Reevaluating "Cluster Failure" Using Nonparametric Control of the False Discovery Rate

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I n a substantial contribution to the functional magnetic resonance imaging (fMRI) field, Eklund et al. [1] use nonparametric methods to demonstrate that random field theory (RFT)-based family-wise error (FWE) correction for cluster inference does not control errors appropriately, and this discrepancy is more pronounced for lenient cluster defining thresholds (CDT). Moreover, they point to violations of RFT assumptions as the culprit for this discrepancy.

Given these results, how should we interpret existing fMRI literature that used RFT-based FWE-corrected p-values ($p_{\text{RFT-FWE}}$)? To suggest caution is reasonable but incomplete; we require concrete, quantitative guidelines to enable appropriate calibration of skepticism.

Here, we undertake an initial attempt at such guidance. We heed [1]'s warning and prefer nonparametric null distributions to RFT. However, we focus on the False Discovery Rate (FDR); [2]), which is a more natural target for multiple testing control (as recognized by Nichols in previous work; [3]): A researcher is naturally more concerned with the proportion of reported clusters that are false positives (FDR) than whether *any* are false positives (FWE). Thus, a reader considering a table of clusters significant under RFT-FWE might ask: Which of these results would have survived had the study instead employed a nonparametric FDR-based method?

We address this question using task fMRI data [4, 5] analyzed in [1] (available from openfMRI [6]).

For each contrast, we generate 5,000 realizations of the data through sign-flipping (code, data, Extended Methods: http://github.com/mangstad/FDR_permutations). To obtain a null distribution of cluster extents (for an arbitrary cluster), we combine normalized frequencies of extents at each realization. This distribution is used to assign uncorrected p-values to each observed cluster. We next submit the vector of uncorrected p-values for each contrast to Benjamini and Hochberg's [2] FDR procedure with $\alpha_{\text{FDR}} = .05$ (cf. [7] for a parametric implementation of cluster-wise FDR).

We compare $p_{\text{RFT-FWE}}$-values to q_{FDR}-values and note whether they survive FDR-correction under $\alpha_{\text{FDR}} = .05$. We generate separate plots for this analysis conducted at CDT={.001, .01}.

Based on our results (Figure 1), we suggest nearly all clusters identified as significant when using CDT=.001 and RFT-FWE correction are trustworthy by the nonparametric FDR benchmark. For clusters identified as significant with CDT=.01 and RFT-FWE correction, the guidance depends on the corrected p-value: clusters with $p_{\text{RFT-FWE}} < .00001$ appear consistently trustworthy by the nonparametric FDR benchmark, whereas clusters with $p_{\text{RFT-FWE}} > .00001$ are not reliably trustworthy.

These findings have promising implications for past fMRI studies using RFT-based cluster-level inference that used this stricter CDT=.001, estimated to be upwards of 8,500 reports [8, 9]. While the story is mixed for CDT=.01 (used in approximately 3,500 studies [8, 9]), our findings suggest that not all such previously reported clusters are unreliable: we identify .00001 as a potential cutoff for trustworthiness.

Our results offer initial guidance on interpreting past literature that employed RFT-based FWE, providing a more granular appreciation of the relationship between $p_{\text{RFT-FWE}}$ and trustworthiness of the result. A more comprehensive examination of fMRI task data sets that used RFT-based FWE may further refine this guidance.

