Maximized likelihood ratio tests for functional localization in fMRI

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Introduction

- fMRI: what task activates which brain region? Brain is divided in over 100,000 voxels.
  - Mass univariate approach: a general linear model is fitted and a statistical test is performed in each voxel.
  - Multiple testing problem: explosion of false positives. Corrections are available but accompanied by a lack of power.
- Whole brain vs. regions of interest: reduction of number of voxels => impact of multiple testing ↓
- **functional** ROI:
  - Independent localizer task before main experiment to define the ROI functionally in each individual separately. Typically small brain regions detected with a small number of scans.
  - Only this region is analyzed in main experiment.
- Advantages:
  - Increased sensitivity
  - Input for further hypothesis testing: connectivity, TMS, biomarker,...

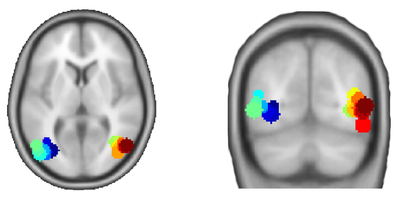


Figure 1: Example of an fROI (left = coronal, right=axial). Identifying hMT/V5+ in 9 subjects.

- Challenges when detecting fROIs:
  1. **Need for better balance between false positives (FPs) and false negatives (FNs):** both should be avoided to obtain maximal spatial accuracy and to avoid biased results in the main experiment.
  2. **Need for thresholding procedure that adjusts to general level of baseline activation:** huge interindividual differences in general level activation, which results in ad hoc threshold adjustments in each individual in order to obtain anatomically plausible activation.

Simulations

- We simulated 500 subject images, each image had a different effect size (ES) that ranged between 0.5% and 2% BOLD signal change.
- The active region was 0.02% of the whole brain, since this proportion is typical for localizers.
- Cut-off LR and mLR statistic (k) = 8, 20 or 32
- σ_{noise} = 6%, 8% or 10% BOLD signal change
- We evaluated the mLR method with the 5th and 50th percentile of the true underlying ESs and the LR approach using the 95th percentile. Due to misspecification of proportion of active voxels, ES is underestimated in LR approach.
- Evaluation: true positives, false positives, false negatives and the mean number of errors.

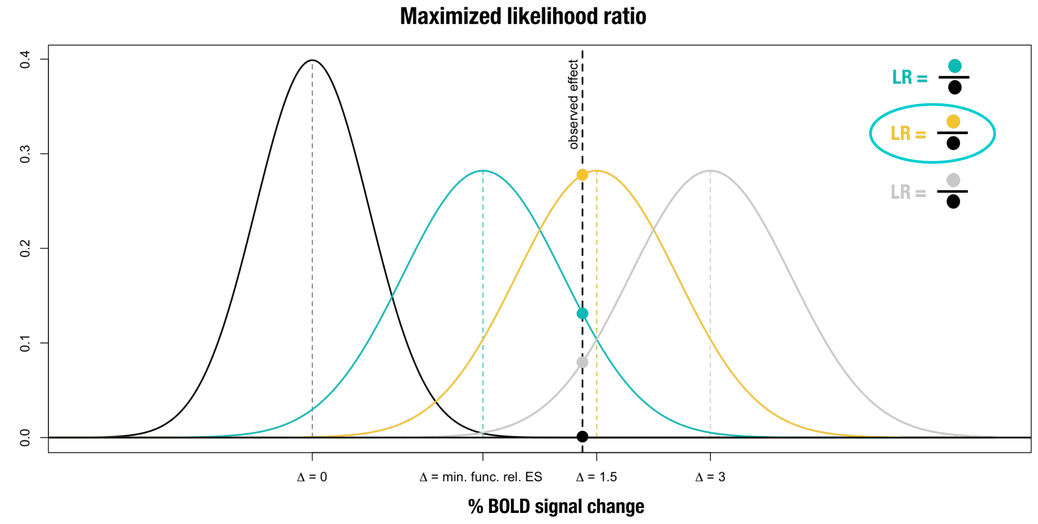
Aims

To address challenge 1:

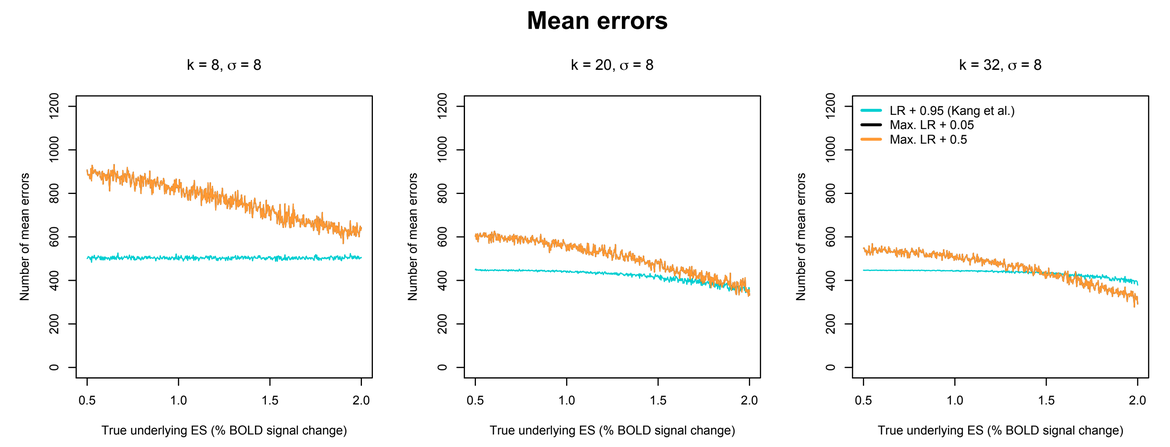
- Likelihood ratio (LR) approach combines evidence in favor of both the null and a specified alternative. It was introduced by Kang et al. (2015) for fMRI. Alternative is specified as a percentile of estimated ESs over voxels within individual.

