Testing for difference between two groups of functional neuroimaging experiments

Finn Årup Nielsen*† , Andrew C. N. Chen‡ , Lars Kai Hansen†

*Neurobiology Research Unit, Rigshospitalet, Copenhagen; †Informatics and Mathematical Modeling, Technical University of Denmark, Lyngby; ‡Center of Sensory-Motor Interaction, Aalborg University, Aalborg.

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Abstract

We describe a meta-analytic method that tests for the difference between two groups of functional neuroimaging experiments. We use kernel density estimation in three-dimensional brain space to convert points representing focal brain activations into a voxel-based representation. We find the maximum in the subtraction between two probability densities and compare its value against a resampling distribution obtained by permuting the labels of the two groups. As such it appears as a general method for comparing the local intensity of two non-stationary spatial point processes. The method is applied on data from thermal pain studies where "hot pain" and "cold pain" form the two groups.

Overview

Our study = Kernel density estimators

+ Resampled-based maximum statistics

+ Talairach coordinates

Functional neuroimaging experiments

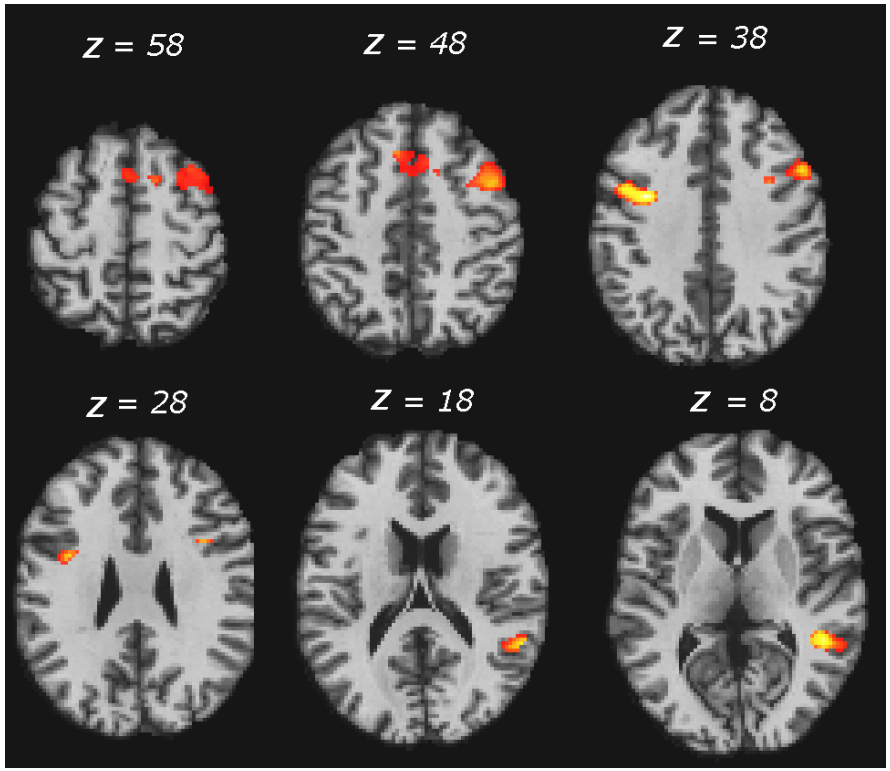

Figure 1: Results from a functional neuroimaging study (Balslev et al., 2004, figure 2).

PET or fMRI brain scans of the human brain while subjects are engaged in different mental processes.

