Reducing type II error: Sample size affects fMRI

cluster-extent threshold to correct for multiple comparisons

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Abstract

Many procedures to correct for multiple comparisons in functional magnetic resonance imaging (fMRI) analysis require a minimum cluster-extent threshold; however, sample size is often not modeled. In the present study, a series of simulations was conducted where sample size was varied to determine whether this parameter affected cluster threshold. The primary hypothesis was that modeling sample size in the simulations would reduce cluster thresholds. A secondary hypothesis was that this reduction in cluster size was due to between-subject variability, which was tested by eliminating the corresponding standard error term. Whole-brain acquisition volume parameters were fixed, while the following key parameters were varied to reflect commonly employed ranges: sample size (N = 10, 20, or 30), corrected p-value (.05, .01, or .001), individual-voxel p-value (.01, .005, or .001), FWHM (3, 5, or 7 mm), and voxel resolution (2 or 3 mm). Each simulation consisted of 100 iterations repeated 100 times, with a total of 4,860,000 iterations and 66,420,000 simulated subjects. There was a significant effect of condition; clusters were approximately 18% smaller with versus without N modeled (and there was a significant increase in cluster thresholds for larger sample sizes). Bayesian analysis provided very strong support for the secondary hypothesis. The present findings indicate that sample size should be incorporated into all methods to provide the most accurate thresholds possible and reduce type II error. A broader range of topics is discussed including balancing type I and type II error along with the fallacy that non-task fMRI activity reflects null data.

Keywords: correction for multiple comparisons, fMRI, power, type I error, type II error

Analysis of functional magnetic resonance imaging (fMRI) data typically involves conducting statistical tests for hundreds of thousands of voxels in the brain volume such that it is necessary to correct for multiple comparisons. There are multiple methods to correct for multiple comparisons in fMRI analysis. Bonferroni correction requires dividing the desired corrected p-value (i.e., the familywise type I error rate) by the total number of comparisons, but this is method is too strict for a whole-brain analysis because of the high rate of type II error (i.e., failure to detect real effects). With the aim of balancing type I and type II error, Benjamini and Hochberg (1995) derived a procedure to limit the false discovery rate (i.e., the ratio of false activations to the sum of true and false activations; see also, Benjamini et al., 2006). In the original version of the analysis software AFNI (Cox, 1996), Monte Carlo simulations were conducted with brain activity in the acquisition volume modeled by random values with Gaussian spatial autocorrelation, and the minimum spatial extent of contiguous activity across simulations was computed to correct for multiple comparisons (as larger clusters of spurious activity are less likely by chance). Slotnick et al. (2003) developed a stand-alone script in MATLAB (Natick, MA), cluster_threshold_beta (Slotnick, 2025a), that used a similar cluster-extent correction procedure (see the Methods). A limitation of these cluster-extent threshold procedures is that they do not implement sample size. This may result in increased type II error due to overly strict (large) cluster thresholds.

Other methods to correct for multiple comparisons use actual brain activity, rather than simulated brain activity, to correct for multiple comparisons. The analysis software SPM assumes the group residual activation map, which remains after all events of interest are modeled, along with Gaussian random field theory (Kiebel et al.,

1999), to conduct cluster-extent correction for multiple comparisons. The analysis

software FSL employes the same method (Jenkinson et al., 2012). Eklund et al. (2016)

assumed that resting-state (non-task) data reflected null data and compared familywise

type I error rates for AFNI, SPM, FSL, and their own (non-cluster-extent) nonparametric

method, and presented evidence indicating that all cluster-extent correction methods

had unacceptable false-positive rates. In a Discussion paper (Slotnick, 2017a), I argued

Eklund et al.'s assumption that resting-state data reflected null data was incorrect

because the corresponding activation maps showed robust activation in default-network

regions that falsely inflated type I error, while true null data should reflect noise and be

evenly distributed across the brain (for further discussion, see Nichols et al, 2017;

Slotnick, 2017b). Seemingly motivated by Eklund et al. (2016), AFNI implemented a

new cluster-extent correction method that assumes the spatial-autocorrelation function

has a 'long tail' (deviating from the previous Gaussian assumption; Cox, 2017), which is

the currently recommended method to correct for multiple comparisons for that software

(AFNI program, 2025a). Of importance, the use of the residual brain activation map in

SPM and FSL, which reflects non-task activity, can be expected to similarly include true

activations from default-network regions that will yield larger cluster-extent thresholds

than if true null data volumes were employed. As such, the methods commonly

employed in these analysis software programs (AFNI, SPM, and FSL) may be overly

conservative and yield inflated type II error rates.

Although the large majority of fMRI users seem primarily concerned with type I

error, compelling arguments have been made that we should balance type I and type II

error (see the Discussion; Liberman & Cunningham, 2009; Hopfinger, 2017). That is,

rather than using stricter thresholds and focusing on only type I error, we should use optimal methods to balance type I and type II error. In the present study, with the aim of potentially reducing type II error, in a series of Monte Carlo simulation experiments, sample size was parametrically varied to determine whether this parameter affected cluster threshold using a new script called cluster_threshold_gamma (Slotnick, 2025b). The primary hypothesis was that incorporating sample size into the simulations would reduce the cluster-extent threshold, as the magnitude of activity in voxels at cluster boundaries was expected to be particularly variable across subjects (such that activity in these voxels would drop out, thereby reducing cluster size). It was also expected that cluster thresholds estimated by cluster_threshold_gamma would systematically increase for larger sample sizes, which are associated with lower standard errors and thus higher t-values.

