A New Adaptive Signal Detection Method for Neuroimage Analysis

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Abstract

We present and evaluate a new approach to neuroimage analysis motivated by the concept of matched filtering in signal detection theory. In the case of discrete-time signals, matched filtering for signal detection consists of creating a weighted sum (convolution) of a noise-contaminated signal and then declaring the signal present if the weighted sum exceeds the threshold corresponding to the significance level. Our neuroimaging analog of this signal testing procedure consists of testing the global null of no relationship between the brain images and a covariate using a weighted sum of the statistical parametric map (SPM) as the test statistic. If the magnitude of this test statistic is sufficiently large, the null is rejected. Since there is usually insufficient information to compute the optimal weights of the matched filter, we propose using an approximate matched filter consisting of 0/1 weights determined by cross-validation. Since the distribution of the resulting weighted sum of the SPM is not known, we test the global null using permutation. We compare the performance of this adaptive signal detection procedure (ASD) with random field theory (RFT) peak and cluster methods on both simulated and actual (ADNI) hippocampal morphometry data. These comparisons indicate our new procedure has substantially greater power than the RFT methods (as implemented in Surfstat) on the simulated data and greater power on the ADNI hippocampal morphometry data.

Key Words: random field theory, signal detection, matched filter, cross-validation, statistical parametric map, permutation

1. Introduction

Image analysis methods which are both more robust and more powerful are needed as shown by recent developments. The validity of cluster-based random field theory (RFT) inference has been questioned and investigated; see, for example, the May 2020 issue of Human Brain mapping which contains a special section on this topic. More generally, producing more reproducible research is currently a major concern of the statistics and research communities.

On a more positive note, researchers are the beneficiaries of both ever-increasing computing power and ever-expanding memory capacity. Petabyte solid state disk drives are on the horizon as are exascale super computers for which computational speed will be measured in exaflops, one billion billion (10^{18}) floating point operations per second.

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Given the preceding, it seems worthwhile to pursue increased robustness and power by developing new, more computationally intense algorithms which capitalize on increasing computational resources. For example, permutation methods can be used to achieve robustness by minimizing distributional assumptions. Similarly, cross-validation can be used to increase power by providing data-adaptive methods. Our proposed algorithm employs both of these methods.

2. Methods and Materials

2.1 New Signal Detection Method: Overview

Like random field theory procedures, our method analyzes statistical parametric maps (SPMs). SPMs assign to each voxel a statistic measuring the strength of the relationship between brain features at that location and one or more covariates. Unlike standard RFT methods which attempt to identify discrete topological features, e.g. peaks and clusters, our method is concerned only with testing the global null of no relationship between any brain region (voxel subset of the SPM) and the covariate(s) of interest. If detailed information about the possible relationship between SPM voxels and the covariates were known a priori, for example, if the null and alternative distributions of the voxel statistics were known, then matched filtering could be used to optimally test for the presence of non-null voxels (the "signal"). Since such a priori information is not available, in our approach approximate matched filters consisting of 0's and 1's are computed and applied to the data. These matched filters or masks are determined and used via cross-validation: a mask is determined from one subset of the data (training data) and then applied to the remaining data (test data) to obtain the average of the voxels selected by the mask. This process is repeated until a mask has been determined and applied to generate a voxel average for the SPM of each of k cross-validation partitions or folds. These averages plus associated associated statistics are computed for the actual data and then for permutations of the data. The resulting statistics are used to compute a permutation p-value for testing the global null.

2.2 New Signal Detection Method: Detailed Description

Consider analyzing a dataset of n neuroimages, each consisting of J voxels, to determine if a relationship exists between any brain region and some predictor p. Let $S_{i,j}$ denote the jth voxel of image i. Let T denote the corresponding statistical parametric map (SPM) for testing the significance of p in the general linear model

$$S_{i,j} = \beta_{0,j} + \beta_{1,j}x_{1,i} + \beta_{2,j}x_{2,i} + \cdots + \beta_{k-1,j}x_{k-1,i} + \beta_{k,j}p_i + \epsilon_{i,j}$$

where $x_1, x_2, \ldots, x_{k-1}$ are nuisance covariates. In order to detect the existence of a linear relationship between p and any brain region we test the global null H_0: $\beta_{k,j} = 0$, $j = 1, \ldots, J$ against the alternative H_1: $\beta_{k,j} \neq 0$ for at least one voxel j. Note that although not required by our approach, we will assume the SPM T consists of t statistics. If we knew a priori the location of the possibly non-null voxels, their noncentrality parameters, and their covariances, we could use an optimally weighted sum of these voxels to test the global null. Since we don't have this information, we approximate the unknown optimal weights by weights which are 0 or 1 in value. These 0/1 weights are computed using cross-validation and used to test H_0 as follows:

1. Compute lower and upper percentiles L_i and U_i, $i = 1, 2, \ldots, I$, where each (L_i, U_i) pair satisfy $\hat{P}(T \leq L_i) = \hat{P}(T > U_i)$, where $\hat{P}$ is the empirical distribution of the t statistics comprising the SPM T.

