Combining Voxel Intensity and Cluster Extent with Permutation Test Framework

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Introduction: In a massively univariate analysis of fMRI data, statistical inference is based on intensity or spatial extent of signals. Voxel intensity-based tests provide great sensitivity for high intensity signals, whereas cluster extent tests are sensitive to spatially extended signals. To benefit from the strengths of both, the intensity and extent information can be assessed jointly. While two methods have been proposed [1,2], in this work, we study general methods for intensity-extent inference using combining functions [3] and permutation framework [4]. This apporach allows us to examine different ways of combining intensity and cluster size information without knowing their distribution. Furthermore, we propose meta-combining, a combining function of combining functions which incorporates strengths of multiple combining functions into a single statistical test.

Methods & Materials: From a permutation test [4], corrected p-values for the peak intensity and the extent of each cluster, P_i^t and P_i^s respectively, are obtained. Then the p-values are combined in two types of combined functions, the Tippet combining function $W_i^T = 1- \min(\log P_i^t, \log P_i^s)$ and in the Fisher combining function $W_i^F = -2(\log P_i^t + \log P_i^s)$. The Tippet function works well when either P_i^t or P_i^s is significantly small, while the Fisher function has increased sensitivity when both P_i^t and P_i^s are sufficiently small but not necessarily significant on their own. In addition, we consider the cluster mass combining function W_i^M, the cluster mass calculated as the integration of the statistic image above the cluster defining threshold. Each of these combining functions is used as a test statistic in a permutation test, and corrected p-values are calculated for the Tippet, Fisher, and cluster mass combining functions as P_i^T, P_i^F, and P_i^M respectively. Since we inevitably would like to use the smallest of all these three p-values, we additionally consider a meta-combining function $W_i^A = 1- \min(\log P_i^T, \log P_i^F, \log P_i^M)$. A meta-combined test is performed using W_i^A as a test statistic in a permutation test.

The combined and meta-combined tests were applied to a second-level fMRI data set on working memory [5]. For each of 12 subjects, 528 images were acquired at TR=2s while he or she performed working memory tasks. Then a contrast image for the item recognition task versus the control task was calculated. The resulting 12 contrast images were analyzed in a one-sample t-test using the Tippet, Fisher, and cluster mass combining functions as well as the meta-combining function.

Results: Figure 1 shows the critical regions from the different combined tests, as well as that of the voxel and cluster size tests. Though all these critical regions have 0.05 significance level, they apportion this 0.05 probability differently.

Figure 2 shows the five activation clusters found by the three combined tests. Clusters 1-4 are located in areas known to be associated with working memory tasks [5]. For Clusters 1-3, The Fisher and cluster mass tests produced smaller p-values than the voxel test or the cluster size test alone, indicating that these tests have increased sensitivity when both intensity and extent are large at the same time (See Table 1). Only the extent is significantly large for Clusters 4-5, and in these clusters the Tippet test is the most sensitive of the three. Though it never produces the smallest p-values, the meta-combined test is sensitive to all of these clusters, suggesting that it can be used as a single test summarizing the results of the three combined tests.

Conclusion: With a use of combining functions and the permutation framework, we were able to develop intensity-extent combined tests sensitive to both high intensity and large extent signals. Though none of our combining functions dominated over the other, our meta-combining function was able to incorporate the strengths of individual combining functions into a single valid statistical test.

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Reserences: [1] Poline et al. *NeuroImage* 5: 83-96 (1997) [2] Bullmore et al. *IEEE Trans Med Img* 18: 32-42 (1999) [3] Pesarin. *Multivariate Permutation Tests.* Wiley. (2001) [4] Holmes et al. *JCBFM* 16: 7-22 (1996) [5] Marsheutz et al. *J Cog Neuro* 12(S2): 130-144 (2000)

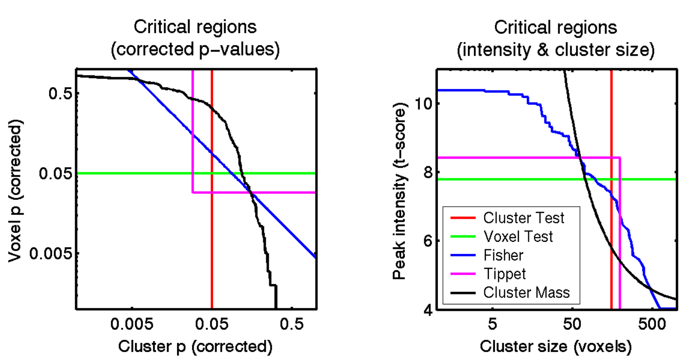

Figure 1: Critical regions for the three combined tests, as well as that of the voxel and cluster size tests. The left panel shows the regions in terms of p-values, while the right panel shows in terms of intensity and cluster size.

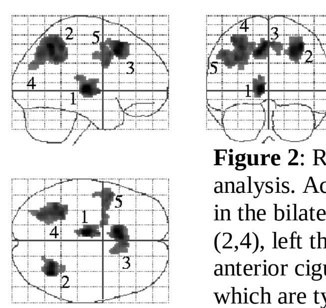

Figure 2: Results from the data analysis. Activations are found in the bilateral posterior parietal (2,4), left thalamus (1), and anterior cigulate (3) regions which are typical of working memory studies, as well as in the left pre-motor region (5).

Cluster	Size (voxels)	p-values Cluster	Fisher	Tippet	Mass	Meta	Peak	T^*
1	345	0.010	0.001	0.001	0.003	0.001	0.001	13.15
2	529	0.005	0.002	0.009	0.001	0.001	0.007	10.19
3	520	0.005	0.002	0.009	0.002	0.003	0.012	9.37
4	1138	0.001	0.004	0.001	0.001	0.001	0.083	7.36
5	436	0.006	0.021	0.011	0.012	0.016	0.208	6.31

Table 1: P-values from the various tests in the working memory data analysis