Experiment 1

Methods

    fMRI simulations. Simulations were conducted using the cluster_threshold_beta script (Slotnick, 2025a) and the cluster_threshold_gamma script (Slotnick, 2025b), which were written in MATLAB and are published on the Open Science Framework (https://osf.io/). In brief, cluster_threshold_beta is a function where a user inputs fMRI acquisition volume dimensions (x_matrix, y_matrix, slices), voxel dimensions (in mm; dim_xy, dim_z), the size of the full-width-half-maximum (FWHM) smoothing kernel (in mm), resampled voxel dimensions (in mm), desired corrected p-value, specified

individual-voxel p-value, and the number of Monte Carlo simulations. The critical output

is the minimum number of contiguous resampled voxels that are required to correct for

multiple comparisons, which is referred to as the cluster-extent threshold or cluster

threshold. Within the function, brain activity is modeled at each voxel within the

acquisition volume using a normally distributed random number (from 0 to 1), this

activity is smoothed using a three-dimensional gaussian kernel, the activity is

thresholded to produce significant activations corresponding to the individual-voxel p-

value employed (e.g., at a p-value of .001, across the entire brain volume,

approximately 1 out of every 1,000 voxels will significant), the size of all contiguous

clusters of activity are counted in the brain volume, and this process is repeated

according to the number of specified iterations (typically 10,000). The cluster sizes are

summed across all iterations, and the cluster threshold is determined where that cluster

size or larger occurs less than the desired corrected p-value. Cluster_threshold_gamma

is identical except that the number of subjects (N) is specified as an input parameter,

brain activity for each subject is modeled using normally distributed random numbers,

and then this activity is smoothed for each subject using the specified gaussian kernel.

A group t-map null volume is created where the t-value at each voxel is computed by

dividing the between-subject mean magnitude of activity by the standard error (i.e., a

random-effect analysis is conducted). This t-map is thresholded to produce the specified

individual-voxel p-value and the remaining steps are identical to those described above

for cluster_threshold_beta.

        For the simulations conducted, acquisition volume parameters were fixed with

x_matrix = 64, y_matrix = 64, slices = 45, dim_xy = 3 mm, dim_z = 3 mm, and

dim_resampled = 2 mm to simulate a standard whole-brain acquisition and analysis

protocol. Other key input parameters were parametrically varied to reflect commonly

employed ranges including sample size (N = 10, 20, 30), corrected p-value (.05, .01,

.001), individual-voxel p-value (.01, .005, .001), and FWHM (3, 5, 7). Although N was

not a parameter for cluster_threshold_beta, new simulations were conducted for each of

the values such that all data points were independent. For a given input parameter set,

each Monte Carlo simulation consisted of 100 iterations resulting in a single cluster-

extent threshold and each simulation was repeated 100 times to provide a measure of

variance and allow for statistical analysis. Of importance, this translates to each data

point in the figures reflecting 10,000 iterations. It is notable that for the two conditions

(cluster_threshold_beta, cluster_threshold_gamma), there were a total of 1,620,000

iterations with 17,010,000 simulated subjects (assuming each cluster_threshold_beta

iteration consisted of a single subject). These stimulations were conducted using the

Boston College Linux High-Performance Computing (HPC) cluster, simultaneously

running 400 jobs, each with 1 CPU and 8 GB of memory, for approximately 1 week.

To illustrate the primary results, for each condition (cluster_threshold_beta,

cluster_threshold_gamma) and each parameter set, the mean cluster threshold (for 100

iterations) was plotted with 95% confidence intervals. To quantify cluster threshold sizes

between conditions, the ratio of cluster threshold means was also computed along with

95% confidence intervals, assuming standard error propagation theory of independent

normally distributed random variables (Holmes & Buhr, 2007).

Statistical analysis. Statistical analysis was conducted using JASP (JASP

Team, 2024). A frequentist two-factor ANOVA was used to test the primary hypothesis

that the cluster threshold (the dependent variable) was modulated by condition (cluster_threshold_beta, cluster_threshold_gamma) and also assessed whether there was a condition x sample size interaction. A Bayesian ANOVA with the same factors was used to determine the strength of evidence in support of the null hypothesis or the alternative hypothesis (Wagenmakers et al., 2018). For completeness, a series of two-factor ANOVAs was also conducted to confirm that cluster threshold was modulated by corrected p-value, individual-voxel p-value, and FWHM, along with exploratory analyses to determine whether condition interacted with each of these factors. Given that 40 independent statistical tests were conducted across three experiments, a single test was deemed significant if the p-value was less than .00125 (i.e., .05/40; Bonferroni corrected for multiple comparison).

Results

Figure 1a shows the cluster-extent thresholds for each condition with a FWHM smoothing kernel value of 3 mm. Figures 1b and 1c show the same plots with FWHM smoothing kernel values of 5 mm and 7 mm, respectively. It is notable the 95% confidence intervals were very small (often zero in magnitude), illustrating that the cluster-extent thresholds were very stable, even with only 100 iterations. Of direct relevance to the primary hypothesis under investigation, there was a clear difference between conditions, with cluster_threshold_gamma (in red) producing smaller thresholds than cluster_threshold_beta (in blue) for most of the comparisons. As expected, cluster_threshold_beta thresholds did not change as a function of N; however, cluster_threshold_gamma thresholds usually increased as a function of N. A

frequentist analysis confirmed that there was a significant main effect of condition

(cluster_threshold_beta vs. cluster_threshold_gamma, $F(1,16194) = 205.180$, $p < .001$,

$\eta^2 = .012$), a significant main effect of N ($F(2,16194) = 20.903$, $p < .001$, $\eta^2 = .003$), and

a significant condition x N interaction ($F(2,16194) = 20.601$, $p < .001$, $\eta^2 = .002$). A

Bayesian analysis supported these findings as the interaction model (with Condition + N

+ Condition x N) had a posterior model probability close to unity ($P(M) = 1.000$), and all

other models, including the null model, had Bayes factor values close to zero (all BF_{10}

values $< 8.605 \times 10^{-7}$), which is extreme evidence against the null model. Follow-up

analyses showed that cluster size was modulated by N in the cluster_threshold_gamma

condition (frequentist, $F(2,8097) = 50.313$, $p < .001$, $\eta^2 = .012$; Bayesian, N model $P(M)$

$= 1.00$, null model Bayes factor $= 1.584 \times 10^{-19}$, which is extreme evidence against the

null model), but was not modulated by N in the cluster_threshold_beta condition

(frequentist, $F(2,8097) = .005$, $p = .995$, $\eta^2 = 1.299 \times 10^{-6}$; Bayesian, null model $P(M) =$

$.999$, N model Bayes factor $= 0.001$, which is extreme evidence favoring the null model).