2. Randomly partition the n observations into K subsets or folds.

3. For each fold compute the SPM T_{-k} from all observations except those in the kth fold and the SPM T_k from all the observations in the kth fold.

4. For each i, compute lower and upper masks $LM_{k,i}$ and $UM_{k,i}$ for each fold k where $LM_{k,i,j} = 1$ if $T_{-k,j} \leq L_i$ and 0 otherwise. Similarly $UM_{k,i,j} = 1$ if $T_{-k,j} \geq U_i$ and 0 otherwise.

5. For each i, compute lower and upper averages $AL_{k,i}$ and $AU_{k,i}$ for each fold k where

   - $AL_{k,i}$ = Average of elements of SPM T_{-k} for which $LM_{k,i} = 1$;
   - $AU_{k,i}$ = Average of elements of SPM T_{-k} for which $UM_{k,i} = 1$.

6. For each i and each fold k, if $|AU_{k,i}| > |AL_{k,i}|$, $A_{k,i} = AU_{k,i}$, else $A_{k,i} = AL_{k,i}$.

7. For each i, compute $T_i = \bar{A}/S_A$ where $\bar{A}$ and S_A are the mean and standard deviation of $A_{k,i}$, $k = 1, 2, \ldots, K$.

8. Compute T_m where $m = \arg\max\{|T_1|, |T_2|, \ldots, |T_I|\}$.

9. Repeat steps 2-8 M times and average the resulting T_m's to get $\bar{T}$.

10. Test H_0 using a permutation test based on $\bar{T}$.

2.3 Simulation Study

We conducted a power study comparing the performance on simulated surface data of our adaptive signal detection approach (ASD) - implemented in R (R Core Team [2019]) - with Gaussian random field theory peak (RFP) and cluster (RFC) methods - as implemented by SurfStat (Worsley et al. [1996]). We generated pseudorandom morphometric datasets obeying the following general linear model on a 652 vertex hippocampal template surface.

$$\begin{aligned} S_{i,j} &= \beta x_i + \epsilon_{i,j},\ i = 1, 2, \ldots, 72,\ j = 1, 2, \ldots, 126, \\ &= \epsilon_{i,j},\ i = 1, 2, \ldots, 72,\ j = 127, 128, \ldots, 652, \end{aligned}$$

where $S_{i,j}$ represents the surface value at vertex j for subject i. Each dataset corresponds to a two-sample study with the predictor x_i equal to -1 for $i = 1, 2, \ldots, 36$ and 1 for $i = 37, 37 \ldots, 72$. We investigated four signal amplitudes: $\beta = 0$, $1/12$, $1/6$, and $1/3$. We considered both independent and correlated random errors $\epsilon_{i,j}$. The random errors $\epsilon_{i,j}$ were independent standard normal pseudorandom numbers. The correlated standard errors were independent standard normal pseudorandom errors which were smoothed using heat kernal smoothing (Chung et al. [2005]) prior to being added to the signal. For each of the eight possible combinations of signal amplitude and random error correlation, we generated 100 72-subject data sets and then analyzed them using the three methods.

2.4 ADNI Hippocampal Morpohometry Analysis

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

To test our method on real data we analyzed ADNI hippocampal morphometric data. MRI scans for 172 healthy controls (HC) and 267 early mild cognitive impairment (EMCI) subjects were processed and the voxels of each hippocampus determined by segmentation. The resulting three dimensional hippocampal surfaces were smoothed via spherical harmonics using the SPHARM method (Shen et al. [2009]). The differences between each smoothed hippocampal surface and the overall average (surface atlas) were computed at each of 2562 vertices. The surface image for each subject consisted of the sign and magnitude of the orthogonal component of these differences with negative and positive values denoting shrinkage and expansion respectively. A more detailed description of the pre-processing of these data is provided in (Shen et al. [2017]) and (Inlow et al. [2016]). After generating the surface images, we analyzed them using the three methods in conjunction with the general linear model

$$S_{i,j} \quad = \quad \beta_{0,j} + \beta_{1,j}\text{GENDER}_i + \beta_{2,j}\text{AGE}_i + \beta_{3,j}\text{EMCI}_i + \epsilon_{i,j}$$

$i = 1, 2, \ldots, 439$, $j = 1, 2, \ldots, 5124$, where EMCI is the EMCI indicator variable. Note that we combined the left and right hippocampal surfaces, treating them as a single image with 5124 vertices.

