A bootstrap approach for assessing lateralization in functional imaging data

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Introduction

The calculation of a lateralization index $LI = (\Sigma_{left} - \Sigma_{right}) / (\Sigma_{left} + \Sigma_{right})$ is a commonly-used approach to assess laterality effects in neuroimaging data. However, while a single number is convenient, its strong threshold dependency lead to the implementation of lateralization curves, exploring the whole range of intensity values in an image [1]. Still unresolved, though, is the fact that even a laterality curve does not allow to assess the influence of (statistical or artifactual) outliers, severely hampering the reliability of such an approach.

Here, we present a new approach to calculate LI's and assess the homogeneity of the underlying data, using a bootstrap approach. This method makes no assumption on the distribution of the underlying data but instead iteratively re-samples, with replacement, the dataset to assess its structure.

Methods & Results

Bootstrap approach: The concept of threshold-dependent laterality curves was adopted, thresholding the input (e.g., a statistical image volume) at regular intervals (default: 20). At each threshold, a bootstrap procedure was employed to generate 100 re-samples from each side, with the following characteristics: re-sample size (default: 25% of input size), minimum re-sample size (default: 5 voxels), maximum re-sample size (default: 10.000 voxels). From these 100 bootstrapped re-samples from each side, all possible lateralization indices (10.000) were calculated at each threshold. The algorithm was written in Matlab (Mathworks, Natick, MA, USA) and implemented in spm2 (FIL, UCL, UK).

Specificity: In order to emphasize robustness and specificity, a trimmed mean $_{25}$ was used to derive a mean LI at each threshold, disregarding the upper/lower 25% of the LI-matrix. This will effectively exclude outliers. In order to gain regionally specific information, standard anatomical masks [2] were implemented to restrict analyses to pre-defined regions of interest.

Sensitivity: To derive a single overall LI value, a mean from all trimmed mean values was obtained. Emphasizing sensitivity, a weighted mean was used here, weighting the mean value from each step with the corresponding threshold height. This will over-proportionally weight LI's from higher thresholds.

Outlier detection: Even very few voxels with extreme values will severely influence lateralization index calculations. In order to detect such outliers, the bootstrap algorithm was fine-tuned to only sample a subset of the initial input sample (default: 25%), pronouncing the influence of such extreme values even more. The resulting LI-matrix was then converted to normalized z-scores and plotted as a histogram, allowing to detect outliers. Additionally, the minimum and maximum values from each step were plotted in the laterality curves to further illustrate data homogeneity.

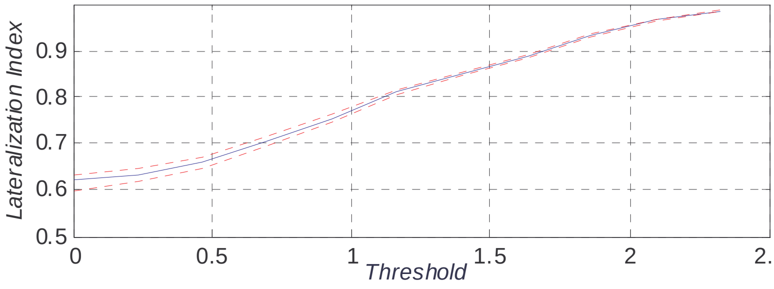

***Fig. 1**: results from the vowel-identification task: consistent left-dominant lateralization within the frontal lobe. Note narrow spread of minimum and maximum values (red lines). Over all thresholds, the resulting standard LI is .8 ± .13; the weighted LI is .88*

Data: Data from a real-life fMRI experiment was used to illustrate the results from the algorithm, from a subject performing a left-lateralizing language task [subject #2 in 3]. Additionally, phantom data was generated in the form of a random noise dataset; to illustrate the outlier detection capabilities, 2 voxels were designated to be outliers with 10 times the maximum image value.