As illustrated in Figure 1, as expected, there also appeared to be greater

differential condition effects for stricter corrected p-values (which corresponds to larger

cluster thresholds) and greater differential condition effects for stricter individual-voxel p-

values (which corresponds to smaller cluster thresholds). For corrected p-values, there

was a significant main effect of corrected p-value ($F(2,16194) = 2233.825$, $p < .001$, η^2

$= .213$), and a significant condition x corrected p-value interaction ($F(2,16194) = 18.289$,

$p < .001$, $\eta^2 = .002$; this is illustrated by parametrically increasing condition effects from

top to bottom in the panels of Figure 1). Bayesian analysis supported these findings as

the interaction model (with condition + corrected p-value + condition x corrected p-

value) had a posterior model probability close to unity (P(M) = 1.000) and all other

models had Bayes factor values close to zero (all BF_{10} values < 8.533x10^{-6}), which is

extreme evidence against the null model. For individual-voxel p-values, there was a

significant main effect of individual-voxel p-value (F(2,16194) = 1261.115, p < .001, η^2 =

.133), but the condition x individual-voxel p-value interaction was not significant

(F(2,16194) = 3.537, p < .029, η^2 = 3.731x10^{-4}; this is illustrated by the relatively similar

condition effects from left to right in the panels of Figures 1a, 1b, and 1c). Bayesian

analysis supported these findings as the condition + individual-voxel p-value model had

a very high posterior model probability (P(M) = .954), the interaction model (with

condition + individual-voxel p-value + condition x individual-voxel p-value) had the

second highest posterior model probability (P(M) = .046), the sum of these posterior

probabilities was close to unity (P(M) = 1.000), and all other models had Bayes factor

values close to zero (all BF_{10} values < 8.576x10^{-50}), which is extreme evidence against

the null model.

Figures 1a, 1b, and 1c also appeared to show the expected greater differential

condition effects with increasing FWHM smoothing kernels (which correspond to larger

cluster thresholds). As a function of FWHM, there was a significant main effect of

FWHM (F(2,16194) = 6384.941, p < .001, η^2 = .433), and a significant condition x

FWHM interaction (F(2,16194) = 83.042, p < .001, η^2 = .006). Bayesian analysis

supported these findings as the interaction model (with condition + FWHM + condition x

FWHM) had a posterior model probability close to unity (P(M) = 1.000) and all other

models had Bayes factor values close to zero (all BF_{10} values < 1.207x10^{-33}), which is

extreme evidence against the null model.

Figure 1a. Cluster-extent thresholds (3 mm isotropic voxels) produced by

cluster_threshold_beta (in blue) and cluster_threshold_gamma (in red) as a function of

corrected p-value (p_cor) and individual-voxel p-value (p_vox) with a full-width-half-

maximum (FWHM) smoothing kernel of 3 mm. In each panel, for each simulation set (N

= 10, 20, and 30), the mean and 95% confidence intervals are shown, with lines

connecting the means for each condition to illustrate trends as a function of N.

Figure 1b. Cluster-extent thresholds produced by cluster_threshold_beta (in blue) and cluster_threshold_gamma (in red) as a function of corrected p_cor and p_vox with a FWHM smoothing kernel of 5 mm.

Figure 1c. Cluster-extent thresholds produced by cluster_threshold_beta (in blue) and cluster_threshold_gamma (in red) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm.

As mentioned above, cluster thresholds produced by cluster_threshold_gamma were usually smaller than those produced by cluster_threshold_beta. To quantify this effect, the cluster threshold produced by cluster_threshold_gamma was divided by the

cluster threshold produced by cluster_threshold_beta to produce a ratio. These results

are illustrated in Figures 2a, 2b, and 2c for 3, 5, and 7 mm FWHM smoothing kernels,

respectively. This ratio ranged from 0.5968 to 1.0000, had a mean of 0.8391, and had a

median of 0.8570. Thus, the average cluster threshold size produced by

cluster_threshold_gamma was 16.09% smaller than the average cluster threshold size

produced by cluster_threshold_beta.

Figure 2a. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 3 mm (the dotted line demarcates a ratio of 1, for reference). In each panel, for each simulation set (N = 10, 20, and 30), the ratio of means and 95% confidence intervals are shown, with lines connecting the means for each condition to illustrate trends as a function of N.

Figure 2b. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 5 mm (the dotted line demarcates a ratio of 1, for reference).

Figure 2c. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm (the dotted line demarcates a ratio of 1, for reference).

Experiment 2

The previous results provided evidence that cluster thresholds produced with cluster_threshold_gamma were often smaller than those produced by cluster_threshold_beta. For the cluster_threshold_gamma simulations, this may have been due to activations near the outer border of clusters being less consistent across subjects (reflected by larger standard errors in the corresponding voxels) that would decrease the likelihood that these activations would be significant in the random-effect group analysis and thus reduce cluster threshold sizes. To test this hypothesis, a new set of simulations was conducted by slightly altering the cluster_threshold_gamma script, with the only change being that the between-subject mean value was not divided by the standard error (i.e., voxel activity was simulated by the between-subject mean value rather than the corresponding t-value). These simulations are subsequently referred to as cluster_threshold_nose (cluster_threshold_gamma with no between-subject standard error). If the hypothesis is correct, cluster thresholds produced by cluster_threshold_nose should be identical to those produced by cluster_threshold_beta, which was tested in this experiment.