Result represented in the literature with lists of three dimensional coordinates (in standardized "Talairach" brain space) of the hot spot activations, e.g.,

(x, y, z)	z-score
$-38, 0, 40$	4.91
$48, -42, 8$	4.66
$52, 14, 38$	4.07

Brede database

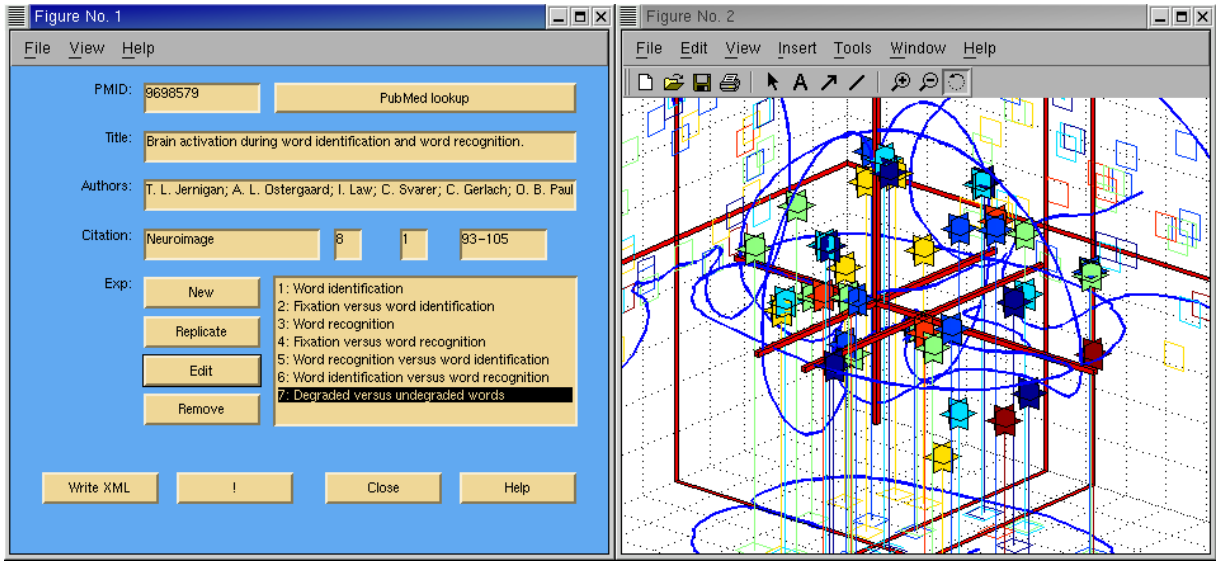

Figure 2: Screenshot of main window of Matlab program for data entry of one of the studies in the Brede database (Jernigan et al., 1998).

Main component: Talairach coordinates.

Presently contains 129 papers, 401 experiments and 2828 stereotaxic coordinates.

Each experiment is labeled with the specific function under investigation, e.g., response to “hot pain” or “cold pain” stimulus.

Multiple comparison problem

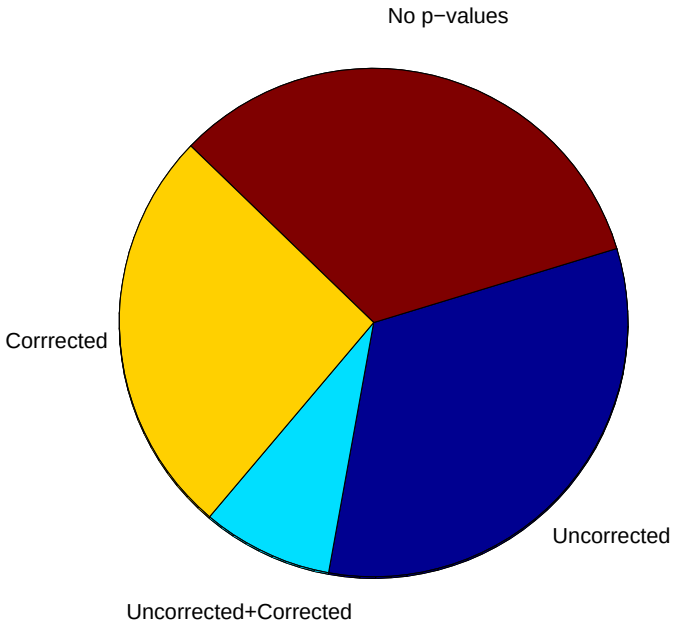

Figure 3: Distribution of coordinates in the Brede database where the "uncorrected" or "corrected" P-values are given.

Mass-univariate test made across all voxels will give rise to the multiple comparison problem.