3. Results

3.1 Simulation Study Results

Tables 1 and 2 present the results of our simulation studies. Table 1 provides the number of rejections (out of 100 72-subject datasets) of the adaptive signal detection (ASD), Gaussian random field peak (RFP), and Gaussian random field cluster (RFC) methods for significance level $\alpha = 0.05$. Table 2 provides the results for $\alpha = 0.01$. For the null (signal amplitude $\beta = 0$) scenarios, the random field methods are conservative whereas our method achieves the specified Type I error as expected since it uses permutation testing. For all non-null scenarios, our new ASD method dominates the random field cluster (RFC) method, exhibiting substantially greater power at all signal amplitudes. It also dominates the random field peak (RFP) method in all but the largest signal amplitude case. In particular, it is substantially more powerful for the weakest signal amplitude where its power is at least nine times greater than RFP for all $\beta = 1/12$ scenarios.

3.2 ADNI Hippocampal Morphometry Results

Neither random field method detected a significant difference in hippocampal morphometry between EMCI and HC groups. RFC was not significant at $\alpha = 0.05$ nor was RFP which yielded a p-value of 0.151, indicating any differences present

Table 1: Simulation study results: The number of rejections (out of 100 runs) at $\alpha = 0.05$ for the ASD, RFP, and RFC methods.

Signal Strength	Unsmoothed Data			Smoothed Data		
β	ASD	RFP	RFC	ASD	RFP	RFC
0	4	1	0	5	2	0
1/12	94	7	1	89	10	0
1/6	100	57	6	100	47	51
1/3	100	100	5	100	100	49

Table 2: Simulation study results: The number of rejections (out of 100 runs) at $\alpha = 0.01$ for the ASD, RFP, and RFC methods.

Signal Strength	Unsmoothed Data			Smoothed Data		
β	ASD	RFP	RFC	ASD	RFP	RFC
0	0	0	0	1	1	0
1/12	77	3	0	71	3	0
1/6	100	17	5	100	17	43
1/3	100	100	5	100	100	44

are small compared to between-subject variability. Therefore, if small amplitude differences are present then, based on our simulation study results, we might expect ASD to be able to detect them though RFT methods can't. This appears to be the case since the ASD p-value for comparing HC vs EMCI is 0.0064 based on 10,000 permutations.

These results are graphically depicted by figures 1 and 2. Figure 1 provides a mapping of the t-statistic SPM onto the hippocampi with red regions indicating areas of shrinkage of the MCI hippocampi relative to those of the HC subjects. Figure 2 shows the average of the masks over the k cross-validation folds. In this figure a value of 1 (darkest red) indicates that vertex/voxel received a weighting of 1 (was included in the average of voxel values) for every fold. Likewise a value of 0 (darkest blue) indicates that vertex/voxel received a weighting of 0 (was not included in the average of voxel values) for every fold. Note that the red areas of figure 2 paradoxically align with the blue areas of the SPM in figure 1. This result is due to the fact that the blue areas of image 1 are an artifact of how the hippocampal images were derived from the unsmoothed hippocampal surfaces. Corresponding to areas where the HC hippocampi are expanded relative to those of the MCI subjects, there must be regions where the HC hippocampi appear to be shrunken relative to the MCI hippocampi. Since the ASD method is a two-sided method, that is, it is agnostic regarding whether to select positive or negative t statistics, it unexpectedly selected the negative t statistics corresponding to the processing artifact rather than the positive t statistics. Apparently the negative artifact t statistics are more informative for detecting differences between the HC and MCI surfaces.

