'-p}$ is chosen such that $\mathbb{P}(F_{m,N'-p,0} > f_{1-\alpha,N'-1}) = \alpha$ and where $F_{m,N'-p,\lambda}$ has a non-central F distribution with m and $N'-p$ degrees of freedom and non-centrality parameter λ.

E.2.3 Multiple Regression - Cohen's f

In the case that $C = c^T$ is a contrast vector, we often use the t-statistic as this allows us to perform one-sided tests. In which case we can use Cohen's f which is defined as

$$f = \frac{c^T \hat{\beta} / \sqrt{N-p}}{\sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} c}}$$

and use $\sqrt{N'} f$ as our estimate of the non-centrality parameter using this to calculate an estimate of the power.

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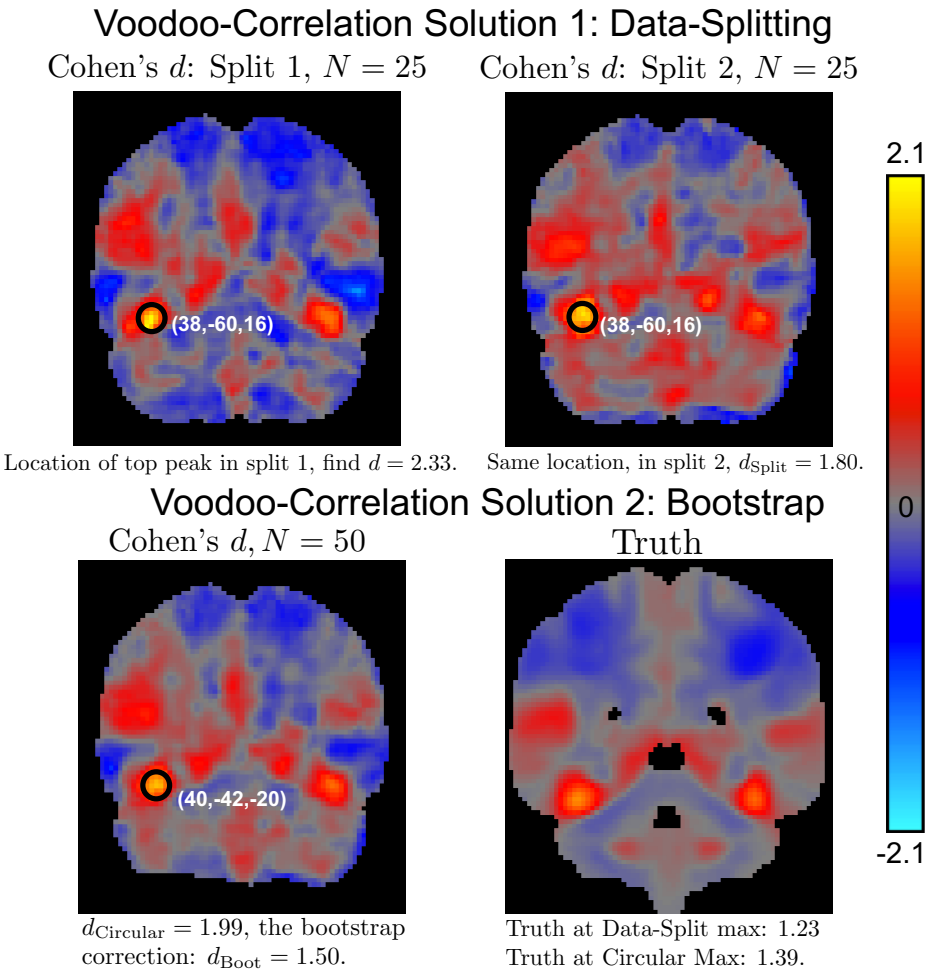

Figure 4: Illustration of a 50 subjects analysis using circular inference, the proposed bootstrap method and data-splitting. Data-splitting requires splitting the data in half, using the first half of the data to determine the locations, but provides a non-circular estimate. Circular inference and the bootstrap both use all of the data to calculate the locations. This figure illustrates the extra variability in data-splitting, with a noisier map and greater variability (estimated d of 1.80 vs truth of 1.23); the bootstrap estimate had smaller bias (estimated d of 1.50 vs truth of 1.39). This illustration is indicative of the extensive evaluations reported below.