Methods

Unless otherwise specified, this experiment used the identical procedures as Experiment 1. For the new cluster_threshold_nose condition, there were 810,000 iterations with 16,200,000 simulated subjects. These stimulations were conducted using

the Boston College Linux HPC, simultaneously running 350 jobs for approximately 1 week. Cluster_threshold_beta values were taken from the previous simulation set.

Results

Figure 3a shows the cluster-extent thresholds for each condition with a FWHM smoothing kernel value of 3 mm. Figures 3b and 3c show the same plots with FWHM smoothing kernel values of 5 mm and 7 mm, respectively. In support of the preceding hypothesis, there was no clear difference between conditions, with cluster_threshold_nose (in green) producing identical or nearly identical thresholds as cluster_threshold_beta (in blue) for nearly all comparisons (note, green lines with no hint of blue indicate perfect overlap). Thresholds did not appear to change as a function of N for cluster_threshold_nose, which is expected given that between-subject standard error values no longer modulated cluster size. A frequentist analysis confirmed that there was no significant main effect of condition (cluster_threshold_beta vs. cluster_threshold_nose, $F(1,16194) = 9.428 \times 10^{-6}$, $p = .998$, $\eta^2 = 5.822 \times 10^{-10}$), no significant main effect of N ($F(2,16194) = 6.498 \times 10^{-4}$, $p = .999$, $\eta^2 = 8.025 \times 10^{-8}$), and no significant condition x N interaction ($F(2,16194) = .006$, $p = .994$, $\eta^2 = 7.336 \times 10^{-7}$). A Bayesian analysis supported these findings as the null model had a posterior model probability close to unity ($P(M) = .982$) and all other models had Bayes factor values close to zero (all BF_{10} values < 0.019), which is very strong evidence favoring the null model.

As illustrated in Figure 3, there did appear to be greater differential condition effects as a function of corrected p-values or individual-voxel p-values, which was expected. For corrected p-values, there was a significant main effect of corrected p-value ($F(2,16194) = 2271.193$, $p < .001$, $\eta^2 = .219$) but no significant condition x corrected p-value interaction ($F(2,16194) = .003$, $p = .997$, $\eta^2 = 2.759 \times 10^{-7}$). Bayesian analysis supported these findings as the corrected p-value model had a posterior model probability close to unity ($P(M) = .983$) and all other models had Bayes factor values close to zero (null model $BF_{10} = 0.000$, all other BF_{10} values < 0.018), which is extreme against the null model. For individual-voxel p-values, there was a significant main effect of individual-voxel p-value ($F(2,16194) = 1187.255$, $p < .001$, $\eta^2 = .128$) but no significant condition x individual-voxel p-value interaction ($F(2,16194) = 8.177 \times 10^{-4}$, $p = .999$, $\eta^2 = 8.807 \times 10^{-8}$). Bayesian analysis supported these findings as the individual-voxel p-value model had a posterior model probability close to unity ($P(M) = .983$) and all other models had Bayes factor values close to zero (null model $BF_{10} = 0.000$, all other BF_{10} values < 0.018), which is extreme evidence against the null model.

Figure 3 also appeared to show the expected greater differential condition effects with increasing FWHM smoothing kernels (which correspond to larger cluster thresholds). As a function of FWHM, there was a significant main effect of FWHM ($F(2,16194) = 7052.289$, $p < .001$, $\eta^2 = .466$) but no significant condition x FWHM interaction ($F(2,16194) = .002$, $p = .998$, $\eta^2 = 1.259 \times 10^{-7}$). Bayesian analysis supported these findings as the FWHM model had a posterior model probability close to unity ($P(M) = .982$) and all other models had Bayes factor values close to zero (null model

$BF_{10} = 0.000$, all other BF_{10} values < .019), which is extreme evidence against the null

model.

Figure 3a. Cluster-extent thresholds (3 mm isotropic voxels) produced by

cluster_threshold_beta (in blue) and cluster_threshold_nose (in green) as a function of

corrected p-value (p_cor) and individual-voxel p-value (p_vox) with a full-width-half-

maximum (FWHM) smoothing kernel of 3 mm. In each panel, for each simulation set (N

= 10, 20, and 30), the mean and 95% confidence intervals are shown, with lines

connecting the means for each condition to illustrate trends as a function of N.

Figure 3b. Cluster-extent thresholds produced by cluster_threshold_beta (in blue) and

cluster_threshold_nose (in green) as a function of corrected p_cor and p_vox with a

FWHM smoothing kernel of 5 mm.

Figure 3c. Cluster-extent thresholds produced by cluster_threshold_beta (in blue) and cluster_threshold_nose (in green) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm.

To quantify the similarity in cluster sizes in both conditions, for each simulation set, the cluster threshold produced by cluster_threshold_nose was divided by the cluster threshold produced by cluster_threshold_beta to produce a ratio. These results

are illustrated in Figures 4a, 4b, and 4c for 3, 5, and 7 mm FWHM smoothing kernels,

respectively. This ratio ranged from 0.9904 to 1.0106, had a mean of 1.0008, and had a

median of exactly 1. Thus, the average cluster threshold size produced by

cluster_threshold_nose was nearly identical to the average cluster threshold size

produced by cluster_threshold_beta.

Figure 4a. Ratio of cluster thresholds produced by cluster_threshold_nose and

cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM

smoothing kernel of 3 mm (the dotted line demarcates a ratio of 1, for reference). In each panel, for each simulation set (N = 10, 20, and 30), the ratio of means and 95% confidence intervals are shown, with lines connecting the means for each condition to illustrate trends as a function of N.

Figure 4b. Ratio of cluster thresholds produced by cluster_threshold_nose and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 5 mm (the dotted line demarcates a ratio of 1, for reference).

Figure 4c. Ratio of cluster thresholds produced by cluster_threshold_nose and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm (the dotted line demarcates a ratio of 1, for reference).

