From BOLD-fMRI signals to the prediction of subjective pain perception through a regularization algorithm

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Objective

The BOLD-fMRI technique [1] plays a dominant role in human brain mapping studies, having the main goal of detecting those brain areas involved in specific functions. Recently, a growing number of studies have taken a different approach, where the direction of analysis is reversed in order to probe whether fMRI signals can be used to predict perceptual or cognitive states [2]. In this study we wished to test the feasibility of predicting the perceived pain intensity in healthy volunteers, based on fMRI signals collected during an experimental pain paradigm lasting several minutes [3]. To this end, we tested and optimized one methodological approach based on new regularization learning algorithms.

Learning and regularization

Learning from examples: given a training set

$$\{(\boldsymbol{x}_i, y_i) \in X \times Y : i = 1, \dots, n\},\ X \subseteq \mathbb{R}^m,\ Y \subseteq \mathbb{R}$$

find the decision function $f_\lambda : X \to Y$ to predict the label y of new examples **x** by solving [4]

$$\min_{f \in \mathcal{H}} (1/n) \sum_{i=1}^{n} V(y_i, f(\boldsymbol{x}_i)) + \lambda \|f\|_K^2 \qquad (1)$$

where: - V is a loss function

- $\mathcal{H}$ is a Reproducing Kernel Hilbert Space with Mercer kernel K [5]
- λ is a positive regularization parameter.

If we consider the quadratic loss $V(y, f(\boldsymbol{x})) = (y - f(\boldsymbol{x}))^2$ and the sampling operator $S_{\boldsymbol{x}} : \mathcal{H} \to \mathbb{R}^n$ defined by $(S_{\boldsymbol{x}} f)_i = f(\boldsymbol{x}_i)$, problem (1) becomes

$$\min_{f \in \mathcal{H}} \|S_{\boldsymbol{x}} f - \boldsymbol{y}\|_n^2 + \lambda \|f\|_K^2 \qquad (2)$$

where $\|\cdot\|_n$ is 1/n the Euclidean norm in $\mathbb{R}^n$ and $\boldsymbol{y} = (y_1, \dots, y_n)^T$. The solution of (2) is the Tikhonov regularized solution of the linear inverse problem $S_{\boldsymbol{x}} f = \boldsymbol{y}$, whose explicit form is given by [6]

$$f_\lambda(\boldsymbol{x}) = \sum_{i=1}^{n} \alpha_i K(\boldsymbol{x}, \boldsymbol{x}_i) \qquad (3)$$

Tikhonov regularization algorithm: $\boldsymbol{\alpha} = (\boldsymbol{K} + n\lambda I)^{-1} \boldsymbol{y}$, where $\boldsymbol{K}_{ij} = K(\boldsymbol{x}_i, \boldsymbol{x}_j),\ \boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_n)^T$

ν – method [7]: $\begin{cases} \boldsymbol{\alpha}^{(i)} = \boldsymbol{\alpha}^{(i-1)} + u_i(\boldsymbol{\alpha}^{(i-1)} - \boldsymbol{\alpha}^{(i-2)}) + \frac{\omega_i}{n}(\boldsymbol{y} - \boldsymbol{K}\boldsymbol{\alpha}^{(i-1)}) \\ \boldsymbol{\alpha}^{(0)} = \boldsymbol{0} \qquad i = 1, 2, \dots, t \end{cases}$

$$u_i = \frac{(i-1)(2i-3)(2i+2\nu-1)}{(i+2\nu-1)(2i+4\nu-1)(2i+2\nu-3)}\ ,\ \omega_i = 4\frac{(2i+2\nu-1)(i+\nu-1)}{(i+2\nu-1)(2i+4\nu-1)}$$

Crucial parameter: the role of the regularization parameter λ is played by the number of iterations t (many iterations lead to overfitting, few iterations give excessively regularized predictiors)

The fMRI experiment

- **7 volunteers** were injected subcutaneously with dilute ascorbic acid solution into the thenar eminence of the left hand
- **intensity pain** registered by moving a computer-controlled visual analogue scale (VAS) with their right (unstimulated) hand
- **functional images** acquired by GE 1.5T scanner, using an EPI BOLD-sensitive sequence (TR=4s, 3.75x3.75x4mm interpolated to 2x2x2mm)
- **300 brain volumes** (in 20 minutes) collected from 24 contiguous axial planes covering the diencephalon and telencephalon
- **20** regions of interest (**ROIs**) in both hemispheres identified based on "a priori" hypotheses