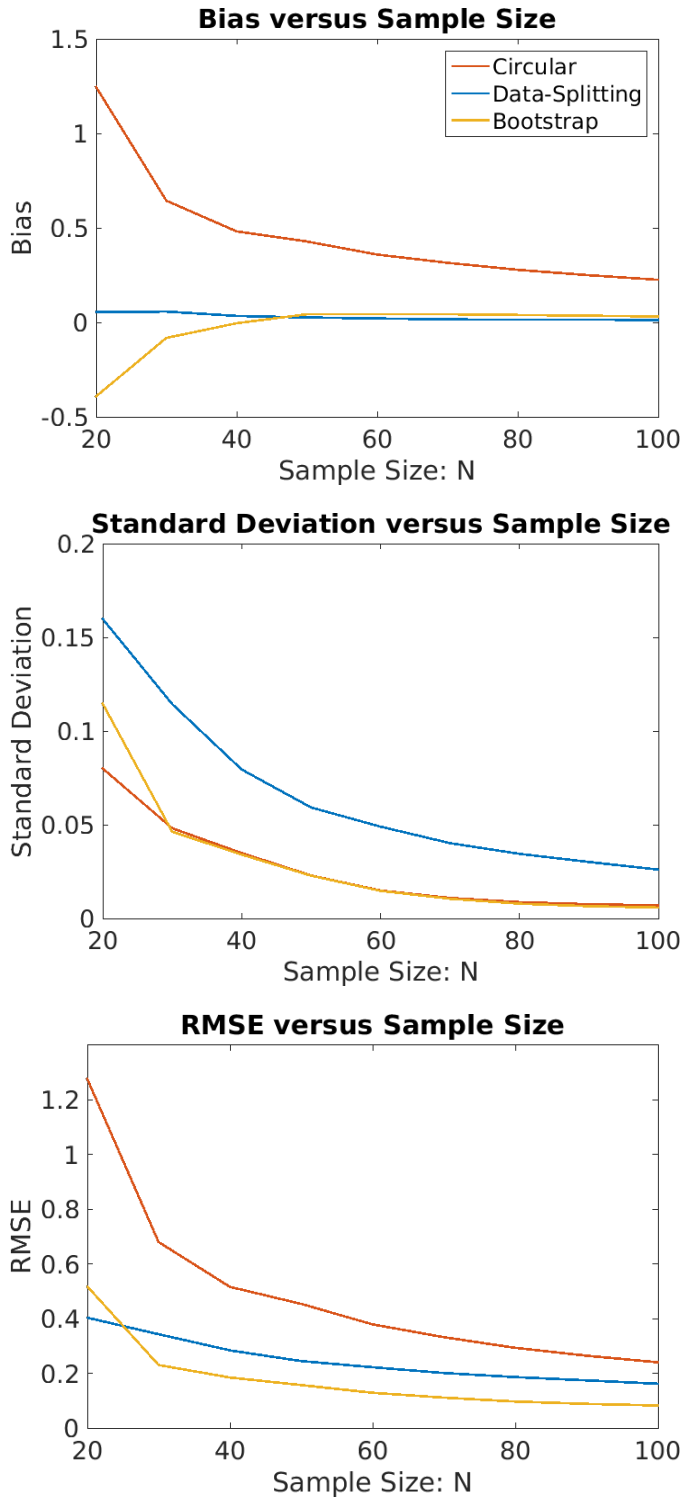

Figure 5: Evaluation of bias correction for Cohen's d peaks (Algorithm 2) on simulated data generated as described in Section 2.3. Each plot shows the bias (top), standard deviation (middle) and RMSE (bottom) calculated over 1,000 realisations, for samples of size $N = 20, 30, \ldots, 100$. By the overall measure of RMSE, the bootstrap method performs the best.

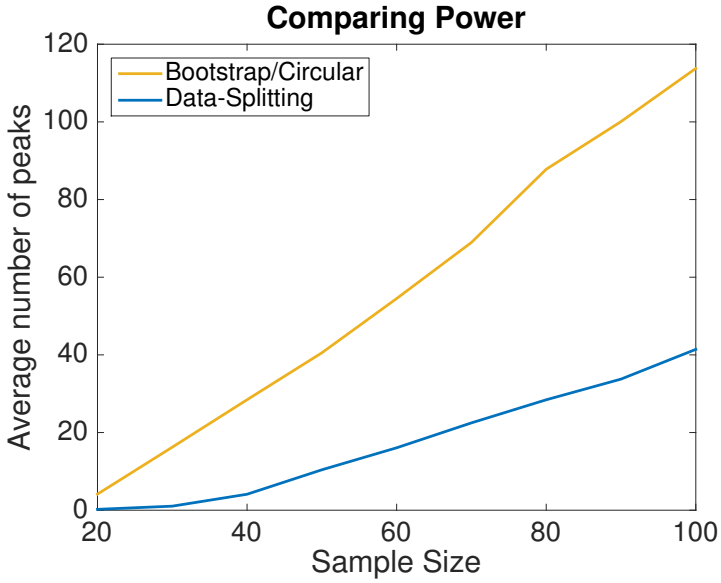

Figure 6: Comparing the power of the methods applied to the one-sample Cohen's d simulations. We have computed the average number of significant peaks found per realization for $N \in \{20, 30, \ldots, 100\}$ over all 1,000 realizations. Circular inference and the bootstrap find considerably more peaks than data-splitting.