Experiment 3

The previous simulations were conducted using an acquisition volume with 3 mm isotropic voxels. With improvements in MRI scanner strength and fMRI acquisition protocols, smaller voxel sizes are becoming more common. In an effort to generalize the findings, this experiment was conducted using the identical procedures as Experiments 1 and 2, but the acquisition volume consisted of 2 mm isotropic voxels. As with the previous experiments, the hypotheses were that cluster_threshold_gamma would produce smaller cluster-extent thresholds than cluster_threshold_beta and that cluster_threshold_nose would produce the same cluster-extent thresholds as cluster_threshold_beta.

Methods

Unless otherwise specified, the methods were identical to Experiments 1 and 2, with the key difference being the acquisition volume voxel dimensions were set to 2 mm. To ensure similar whole-brain coverage to the previous experiments, matrix size was increased by a factor of 3/2 (rounded up) in all dimensions to 96 x 96 x 68 (i.e., 192 x 192 x 136 mm^3, which has the identical spatial extent in the x- and y-dimensions and was 0.74% larger in the z-dimension than the previous experiments). The three conditions (cluster_threshold_beta, cluster_threshold_gamma, cluster_threshold_nose) required a total of 2,430,000 iterations with 33,210,000 simulated subjects.

Results

Figure 5a shows the cluster-extent thresholds for each condition with a FWHM smoothing kernel value of 3 mm. Figures 5b and 5c show the same plots with FWHM smoothing kernel values of 5 mm and 7 mm, respectively. Of direct relevance to the primary hypothesis under investigation, there was a clear difference between conditions, with cluster_threshold_gamma (in red) producing smaller thresholds than both cluster_threshold_beta (in blue) and cluster_threshold_nose (in green).

Mirroring the order of analyses in the previous experiments, the statistical analysis first compared the cluster_threshold_beta and cluster_threshold_gamma conditions (as in Experiment 1). A frequentist analysis confirmed that there was a significant main effect of condition (for cluster_threshold_beta vs. cluster_threshold_gamma, $F(1,16194) = 183.924$, $p < .001$, $\eta^2 = .011$), a significant main effect of N ($F(2,16194) = 18.887$, $p < .001$, $\eta^2 = .002$), and a significant condition x N interaction ($F(2,16194) = 19.227$, $p < .001$, $\eta^2 = .002$). A Bayesian analysis supported these findings as the interaction model (with Condition + N + Condition x N) had a posterior model probability close to unity ($P(M) = 1.000$), and all other models, including the null model, had Bayes factor values close to zero (all BF_{10} values $< 3.184 \times 10^{-6}$), which is extreme evidence against the null model. Follow-up analyses showed that cluster size was modulated by N in the cluster_threshold_gamma condition (frequentist, $F(2,8097) = 46.326$, $p < .001$, $\eta^2 = .011$; Bayesian, N model $P(M) = 1.00$, null model Bayes factor $= 8.022 \times 10^{-18}$, which is extreme evidence against the null model), but was not modulated by N in the cluster_threshold_beta condition (frequentist, $F(2,8097) =$

.005, p = .995, $\eta^2 = 1.194 \times 10^{-6}$; Bayesian, null model P(M) = .999, N model Bayes factor

= 0.001, which is extreme evidence favoring the null model).

As illustrated in Figure 5, there also appeared to be greater differential condition

effects (between cluster_threshold_beta and cluster_threshold_gamma) for stricter

corrected p-values, stricter individual-voxel p-values, and increasing FWHM smoothing

kernels, which were expected. For corrected p-values, there was a significant main

effect of corrected p-value (F(2,16194) = 1839.888, p < .001, η^2 = .183) and a

significant condition x corrected p-value interaction (F(2,16194) = 14.558, p < .001, η^2 =

.001; this is illustrated by parametrically increasing condition effects from top to bottom

in the panels of Figure 5). Bayesian analysis supported these findings as the interaction

model (with condition + corrected p-value + condition x corrected p-value) had a

posterior model probability close to unity (P(M) = 1.000) and all other models had Bayes

factor values close to zero (all BF_{10} values < 3.354×10^{-4}), which is extreme evidence

against the null model. For individual-voxel p-values, there was a significant main effect

of individual-voxel p-value (F(2,16194) = 1116.789, p < .001, η^2 = .120) but the

condition x individual-voxel p-value interaction was not significant (F(2,16194) = 2.743,

p = .064, $\eta^2 = 2.942 \times 10^{-4}$; this is illustrated by the relatively similar condition effects from

left to right in the panels of Figures 5a, 5b, and 5c). Bayesian analysis supported these

findings as the condition + individual-voxel p-value model had a very high posterior

model probability (P(M) = .978), the interaction model (with condition + individual-voxel

p-value + condition x individual-voxel p-value) had the second highest posterior model

probability (P(M) = .022), the sum of these posterior probabilities was close to unity

(P(M) = 1.000), and all other models had Bayes factor values close to zero (all BF_{10}

values < 7.145x10^{-44}), which is extreme evidence against the null model. As a function

of FWHM, there was a significant main effect of FWHM (F(2,16194) = 7171.198, p <

.001, η^2 = .462), and a significant condition x FWHM interaction (F(2,16194) = 93.317, p

< .001, η^2 = .006). Bayesian analysis supported these findings as the interaction model

(with condition + FWHM + condition x FWHM) had a posterior model probability close to

unity (P(M) = 1.000) and all other models had Bayes factor values close to zero (all BF$_{10}$

values < 5.701x10^{-38}), which is extreme evidence against the null model.

Figure 5a. Cluster-extent thresholds (2 mm isotropic voxels) produced by cluster_threshold_beta (in blue), cluster_threshold_gamma (in red), and cluster_threshold_nose (in green) as a function of corrected p-value (p_cor) and individual-voxel p-value (p_vox) with a full-width-half-maximum (FWHM) smoothing kernel of 3 mm. In each panel, for each simulation set (N = 10, 20, and 30), the mean and 95% confidence intervals are shown, with lines connecting the means for each condition to illustrate trends as a function of N.

