Which Findings from the Functional Neuroimaging Literature Can We Trust?

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In their recent "Cluster Failure" paper, Eklund and colleagues [1] cast doubt on the accuracy of a widely used statistical test in functional neuroimaging. Here, we leverage nonparametric methods that control the false discovery rate in order to offer more nuanced, quantitative guidance about which findings in the existing literature can be trusted. We show that, in the task studies examined by Eklund et al., most clusters originally reported to be significant are indeed trustworthy by the false discovery rate benchmark.

In 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 techniques for cluster-level inference do not control errors as they are supposed to, and this discrepancy is pronounced for lenient cluster defining thresholds (CDT). Moreover, they point to violations of RFT assumptions as the culprit for this discrepancy.

Given these results, what advice can we offer to the reader exploring existing fMRI literature when faced with a table of cluster-wise 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 to construct such guidance. We heed Eklund et al.'s warning and prefer null distributions obtained through nonparametric methods rather than 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). Given these considerations, a reader faced with a table of clusters significant under RFT-FWE correction 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 by Eklund et al. (available from openfMRI [6]).

For each contrast, we generate 5,000 realizations of the data through sign-flipping (our code, data, Extended Methods: http://github.com/mangstad/FDR_permutations). To obtain a null distribution of cluster extents (for an arbitrarily chosen 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=$\{.001, .01\}$.

Results (see Figure 1) show that for CDT=.001, only one cluster significant at $\alpha_{\text{RFT-FWE}} = .05$ failed to survive at $\alpha_{\text{FDR}} = .05$, thus suggesting RFT-based FWE closely approximates effective FDR control. This finding has promising implications for past fMRI studies using RFT-based cluster-level inference that used this stricter CDT, estimated to be upwards of 8,500 reports [8, 9]. For CDT=.01, used in approximately 3,500 studies [8, 9], Eklund et al. and others [10] have urged caution and our results agree. We found that $\alpha_{\text{RFT-FWE}}$ must be very strict for effective FDR control (i.e., many $.00001 \leq p_{\text{RFT-FWE}} \leq .05$ fail to survive correction at $\alpha_{\text{FDR}} = .05$).

These 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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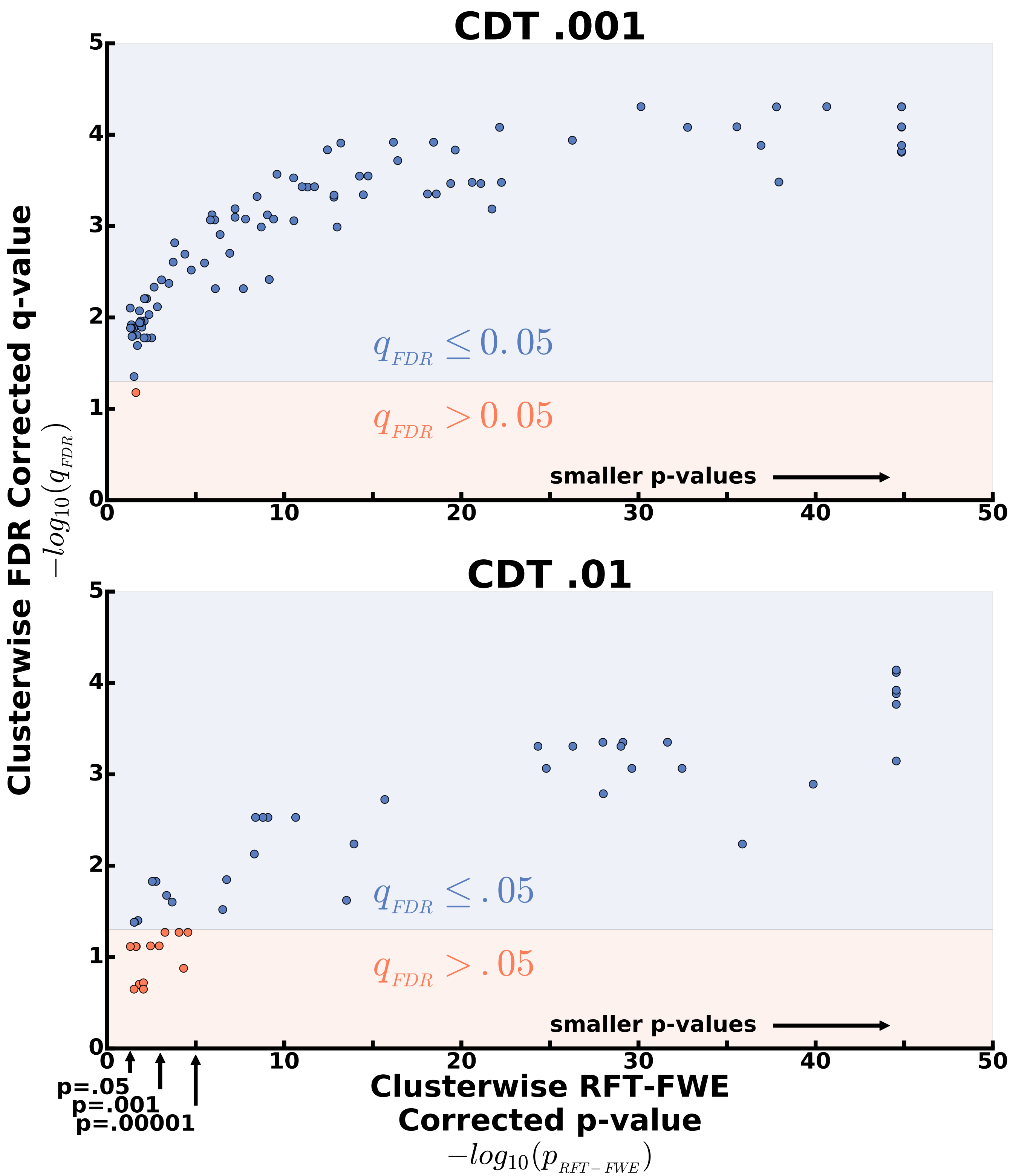

Fig. 1. Assessing RFT-Based FWE Using an FDR Benchmark. We submitted the same task data analyzed by Eklund et al. [1, 5, 6] to nonparametric clusterwise FDR analysis. For CDT $= .001$ (top), RFT-based FWE approximates effective FDR control with $\alpha_{\text{FDR}} = .05$. For CDT $= .01$ (bottom), only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