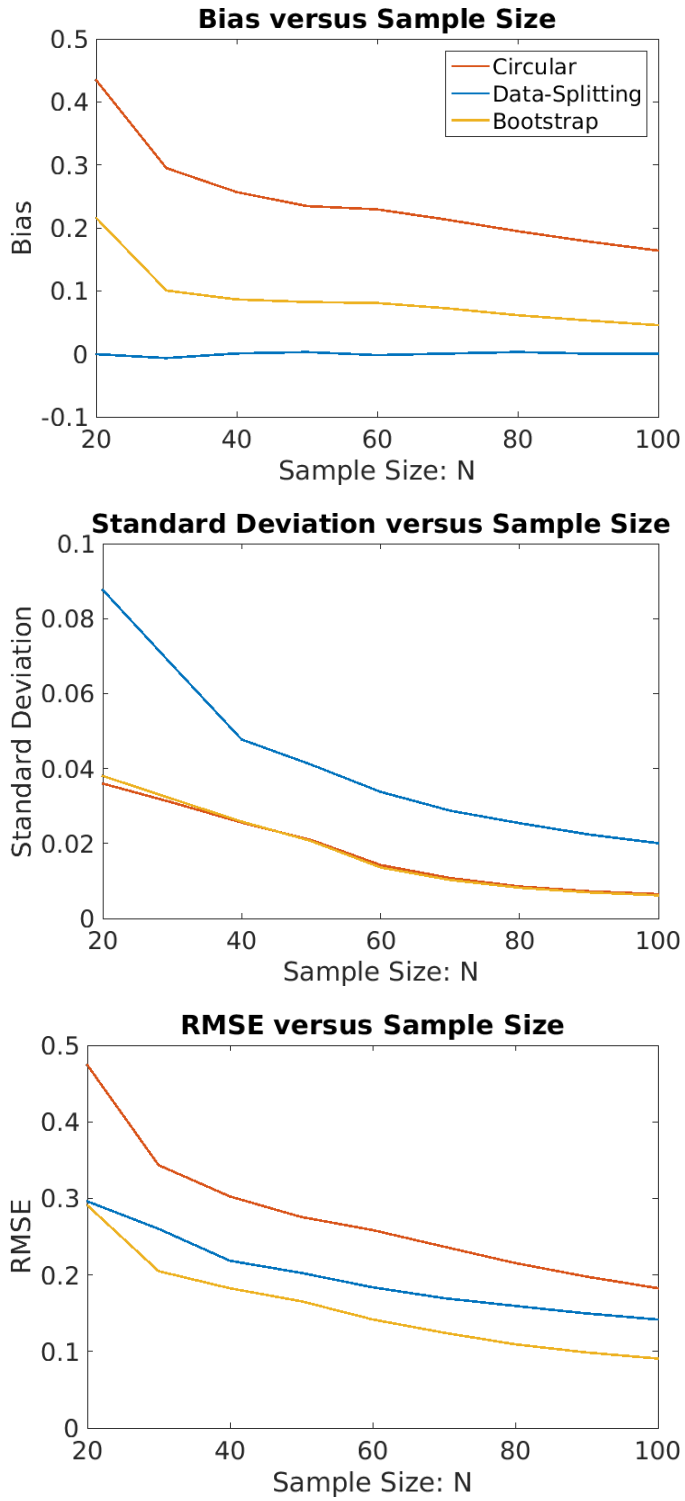

Figure 7: Evaluation of bias correction for the %BOLD mean at locations of Cohen's d peaks on simulated data generated as described in Section 2.3. Each plot shows the bias (top), standard deviation (middle) and RMSE (bottom) calculated over 1,000 realisations, for samples of size $N = 20, 30, \ldots, 100$. In terms of RMSE, the bootstrap method performs the best.

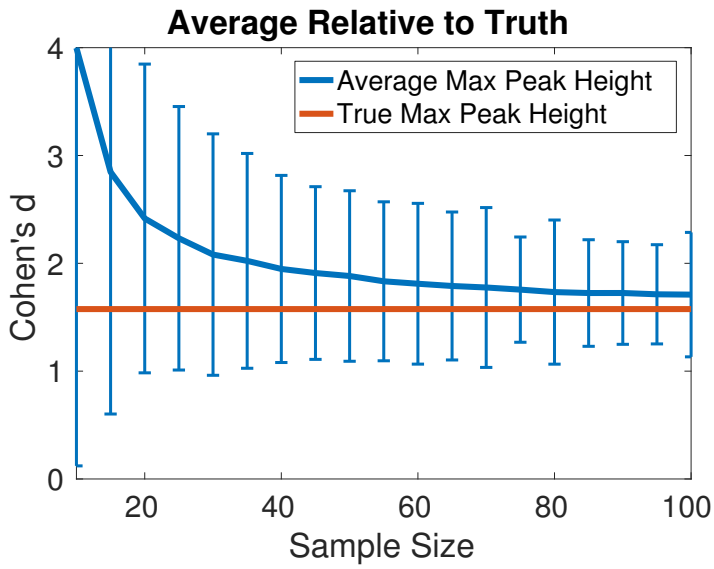

Figure 8: Illustration of the winner's curse: average selection bias in the one-sample Cohen's d: the average peak height of the maximum is plotted against N. For each N we compute Cohen's d for each of the G_N groups of size N find the value of the maximum and take the average over the G_N groups. The 95% error bars are based on the 2.5% and 97.5% quantiles for each sample size. The bias is substantial for small N but is non-negligible even for moderate N.