Figure 5b. Cluster-extent thresholds produced by cluster_threshold_beta (in blue), cluster_threshold_gamma (in red), and cluster_threshold_nose (in green) as a function of corrected p_cor and p_vox with a FWHM smoothing kernel of 5 mm.

Figure 5c. Cluster-extent thresholds produced by cluster_threshold_beta (in blue), cluster_threshold_gamma (in red), and cluster_threshold_nose (in green) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm.

For this set of simulations, cluster thresholds produced by

cluster_threshold_gamma were always smaller than those produced by

cluster_threshold_beta. To quantify this effect, the cluster threshold produced by

cluster_threshold_gamma was divided by the cluster threshold produced by

cluster_threshold_beta to produce a ratio. These results are illustrated in Figures 6a,

6b, and 6c for 3, 5, and 7 mm FWHM smoothing kernels, respectively. This ratio ranged

from 0.5264 to 0.9291, had a mean of 0.8024, and had a median of 0.8392. Thus, the

average cluster threshold size produced by cluster_threshold_gamma was 19.76%

smaller than the average cluster threshold size produced by cluster_threshold_beta.

Figure 6a. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 3 mm (the dotted line demarcates a ratio of 1, for reference). In each panel, for each simulation set (N = 10, 20, and 30), the ratio of means and 95% confidence intervals are shown, with lines connecting the means for each condition to illustrate trends as a function of N.

Figure 6b. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 5 mm (the dotted line demarcates a ratio of 1, for reference).

Figure 6c. Ratio of cluster thresholds produced by cluster_threshold_gamma and cluster_threshold_beta (solid line) as a function of p_cor and p_vox with a FWHM smoothing kernel of 7 mm (the dotted line demarcates a ratio of 1, for reference).

Next, cluster_threshold_beta and cluster_threshold_nose were compared, as in Experiment 2. As illustrated in Figure 5, There was no clear difference between conditions, with cluster_threshold_nose (in green) producing identical or nearly identical

thresholds as cluster_threshold_beta (in blue) for all comparisons (note, green lines with

no hint of blue indicate perfect overlap). A frequentist analysis confirmed that there was

no significant main effect of condition (cluster_threshold_beta vs.

cluster_threshold_nose, $F(1,16194) = .004$, $p =.951$, $\eta^2 = 2.298 \times 10^{-7}$), no significant

main effect of N ($F(2,16194) = .002$, $p = .998$, $\eta^2 = 2.920 \times 10^{-7}$), and no significant

condition x N interaction ($F(2,16194) = .003$, $p = .997$, $\eta^2 = 3.234 \times 10^{-7}$). A Bayesian

analysis supported these findings as the null model had a posterior model probability

close to unity ($P(M) = .982$) and all other models had Bayes factor values close to zero

(all BF_{10} values < 0.019), which is very strong evidence favoring the null model.

As expected, there appeared to be greater differential condition effects for stricter

corrected p-values, stricter individual-voxel p-values, and increasing FWHM smoothing

kernels. For corrected p-values, there was a significant main effect of corrected p-value

($F(2,16194) = 1859.538$, $p < .001$, $\eta^2 = .187$) but no significant condition x corrected p-

value interaction ($F(2,16194) = .007$, $p = .993$, $\eta^2 = 7.188 \times 10^{-7}$). Bayesian analysis

supported these findings as the corrected p-value model had a posterior model

probability close to unity ($P(M) = .983$) and all other models had Bayes factor values

close to zero (null model $BF_{10} = 0.000$, all other BF_{10} values < 0.019), which is extreme

against the null model. For individual-voxel p-values, there was a significant main effect

of individual-voxel p-value ($F(2,16194) = 1042.773$, $p < .001$, $\eta^2 = .114$) but no

significant condition x corrected p-value interaction ($F(2,16194) = 5.436 \times 10^{-4}$, $p =.999$,

$\eta^2 = 5.948 \times 10^{-8}$). Bayesian analysis supported these findings as the individual-voxel p-

value model had a posterior model probability close to unity ($P(M) = .983$) and all other

models had Bayes factor values close to zero (null model $BF_{10} = 0.000$, all other BF_{10}

values < 0.018), which is extreme evidence against the null model. As a function of

FWHM, there was a significant main effect of FWHM ($F(2,16194) = 7928.393$, $p < .001$,

$\eta^2 = .495$) but no significant condition x corrected p-value interaction ($F(2,16194) = .004$,

$p = .996$, $\eta^2 = 2.68 \times 10^{-7}$). Bayesian analysis supported these findings as the FWHM

model had a posterior model probability close to unity ($P(M) = .983$) and all other

models had Bayes factor values close to zero (null model $BF_{10} = 0.000$, all other BF_{10}

values < .019), which is extreme evidence against the null model.

To quantify the similarity in cluster sizes in both conditions, for each simulation

set, the cluster threshold produced by cluster_threshold_nose was divided by the

cluster threshold produced by cluster_threshold_beta to produce a ratio. This ratio

ranged from 0.9885 to 1.0077, had a mean of 1.0001, and had a median of exactly 1.

Thus, the average cluster threshold size produced by cluster_threshold_nose was

nearly identical to the average cluster threshold size produced by

cluster_threshold_beta.

Discussion

The primary hypothesis of the present investigation was that incorporating

sample size into the simulations would reduce the cluster-extent threshold. It was

further hypothesized that this reduction in cluster-extent threshold was due to between-

subject variability. The identical pattern of results was obtained in Experiments 1 and 2,

which used an isotropic voxel size of 3 mm, and Experiment 3, which used an isotropic

voxel size of 2 mm, such that the results of all experiments will be discussed together.