Usually dealt with by considering random field theory (Cao and Worsley, 2001).

Resampling-based multiple testing also possible. Introduced in neuroimaging by Andrew Holmes (Holmes et al., 1996; Nichols and Holmes, 2001) based on (Westfall and Young, 1992). Toolbox available but not widely used.

Compare these!

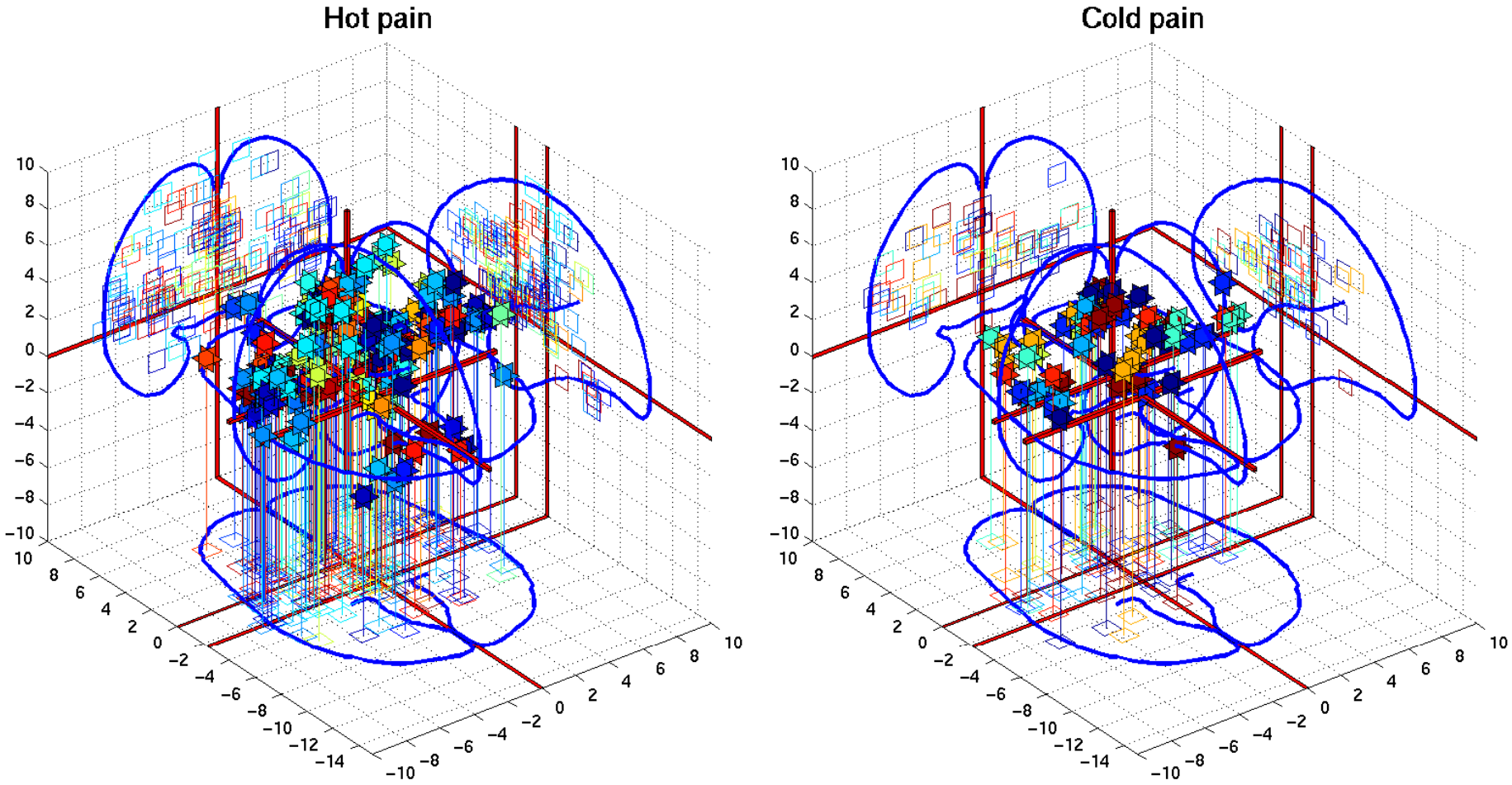

Figure 4: Visualization of the Talairach coordinates from hot pain and cold pain studies