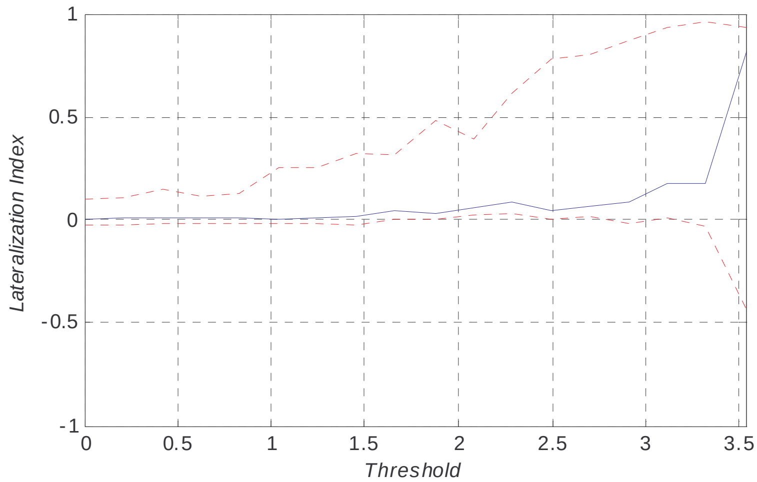

***Fig. 2**: results from the random dataset with 2 outliers on the left: terminal outlier-induced left-dominant lateralization within the frontal lobe. Note very wide and asymmetrical spread between minimum and maximum values (red) and relative robustness of the trimmed mean (blue line). Over all thresholds, the standard LI is .13 ± .25; the weighted LI is .16*

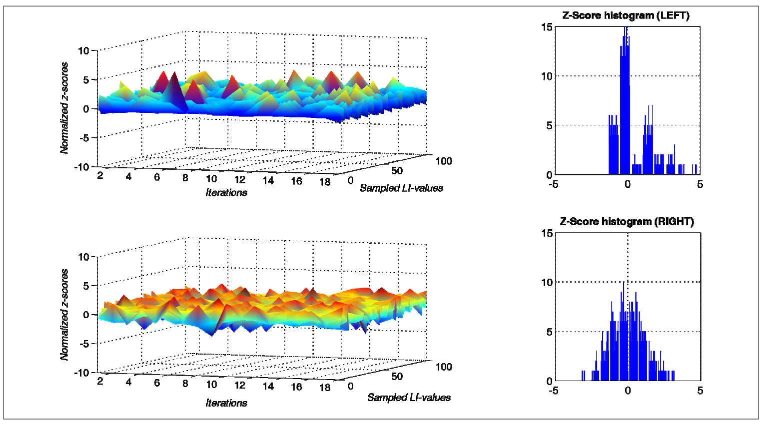

***Fig. 3**: Histogram analyses of the same dataset as in Figure 2, designed to detect the effect of outliers. Left: After transforming all lateralization indices from all thresholding steps to z-scores, outliers are clearly visualized (prominent blue peaks on the left). Right: the same effect is evident in the shift of the 2D-histogram; note normally distributed values on the right (bottom graphs)*

Discussion

Based on the concept of threshold-dependent laterality curves, we applied a bootstrapping approach to calculating lateralization indices from neuroimaging data. At each thresholding step, a LI-matrix of 10.000 values is generated, from which a trimmed mean is calculated (emphasizing specificity). These trimmed mean values from each threshold are then used to generate an overall mean, weighting each value by the corresponding threshold value. This takes into account the fact that lateralization indices from higher values should be more meaningful as more noise is excluded; such a procedure emphasizes sensitivity.

The bootstrap approach allows to explore the available data in such a way that, for the first time, confidence intervals can be attached to a given lateralization index, allowing to routinely assess the underlying data quality (see Figure 1). In a random dataset, even single outliers are detected (see Figures 2 and 3) We therefore believe that this approach is useful in exploring laterality effects in (functional) neuroimaging data.

Literature: [1] Deblaere *et al.*, Neuroradiology 2004; [2] Tzourio-Mazoyer *et al.*, NeuroImage 2002; [3] Wilke *et al.*, NeuroImage 2006

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