In support of the first hypothesis (tested in Experiments 1 and 3), frequentist analyses showed a significant effect of condition (cluster_threshold_beta vs. cluster_threshold_gamma). Specifically, cluster_threshold_gamma clusters were about 18% smaller than cluster_threshold_beta clusters. There was also a significant effect of sample size, showing that cluster-extent threshold was affected by the specific sample size, and a significant condition x sample size interaction. The interaction was driven by significant increases in cluster_threshold_gamma thresholds for larger sample sizes, which can be attributed to lower standard error values resulting in higher t-values (and thus more voxels being classified as significant). All the preceding findings were supported by Bayesian analyses. To test the second hypothesis, between-subject variability modeled in cluster_threshold_gamma was eliminated by removing the standard error term to create cluster_threshold_nose (in Experiments 2 and 3). In support of this hypothesis, frequentist analyses showed no significant effects of condition (cluster_threshold_beta vs. cluster_threshold_nose), sample size, or their interaction. Of importance, the Bayesian analyses produced very strong evidence favoring the null model. These findings show that sample size is an important factor in fMRI methods that correct for multiple comparisons and provides an explanation of how sample size modulates cluster-extent threshold.

In addition to the main hypotheses under investigation, the effects of condition and corrected p-value, individual-voxel p-value, and FWHM were evaluated. As expected, stricter corrected p-values were associated with larger cluster-extent thresholds, stricter individual-voxel p-values were associated with smaller cluster-extent thresholds, and larger FWHM values were associated with larger cluster-extent

thresholds. For the cluster_threshold_beta versus cluster_threshold_gamma

comparison, there were significant condition x corrected p-value and condition x FWHM

interactions, but the condition x individual-voxel p-value interaction was not significant.

For the cluster_threshold_beta versus cluster_threshold_nose comparison, none of

these interactions were significant. Bayesian analyses supported these findings. These

results show that sample size is a critical parameter that can interact with other

parameters. Thus, incorporating sample size into algorithms that correct for multiple

comparisons in fMRI analysis is necessary to accurately estimate cluster-extent

threshold. Toward this aim, cluster_threshold_gamma is now available for use by the

neuroimaging community (Slotnick, 2025b).

Other methods should incorporate sample size

    More broadly, the present finding that sample size can affect cluster-extent

threshold should be incorporated into other methods to reduce type II error. This

includes Monte Carlo simulation methods such as the original version of AFNI (Cox,

1996) and the currently recommended 'long-tail' version of AFNI (Cox et al., 2017). For

nonparametric permutation methods (e.g., Eklund et al., 2017), the actual number of

participants corresponding to the to-be-corrected study should be employed, rather than

an arbitrary sample size that assumes the value of this parameter will not affect the

results.

The fallacy that non-task activity reflects null data

Analysis methods that employ the group residual activation map, including SPM (Kiebel et al., 1999) and FSL (Jenkinson et al., 2012), implicitly take sample size into account. However, these methods assume that the residual map reflects null data, which is questionable given that such data is defined as non-task activity and thus likely reflects activity in the default-mode network (Slotnick, 2017a, 2017b). The default network has been associated with many cognitive processes such as planning for the future, daydreaming, mind wandering, lapses of attention, and retrieval of personal information (for a review, see Buckner, Andrews-Hanna, & Schacter, 2008). As illustrated in Figure 7a, non-task/resting-state activity is associated with robust activity in many brain regions including the dorsolateral prefrontal cortex, the medial prefrontal cortex, the inferior parietal cortex, and the medial parietal cortex. Methods that assume non-task data, such as the group residual map in SPM and FSL, reflects null activity, along with those that explicitly assume resting-state data reflects null activity (Eklund et al., 2017, 2019) or model this type of brain activity (i.e., the long-tail version of AFNI; Cox et al., 2017), likely enforce stricter-than-optimal thresholds resulting in increased type II error. Figure 7, panels b and c, illustrate "false clusters" from two different datasets (Eklund et al., 2019) that clearly reflect default-network activity (compare Figures 7b and 7c to Figure 7a). Although these default-network activations are sometimes referred to as "false clusters" (Eklund et al., 2017, 2019), they actually reflect true clusters that will artifactually inflate cluster-extent thresholds (Slotnick, 2017a; the

primary one-tailed t-tests results in Eklund et al., 2017, also appeared to be artifactually

inflated; Flandin & Friston, 2019; Slotnick, 2017b).

Figure 7. fMRI default-network activity and resting-state activity that has been assumed

to reflect null data. (a) Default-network activity (ovals demarcate default-network

regions; axial view, anterior toward the top; adapted from Figure 3 in NeuroImage, 37/4,

Randy L. Buckner and Justin L. Vincent, Unrest at rest: Default activity and

spontaneous network correlations, 1091–1096, 2007, with permission from Elsevier). (b)

Resting-state "false clusters" from the Cambridge dataset (ovals copied from panel a).

(c) Resting state "false clusters" from the Oulu dataset (ovals copied from panel a; b

and c were adapted from Eklund et al., 2019, Figure 7 and Figure 8, respectively;

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As highlighted in Slotnick (2017a, 2017b), a more accurate way to model null

data would be to contrast odd versus even trials of one event type. Ideally, this event

should correspond to an isolated cognitive process, with minimal true brain activations,

to avoid variability between regressors. Resting-state (or residual) activation maps would be a poor choice given that default-network activity has a broad spatial extent, high magnitude, and high variability (Mao et al., 2015; Figure 7c shows an extreme example). After contrasting well-matched event types (corresponding to minimal activity), it would be expected that true null data would have a relatively uniform distribution across the brain.