Kernel density estimate

Kernel density estimators are used to convert a set g of coordinates to a vector $\mathbf{v}_g$ representing a voxel-volume ("voxelization")

$$\mathbf{v}_g \equiv p(\mathbf{x}|g). \tag{1}$$

Each Talairach coordinate $\mathbf{x}_l$ is convolved with a Gaussian kernel

$$p(\mathbf{x}|l) = (2\pi\sigma^2)^{-3/2} \exp\left[-\frac{(\mathbf{x}-\mathbf{x}_l)^{\mathsf{T}}(\mathbf{x}-\mathbf{x}_l)}{2\sigma^2}\right], \tag{2}$$

where the kernel width is set to $\sigma = 1$cm.

For a set g of coordinates

$$p(\mathbf{x}|g) = \sum_{l \in g} p(\mathbf{x}|l)\, p(l|g), \tag{3}$$

where $p(l|g) = 1/|L_g|$, with $|L_g|$ as the number of coordinates in the g set.

Maximum statistics

Two groups are compared by looking at the subtraction volume image

$$\mathbf{t} = \mathbf{v}_1 - \mathbf{v}_2. \tag{4}$$

The statistic is the maximum in the subtraction image

$$t = \max_i(t_i) \tag{5}$$

A null distribution is established by resampling the labels between the two sets of Talairach coordinates and computing the resampled maximum statistic t_n^* for all N resamplings.

The P-value for the ith voxel is the proportion of resampled maximum statistics above the statistic t_i

$$P_i = 1/N \sum_n^N |t_i < t_n^*| \,. \tag{6}$$

Hot and cold pain example

1	WOEXT: 183 - Hot pain	(Tracey et al., 2000)
2	WOEXT: 186 - Attended heat pain on right hand	(Brooks et al., 2002)
3	WOEXT: 187 - Distracted heat pain on right hand	(Brooks et al., 2002)
4	WOEXT: 188 - Attended heat pain on left hand	(Brooks et al., 2002)
5	WOEXT: 189 - Distracted heat pain on left hand	(Brooks et al., 2002)
6	WOEXT: 217 - Hot pain in right hand	(Craig et al., 1996)
7	WOEXT: 225 - Hot pain on left hand (group 1)	(Becerra et al., 1999)
8	WOEXT: 227 - Hot pain on left hand (group 2)	(Becerra et al., 1999)
9	WOEXT: 230 - Painful heat on right fingers	(Gelnar et al., 1999)
10	WOEXT: 233 - Hot pain on right hand in rest, mental imagery and hypnosis	(Faymonville et al., 2000)
11	WOEXT: 234 - Hot pain on right hand in rest and mental imagery	(Faymonville et al., 2000)
12	WOEXT: 235 - Hot pain on right hand during hypnosis	(Faymonville et al., 2000)
⋮	⋮	⋮

Table 1: Partial list of 32 included hot and cold pain experiments.