Data pre-processing and feature selection

- corrections of head movements and low-pass temporal filter (0.01Hz)
- voxel clustering based on correlation coefficient related to individual psychophysical pain profile (|r|≥0.6, cluster size 400mm³)
- averaging cluster signals, for each ROI, according to the correlation sign

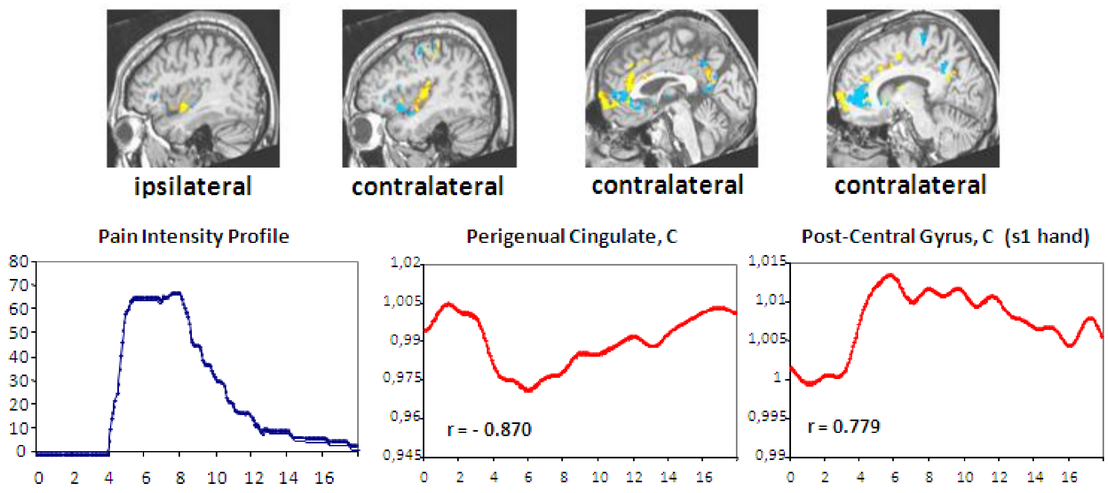
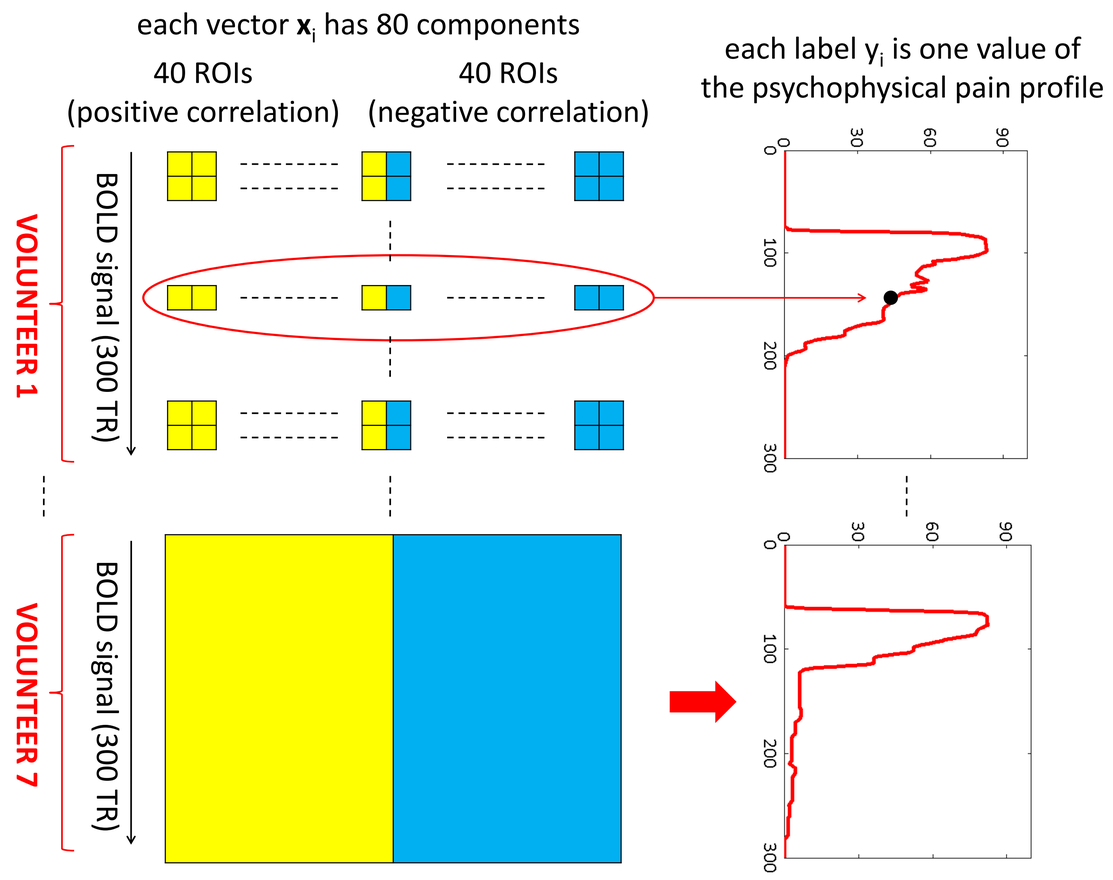