It should be noted that the newest method of the AFNI program (2025b) takes sample size into account and makes a laudable attempt to create a true null volume. Specifically, the procedure generates the null volume by randomizing the sign of the residuals for each subject (Cox et al., 2017). Assuming that residuals reflect default-network activity, this procedure should yield approximately half of the subject with increases in activity in default-network regions and the other half of the subjects with decreases in activity in default-network regions, the sum of which should produce activations that vary around zero in these and other regions. As mentioned above, activity in the default-network regions can be highly variable and thus this procedure may produce significant differences and inflate cluster-extent thresholds. Still, this is the only method employing residuals that may actually eliminate true activity from the analysis and thus is arguably the most accurate of such methods available. To avoid the issues with default-network activity described above, it would likely be more accurate to conduct a similar procedure but use the single event regressor (of all regressors in a particular study) that produces the least number of significant activations (i.e., is most similar to null a priori) and assign exactly half of the participants with a positive sign and the other half with a negative sign, the sum of which should create the most accurate

null volume for that dataset. Optimizing procedures that estimate the null volume to correct for multiple comparisons is an important topic for future research.

More degrees of freedom, more problems

For a given experiment, type I error and type II error are linked. At the desired individual-voxel p-value, if the corrected p-value is made stricter, type I error will decrease and type II error will increase, while if the corrected p-value is made more lenient, type I error will increase and type II error will decrease. Although there is a general focus in the field on reducing type I error, it is now required to correct for multiple comparisons in an acceptable manner for an fMRI study to be published in a respectable journal. That is, at this time, familywise type I error is required to be controlled in virtually all fMRI studies. As such, type II error should be considered a more pressing problem in the field.

One way to reduce type II error is to increase sample size. For a given study, the dual aims of generalizing to the population and increasing power (i.e., detecting an effect when it exists; 1 – type II error) tend to boost sample size, while the high cost of conducting fMRI studies tends to restrict sample size. Button et al. (2013) estimated that the average statistical power of neuroscience studies, which included an analysis of brain volume abnormality studies and animal studies, was between 8 and 31% and to achieve a power of 80% in different rodent maze completion experiments would require 68-134 subjects (an analysis of fMRI data was not conducted). Thus, approximately 100 subjects were recommended to achieve sufficient power. Aligning with Button et al.,

Poldrack et al. (2017) showed that median sample size of fMRI studies has increased from 9 in 1996 to 28.5 in 2015 and estimated the corresponding effects sizes needed to achieve 80% power ranged from about 1.25 to 0.75 (i.e., only large effect sizes had sufficient power for true effects to be detected). Poldrack et al. argued that much larger sample sizes than are typically utilized are needed to achieve sufficient power, acknowledging "given that research funding will probably not increase to accommodate these larger samples, fewer studies may be funded, and researchers with fewer resources may have a more difficult time performing research that meets these standards" (p. 117). Both Button et al. and Poldrack et al. made many assumptions when computing sample size estimates to achieve 80% power and, at least for fMRI, the estimates seem at odds with reality. For example, in 2020, approximately 50% of all episodic memory studies reported activity in the hippocampus (Slotnick, 2023), even though fMRI studies almost never have large sample sizes due to the high cost off scanning. This suggests that fMRI studies with normal sample sizes (e.g., 20 participants) usually have sufficient power to detect activity of interest. Even if the power estimates of Button et al. and Poldrack et al. were correct, other factors need to be considered when deciding whether to conduct one large study versus several smaller studies.

Lieberman and Cunningham (2009) highlighted four negative consequences on focusing on only type I error including: 1) "increased type II errors", 2) "a bias toward publishing large and obvious effects", 3) "a bias against observing effects associated with complex cognitive and affective processes", and 4) "deficient meta-analyses" (p. 424). Along the same lines, Hopfinger (2017) underscored that "replication across labs

remains a most critical part of scientific study" and "an overemphasis on increasingly conservative thresholds can negatively impact the potential for replication of studies and the pursuit and reporting of innovative results" (p. 145). Said another way, if one large study is conducted from a single laboratory (with say, 100 participants) versus many studies from different laboratories (e.g., with 20 participants), this will stifle meta-analyses, replication, and innovation. Relating to points 1 and 2 of Lieberman and Cunningham, we recently published an fMRI study with 864 participants (mining data from the Human Connectome Project; Fritch et al., in press). At a standard individual-voxel threshold of p < .001, a general linear model analysis produced resting-state activity across the entire brain, which can be attributed to the massive degrees of freedom. A p-value $< 1 \times 10^{-30}$ was required for the results to be interpretable, which necessarily translated in a high degree of type II error. A related issue is that large datasets available for mining cannot be used to evaluate specific hypotheses that are of interest to the large majority of scientists. Mining such data puts the answer (i.e., the data from someone else's experiment) before the question, which is not an efficient way to conduct science, where an experiment should be intelligently designed to adjudicate between critical hypotheses (Platt, 1964). Considering the factors above, although at first blush it may seem best to conduct a lower number of fMRI studies with larger sample sizes, it seems prudent to conduct a higher number of fMRI studies with sufficient sample sizes to maximize the chances of revealing important effects in a timely manner. Determining optimal sample size is an important topic for future research.

With the understanding that there are constraints on fMRI sample sizes, Cunningham and Koscik (2017) proposed a novel method to reduce type II error. Given that certain regions are expected to be active in a given experiment, those regions can be subjected to a more lenient threshold (thus decreasing type II error), whereas the error in other regions (e.g., the rest of the brain) could be subjected to a stricter threshold such that the familywise type I error rate across the entire brain would be set to the desired level. This algorithm, or other to-be-derived algorithms that may reduce type II error while controlling familywise type I error, should be incorporated into widely available analysis software or scripts.

Conclusion

The current study showed that increasing sample size can reduce the cluster-extent threshold. Employing these smaller cluster thresholds (that can be easily computed with the cluster_threshold_gamma script; Slotnick, 2025b) will reduce type II error rate, while still maintaining the desired type I error rate. The present finding has ramifications for methods that do not incorporate sample size into their computations, and this should be done to reduce type II error. It was also argued that fMRI group residuals and resting-state data do not reflect true null volumes, employing such volumes will increase type II error, and that null volumes should be estimated using appropriate techniques. Our overall aim should be to optimize the methods we employ to balance type I error with type II error. By doing so, the field can make important discoveries as rapidly as possible.

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