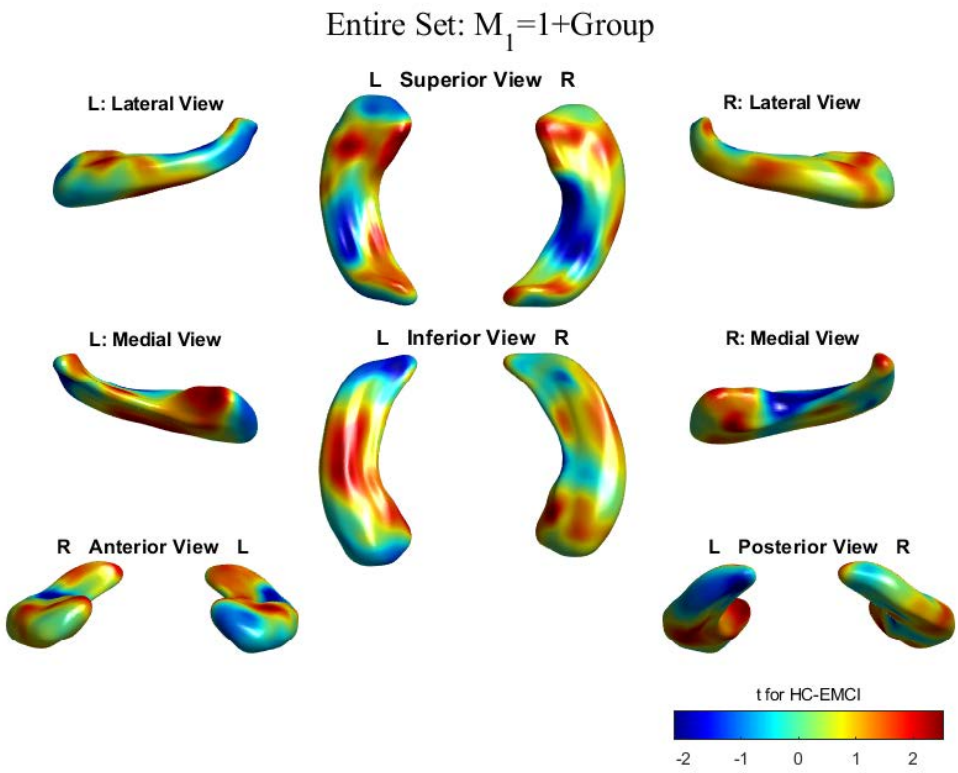

Figure 1: HC vs EMCI Hippocampal Statistical Parametric Map

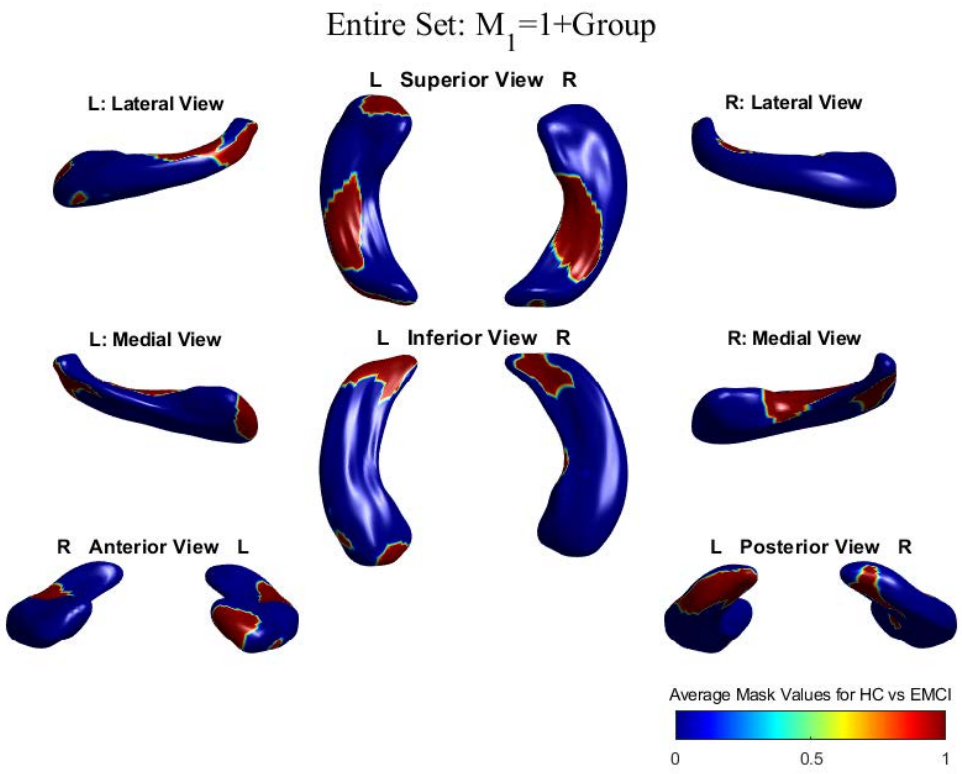

Figure 2: HC vs EMCI Average Mask

4. Comments and Conclusions

Our results demonstrate that our new adaptive signal detection (ASD) approach, which consists of

1. testing the global null of no relationship between any image voxel and the hypothesized predictor(s) by

2. using cross-validation in combination with permutation testing to approximate optimal matched filtering signal detection,

compares favorably with standard RFT methods as implemented in Surfstat. In particular they demonstrate the superiority of ASD to RFT methods for detecting weak signals in both simulated and actual data. Of course, it has been shown elsewhere that image analysis permutation methods have better power than RFT procedures (Nichols et al. [2001]). Thus our next step is to compare our method with other permutation methods, such as the methods implemented by SnPM (Nichols et al. [2019]), across various imaging modalities, e.g., fMRI.

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