Resampling distribution

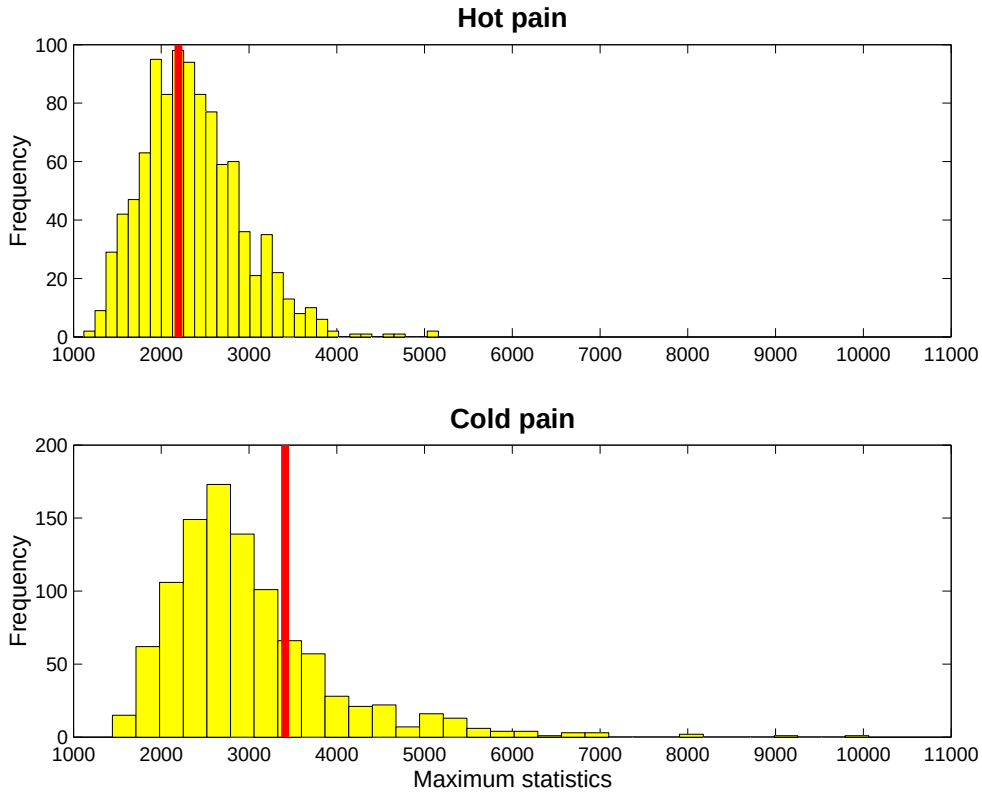

Figure 5: Empirical histograms of the maximum statistics t^* after 1000 permutations. The thick red lines indicate the maxima for the hot and cold pain statistics t_{hot} and t_{cold}.

Histogram of resampled maximum statistics with 1000 resamplings.

Two plot: Different numbers of experiments in hot (24) and cold (8) pain:

$$\begin{aligned} t_{\text{hot}} &= \max(\mathbf{v}_{\text{hot}} - \mathbf{v}_{\text{cold}}) \\ t_{\text{cold}} &= \max(\mathbf{v}_{\text{cold}} - \mathbf{v}_{\text{hot}}). \end{aligned}$$

No difference between hot and cold pain detected.