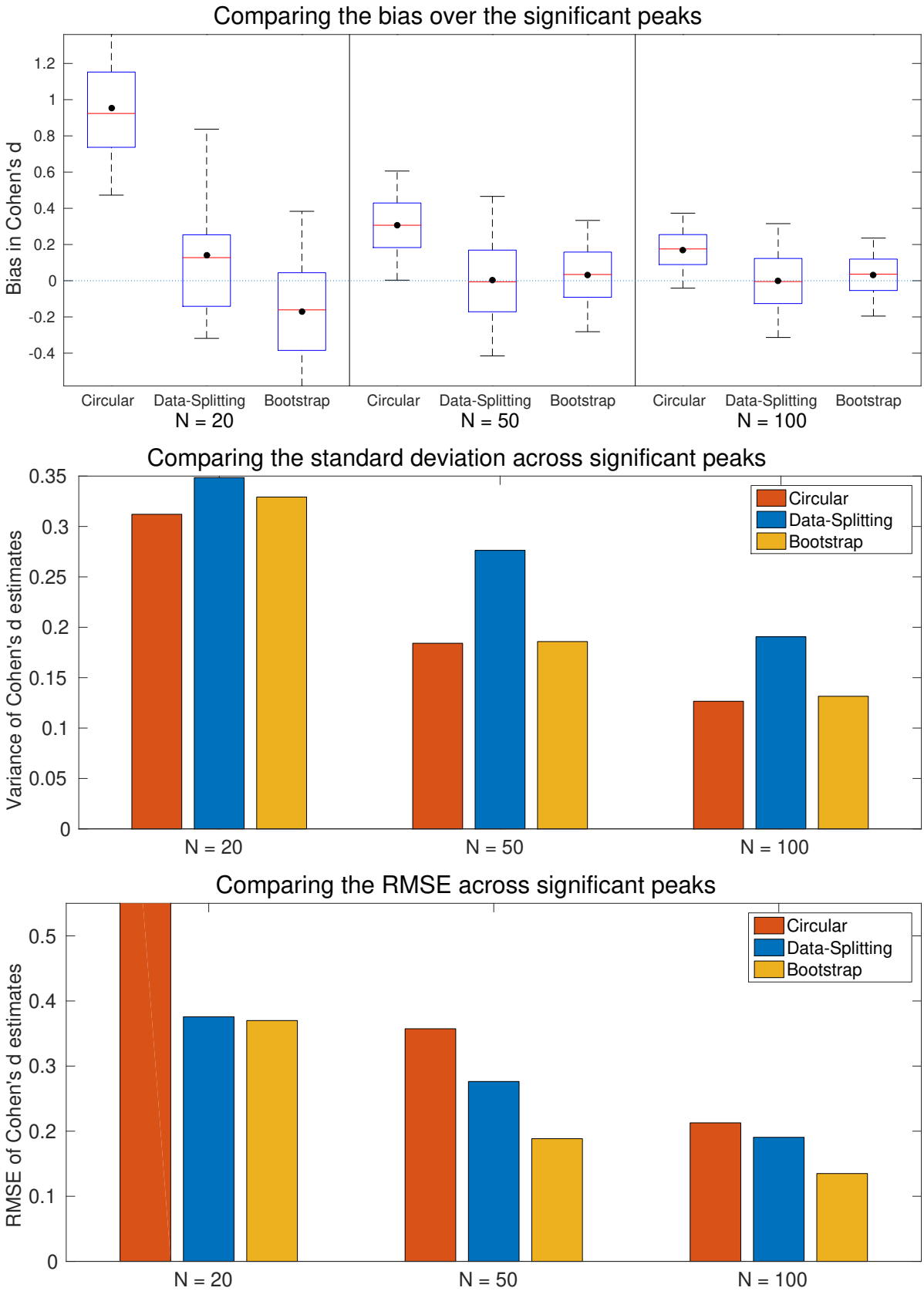

Figure 9: Comparison of one sample Cohen's d estimation for task fMRI. Bias (top), standard deviation (middle), and RMSE (bottom) are shown for $N = 20, 50$ and 100 sample sizes, based on G_N samples. While both data-splitting and bootstrap are generally unbiased, the bootstrap has the smallest RMSE. Note that the $N = 20$ data-splitting values are computed using only 7 data points so may not be representative. Note also that the RMSE for circular inference for $N = 20$ is cutoff and actually has a value of 1.0029.

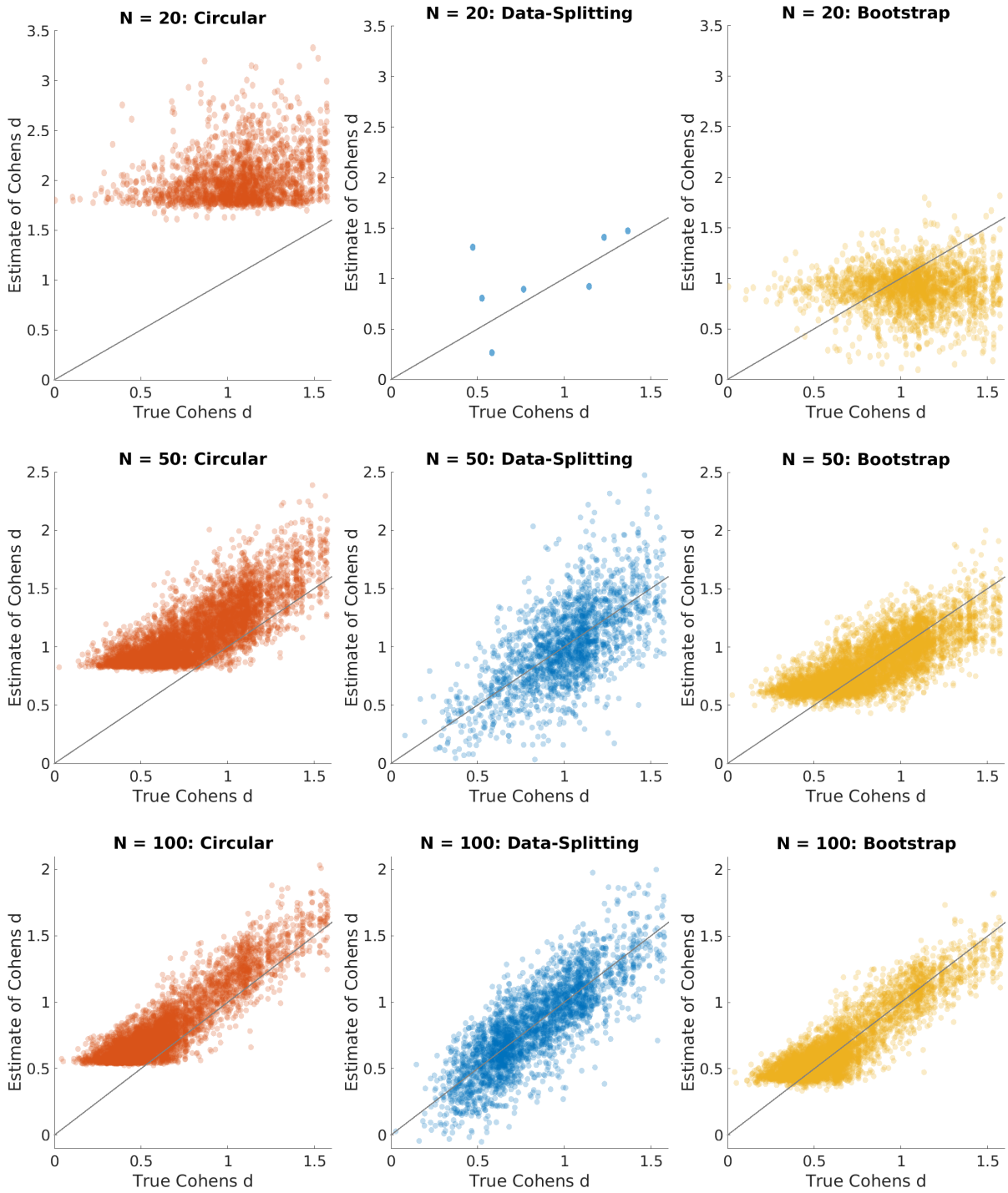

Figure 10: Plots of estimated versus true value of one-sample Cohen's d for task fMRI images, for circular (left), data-splitting (middle), and bootstrap (right). Plots show all peaks found over the G_N samples for each sample size, $N = 20, 50, 100$ (top to bottom). For each peak the true Cohen's d is obtained at that location from the held-out $4,000$ subject Cohen's d image. Note that the number of peaks and their locations are the same for circular inference and the bootstrap but are different for data-splitting as it uses the first half of the subjects in order to determine significant peaks. From these plots we can see that the bootstrap estimates have low bias and standard deviation and improve as the sample size increases. The data-splitting estimates are unbiased but are more variable and reflect fewer detected peaks.