Figure 1: Clusters whose signal positive (yellow) or negative (blue) correlated with the psychophysical pain profile for a representative subject (*top*). Psychophysical pain intensity and averaged signals for two representative ROIs (*bottom*)

Analysis and results

The experimental dataset (7 volunteers x 300 TR)



- **Training set** (6 volunteers x 300 TR)
- **Model selection**: Gaussian kernel $K(\boldsymbol{x}_i, \boldsymbol{x}_j) = e^{-\|\boldsymbol{x}_i - \boldsymbol{x}_j\|^2 / 2\sigma^2}$
- **Learning algorithm**: ν – method (ν=1)

Test set (1 volunteer x 300 TR)

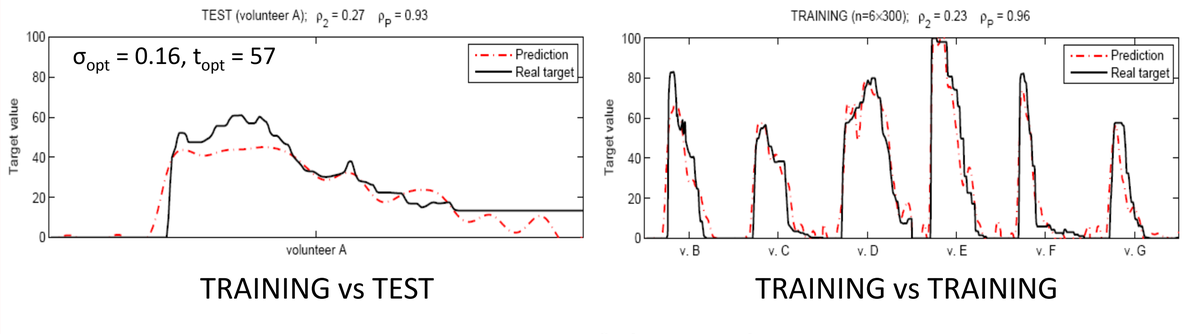
Parameters' choice: the variance σ^2 of the Gaussian kernel and the number of iterations t are chosen via a "**leave-one-volunteer-out**" cross validation

Results

Performance evaluation indices:

- relative reconstruction error $\rho_2(\boldsymbol{f_\lambda}, \boldsymbol{y}) = \|\boldsymbol{f_\lambda} - \boldsymbol{y}\|_2 / \|\boldsymbol{y}\|_2$
- Pearson correlation coefficient $\rho_P(\boldsymbol{f_\lambda}, \boldsymbol{y})$

Predicted pain profile compared to the real target (Volunteer A):



TRAINING vs TEST

TRAINING vs TRAINING

Summary of the results

	Test set							Training set						
ρ_2	0.27	0.38	0.50	0.48	0.40	0.37	0.48	0.23	0.18	0.21	0.20	0.25	0.19	0.19
ρ_P	0.93	0.91	0.95	0.92	0.96	0.93	0.84	0.96	0.97	0.96	0.97	0.95	0.97	0.97
	A	B	C	D	E	F	G	A	B	C	D	E	F	G

Conclusions

Very high values of ρ_P obtained in each test suggest that the considered learning algorithm seems well suited to capture the time course of the psychophysical pain profile. The adopted model of acute prolonged (tonic) pain bears some similarities with clinically relevant conditions, such as prolonged ongoing activity in nociceptors and spontaneous fluctuations of perceived pain intensity over time. Therefore the approach proposed in this study has the potential to establish grounds for being able to obtain an objective measure of the ongoing level of clinical inflammatory pain

References

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