Statistical images

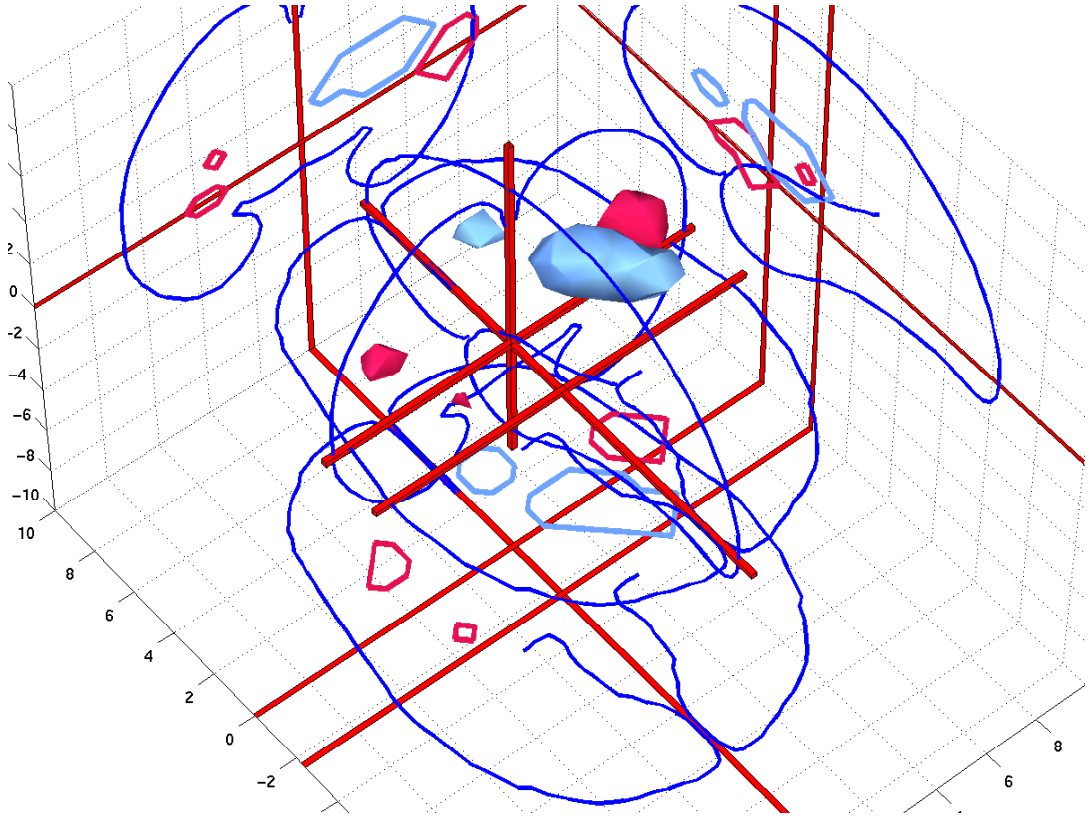

Figure 6: Results from the resampling test. The red isosurfaces are for hot pain $\mathbf{t}_{\text{hot}}$ and the light blue isosurfaces are for cold pain $\mathbf{t}_{\text{cold}}$ based on very low thresholds at $P = 0.95$.

Isosurfaces at threshold in $\mathbf{t}_{\text{hot}}$ and $\mathbf{t}_{\text{cold}}$.

Thresholds are very low thus the difference are most likely statistical fluctuations.