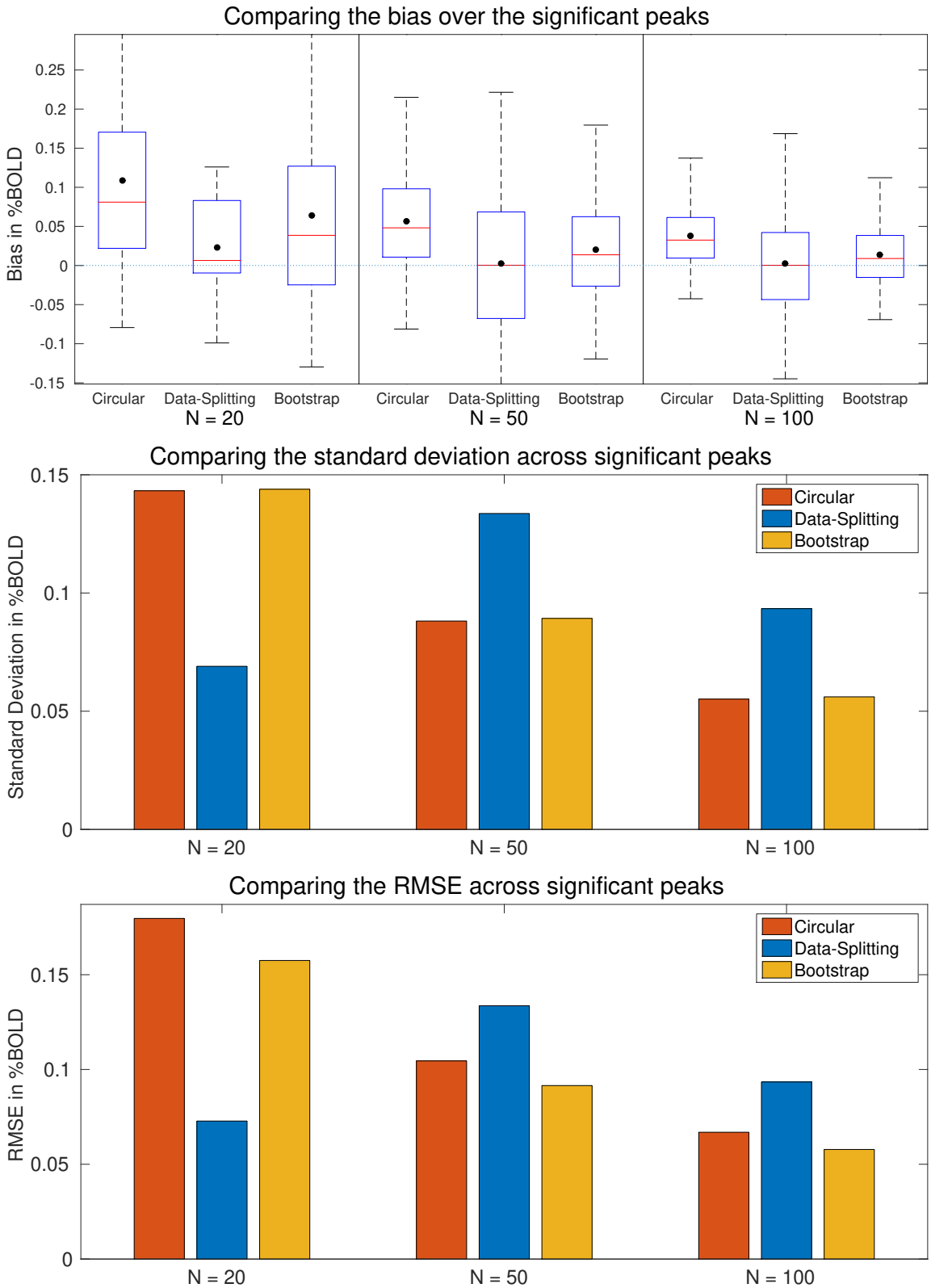

Figure 11: Comparison of one sample mean estimation for task fMRI. Bias (top), standard deviation (middle), and RMSE (bottom) are shown for $N = 20, 50$ and 100 sample sizes, based on G_N samples. While both data-splitting and bootstrap are generally unbiased, the bootstrap has the smallest RMSE for larger sample sizes. Note that the $N = 20$ data-splitting RMSE and standard deviation is computed using only 7 data points so may not be representative. What is particular of note here is that the circular estimates have lower RMSE than data-splitting for $N = 50$ and 100.