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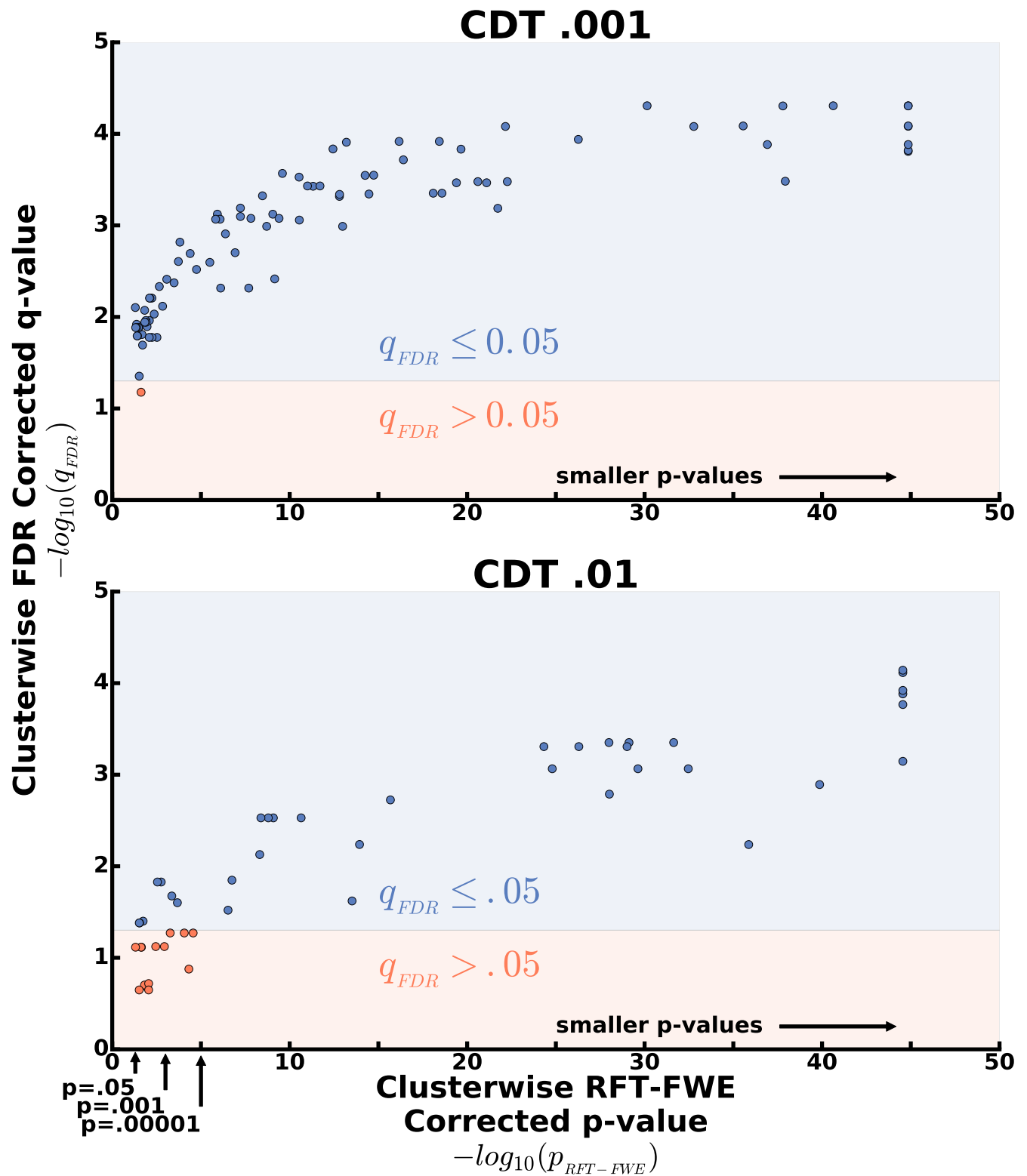
Fig. 1. Assessing RFT-Based FWE Using an FDR Benchmark. We submitted the same task data analyzed by Eklund et al. [1, 5, 6] to nonparametric clusterwise FDR analysis. For CDT $= .001$ (top), RFT-based FWE approximates effective FDR control with $\alpha_{\text{FDR}} = .05$. For CDT $= .01$ (bottom), only clusters with $p_{\text{RFT-FWE}} \leq .00001$ reliably survived correction at $\alpha_{\text{FDR}} = .05$.