Thermal pain and object recognition

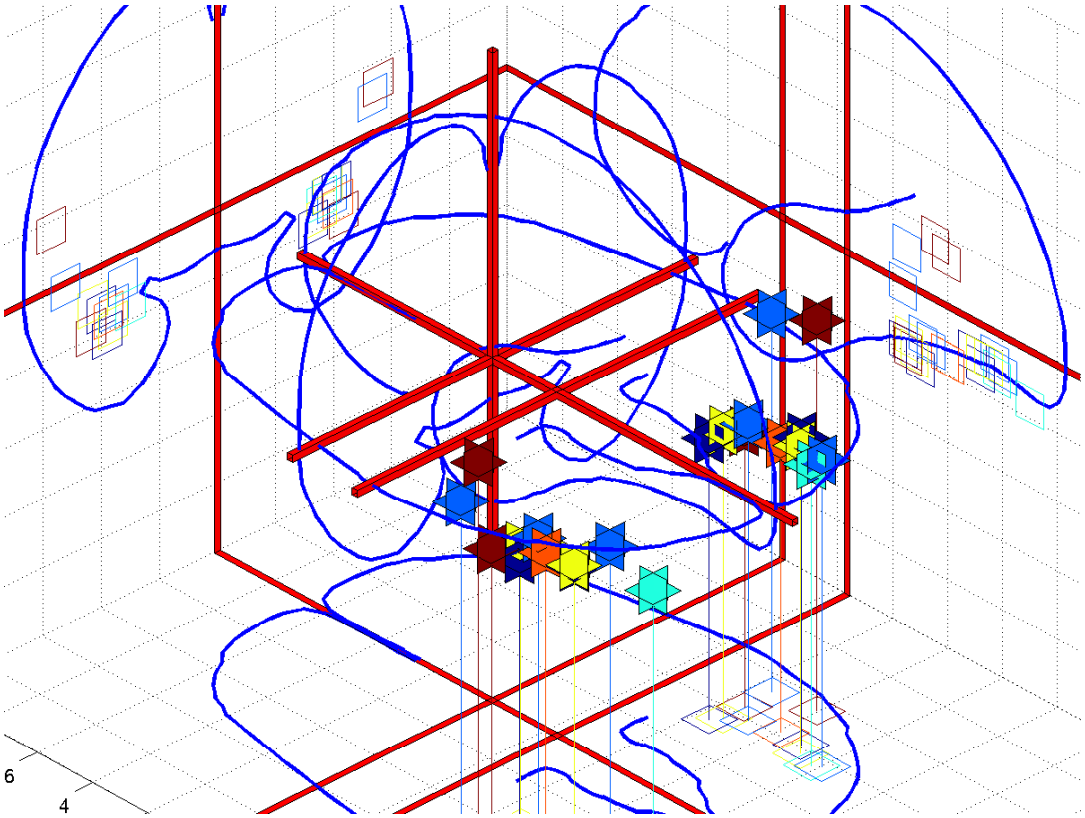

Figure 7: Visualization of Talairach coordinates from 6 visual object recognition studies.

Thermal pain and visual object recognition: Two very different mental processes.

Six visual object recognition exeriments. These are mostly confined to the fusiform parahippocampal gyri.

Difference in statistics should be expected.

Resampling histogram

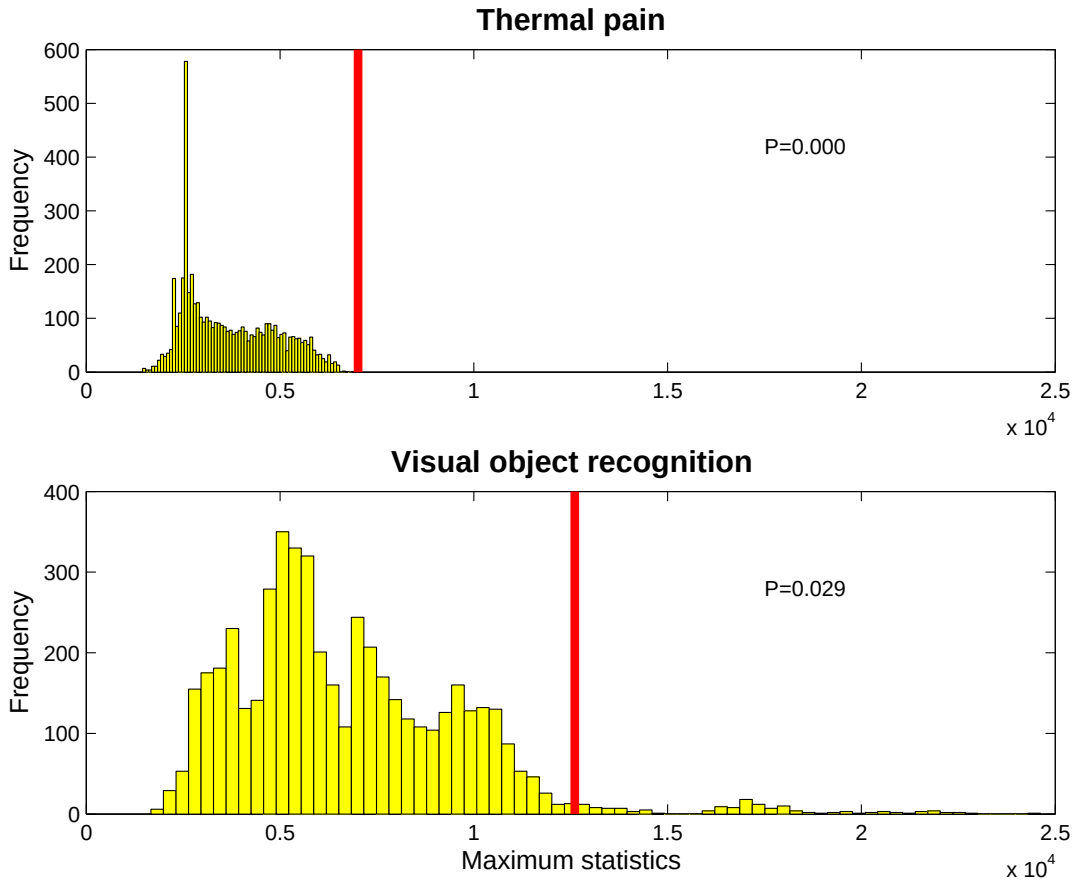

Figure 8: Histogram of resampling distribution.