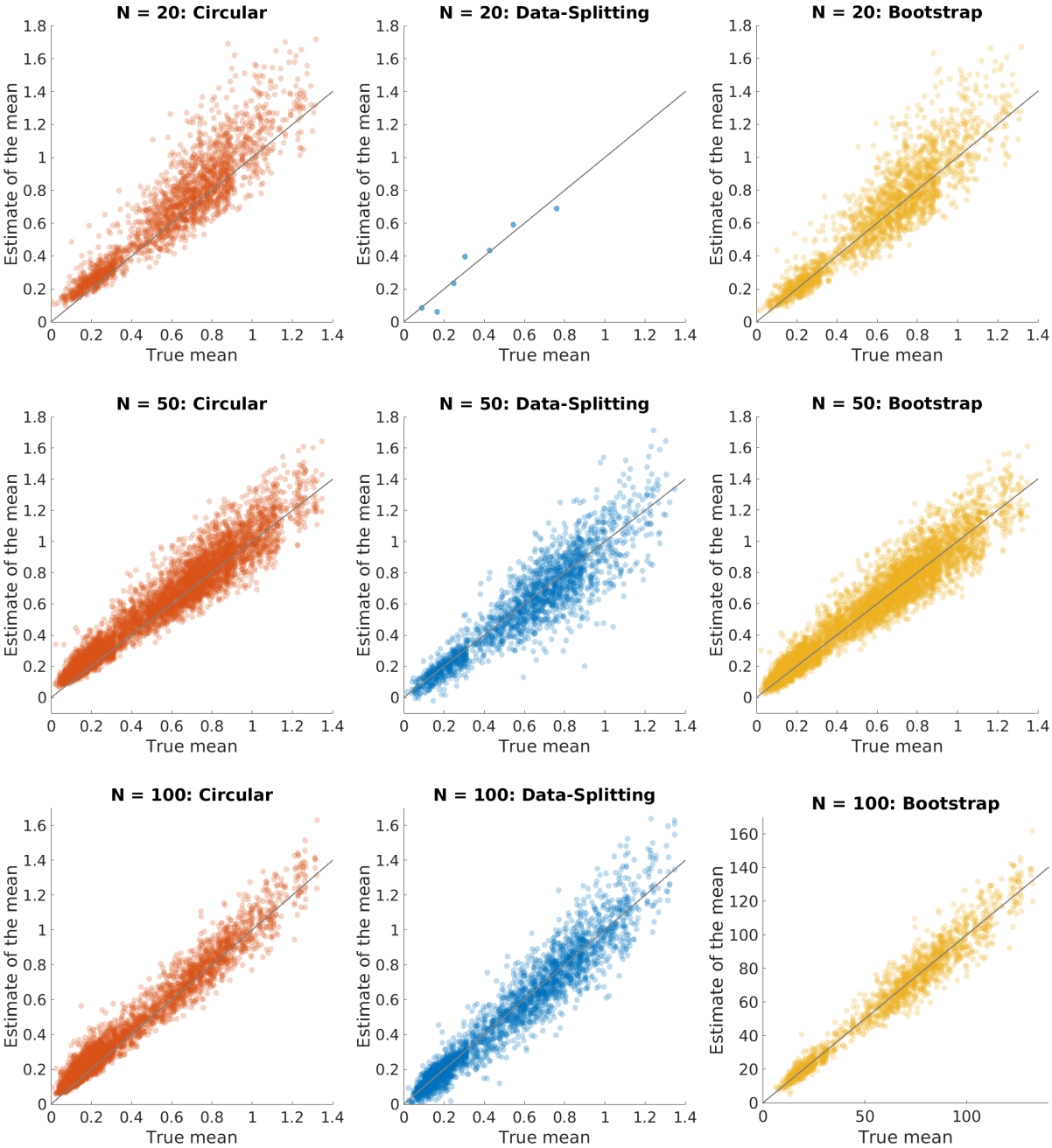

Figure 12: Plots of estimated versus true value of the one-sample mean (in %BOLD) for task fMRI images, for circular (left), data-splitting (middle), and bootstrap (right). Plots show all peaks found over the G_N samples for each sample size, $N = 20, 50, 100$ (top to bottom). For each peak the true sample mean is obtained at that location from the held-out $4,000$ subject sample mean image. Note that the number of peaks and their locations are the same for circular inference and the bootstrap but are different for data-splitting as it uses the first half of the subjects in order to determine significant peaks. From these plots we see that the circularity bias is much less than for Cohen's d and that the bootstrap estimates perform very well. The data-splitting estimates are unbiased but are more variable and reflect fewer detected peaks.