To address challenge 2:

- Extending the LR approach to a maximized LR (mLR) approach (Bickel, 2012): evaluate LR over set of alternatives.



Results and Discussion



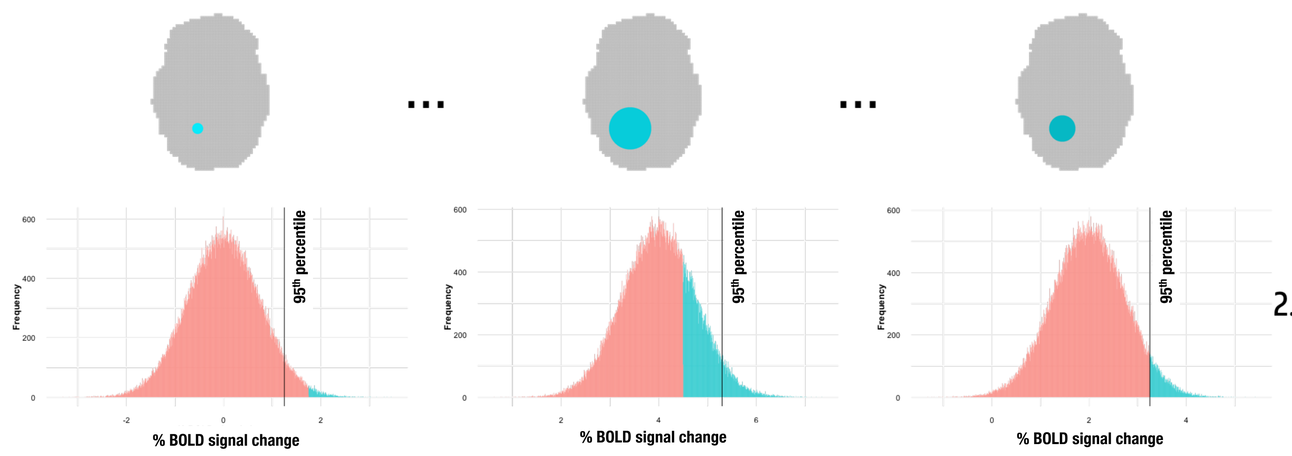
Discussion

- Simulations: other criteria to evaluate performance? Effect of number of scans?
- Real data: not as much variation if percentile is well-chosen. LR approach is a valuable alternative for null hypothesis significance testing.
- ES estimation in fMRI could improve testing by including the alternative in general.

Likelihood ratio testing

Challenge 1 - include effect size (ES) into test criterion in LR approach

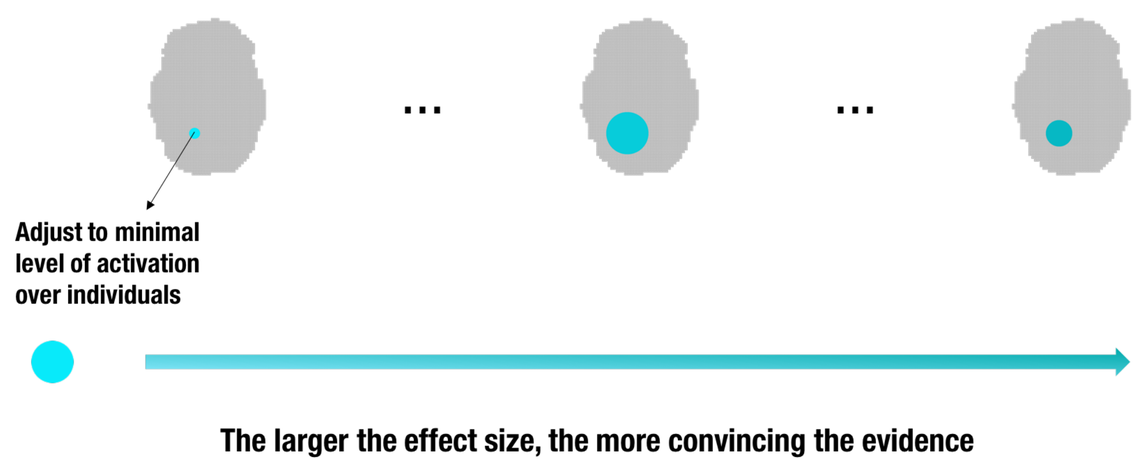
LR + 95th percentile (Kang et al., 2015)



1. Contrast H_1 (activation) with H_0 (inactive)
   - ES under H_1 estimated as pre-specified percentile of observed ESs over voxels
   - Subject-specific
   - No prior knowledge about how large fROI is
2. Not cumulative:
   - Sharp H_1 and H_0
   - Cut-off at ● leads to less convincing results for voxels with a larger ES

Challenge 2 - maximum LR over interval of functionally relevant alternatives

Maximized LR (Bickel, 2012)



1. Interval of functionally relevant ESs:
   - H_1: [● ; +∞ [
   - H_0: [- ∞ ; 0]
2. Cumulative:
   - Cut-off at ● leads to convincing results for subjects with a higher activity level

References: Kang et al., (2015), Neuroimage; Bickel (2012), Statistica Sinica

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