Histogram of resampling maximum statistics with thermal pain and visual object recognition with 5000 resamplings.

Clear differences: $P < 0.001$ and $P = 0.03$.

Slightly different kernel density estimate

$$p(\mathbf{x}|g) = \sum p(\mathbf{x}|l)\, p(l|e)\, p(e|g).$$

Statistical images

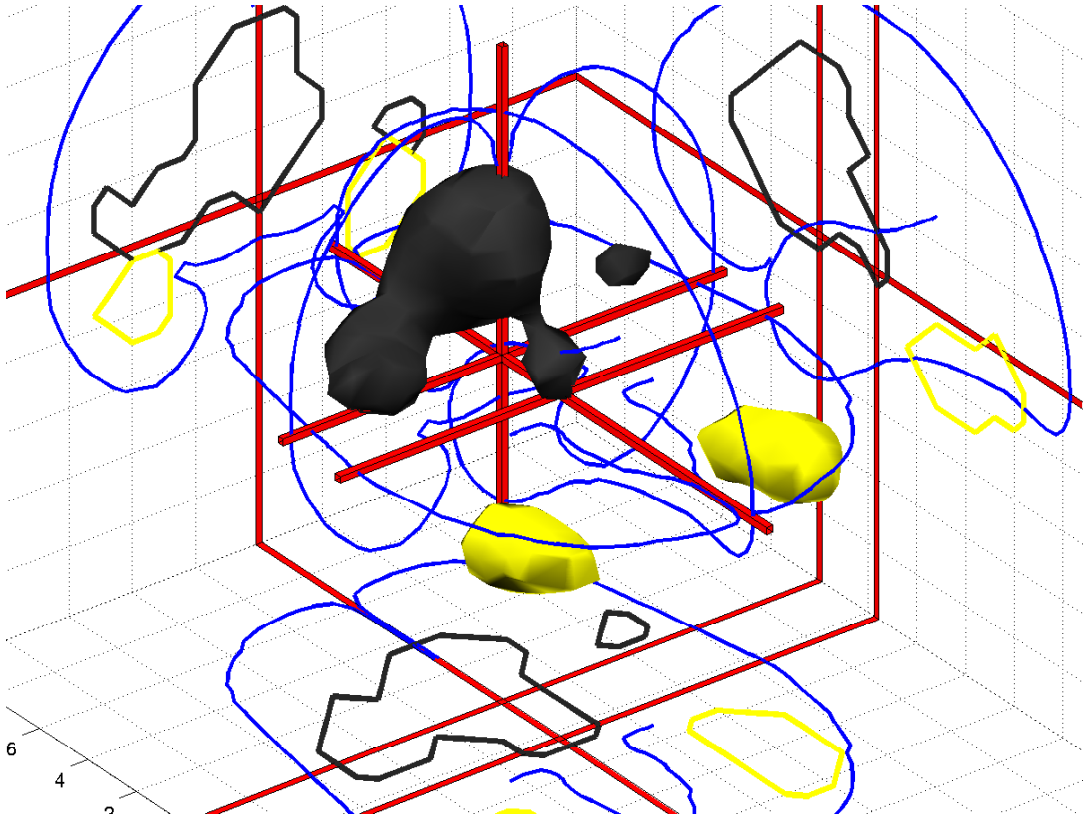

Figure 9: Statistical image. Black is thermal pain and yellow is visual object recognition.

Isosurfaces at thresholds in t_{pain} and t_{object}.

Thresholds are at the usual 0.05-level.

Expected areas appear above threshold. For pain: Anterior cingulate, insula, thalamus. For visual object recognition: fusiform gyrus.

Final remarks

A comparably simple non-parametric method for detection of differences between sets of (Talairach) coordinates.

Individual voxels can be declared different between the two set, — it is not just a global detection.

The method is not able to detect differences between hot and cold pain.

The experiments are not completely exchangeable: Within-paper experiments correlation can be expected.

Covariates not modeled, e.g., left hand/right hand.

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