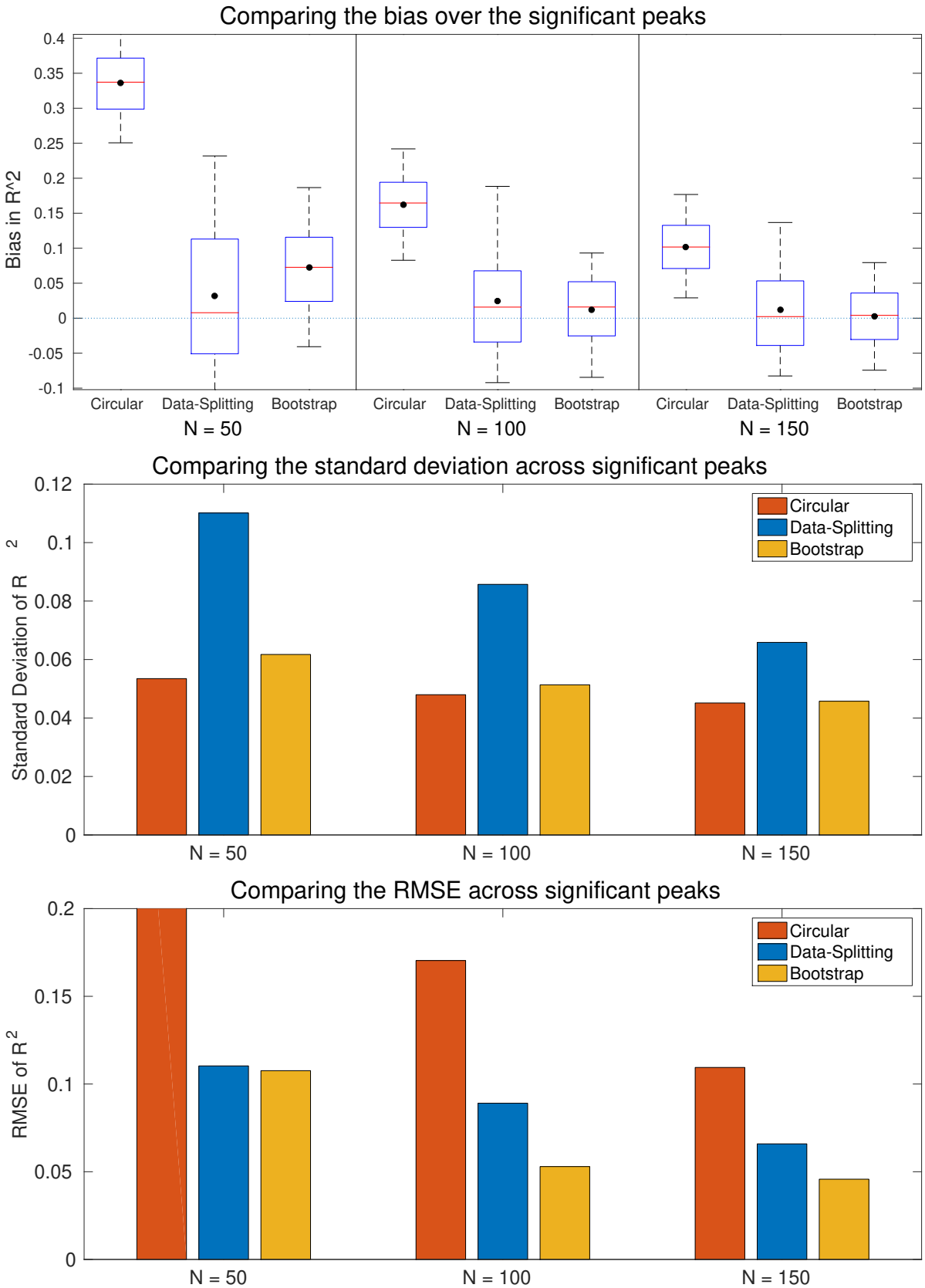

Figure 13: Comparison of estimates for the partial R^2 for age in the presence of sex and an intercept on VBM data. Bias (top), standard deviation (middle), and RMSE (bottom) are shown for $N = 50, 100$ and 150 sample sizes, based on G_N samples. While both data-splitting and bootstrap are generally unbiased, the bootstrap has the smallest RMSE for all sample sizes. Note that RMSE for the circular estimates in the $N = 50$ case is 0.3407 and so is cut off by the graph.

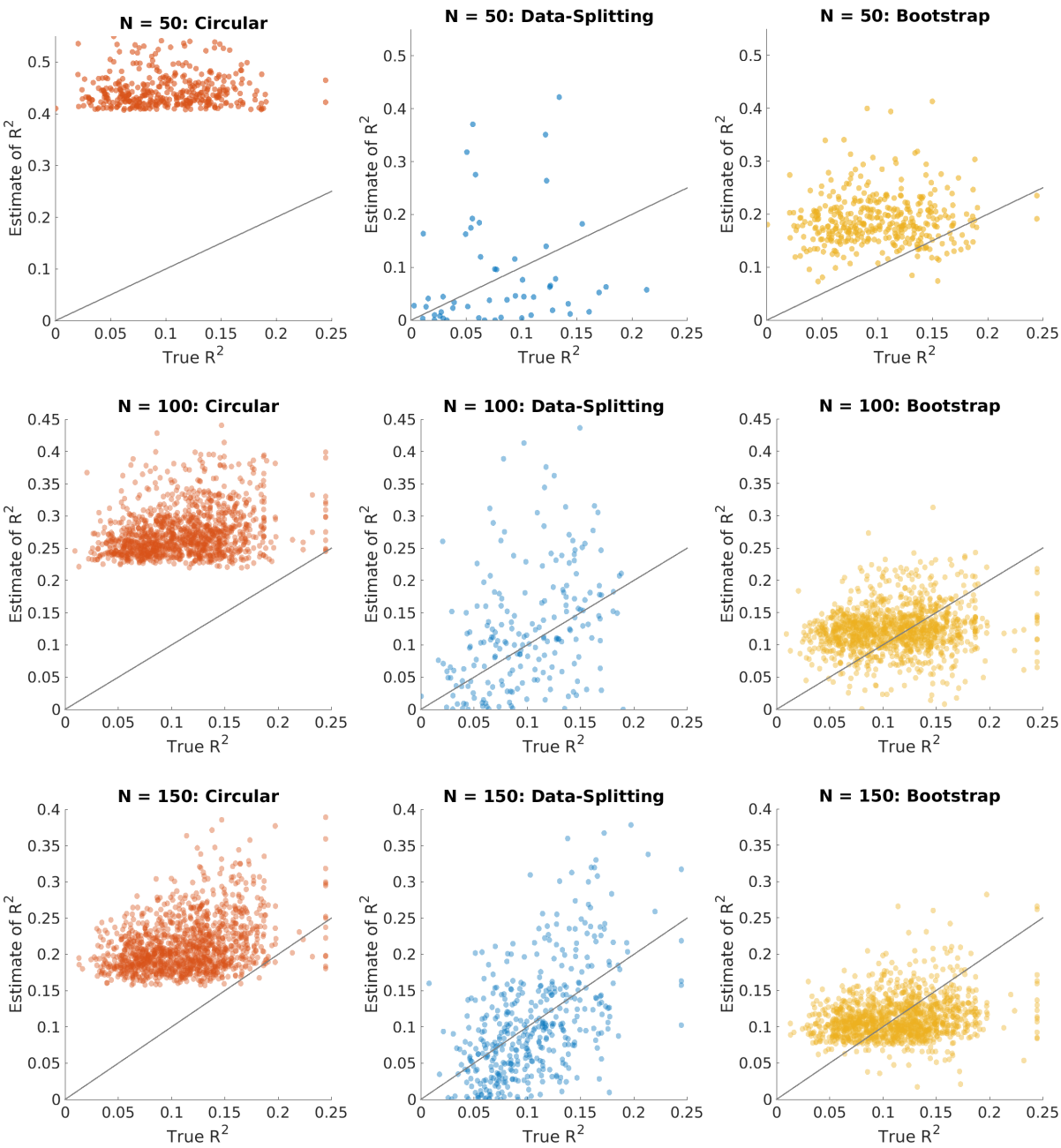

Figure 14: Plots of estimated versus true value of the partial R^2 for age, obtained using a GLM regression on VBM data, for circular (left), data-splitting (middle), and bootstrap (right). Plots show all peaks found over the G_N samples for each sample size, $N = 50, 100, 150$ (top to bottom). For each peak the true partial R^2 for age is obtained at that location from the held-out $4,000$ subject partial R^2 image. Note that the number of peaks and their locations are the same for circular inference and the bootstrap but are different for data-splitting as it uses the first half of the subjects in order to determine significant peaks. From these plots we see that the naive estimates are biased while the bootstrap and data-splitting estimates are unbiased on average. Data-splitting is the most variable, though the bootstrap over corrects values with a large true partial R^2 and under corrects those with a low partial R^2 for $N = 100, 150$. The bootstrap estimates hug the identity line more closely than the data-splitting estimates resulting in the decrease in RMSE, see Figure 13.

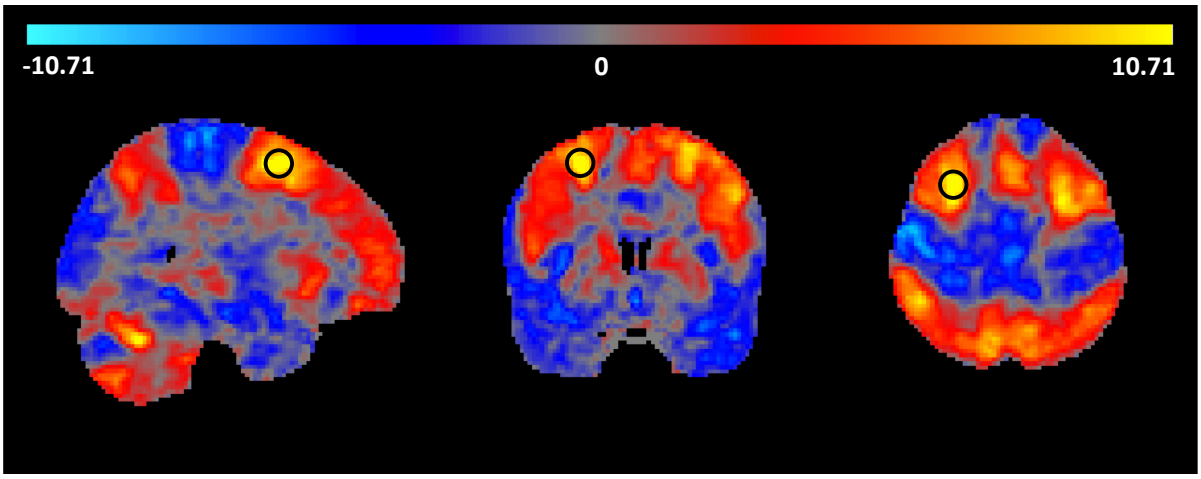

Figure 15: Slices through the one-sample t-statistic for the working memory contrast (2-back − 0-back) for subjects from the Human Connectome Project. Black circles indicate the location of the largest peak of activation which lies at the voxel (28, 8, 56) at the edge of the Medial Frontal Gyrus. At this location the observed (circular) Cohen's d is 1.519, while the bootstrap-corrected value is 1.161; the observed %BOLD change at this voxel is %0.450 and corrected estimate is %0.433.

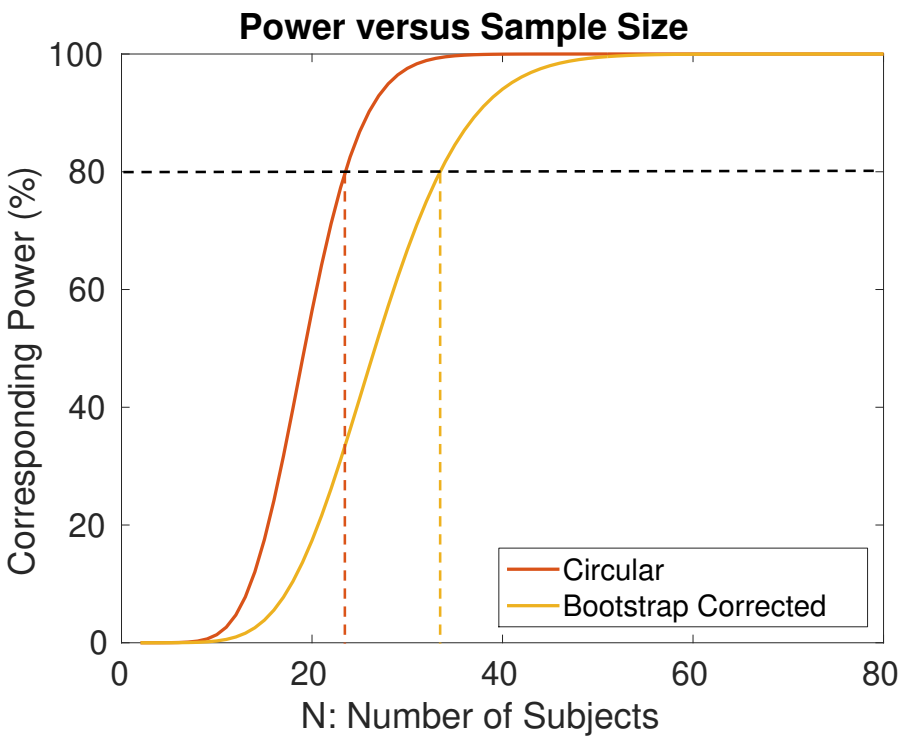

Figure 16: The power corresponding to a given sample size for the one-sample t-statistic when the T-statistic threshold is 5.10. The blue curve is the power curve corresponding to the circular estimate of the Cohen's d for the HCP working memory dataset and the red curve is the power curve corresponding to the corrected Cohen's d. Using the raw value would suggest that only 24 subjects are need to attain 80% power, when in fact the corrected estimate shows that 34 subjects are needed to provide this level of power.