Hemodynamic Response Pattern upon Noxious Electrical Stimulation in Rat Models of Pain

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TARGET AUDIENCE: Scientists interested in pain studies (Clinical/Preclinical) and fMRI data analysis

INTRODUCTION: In human fMRI studies, BOLD response to constant painful electrical[1] and thermal[2] stimulation has shown a biphasic pattern, deviating from the canonical hemodynamic response (HDR) function, and leading to possible false negatives in activation maps when using a boxcar analysis model. In this work, we have considered possible signal variations during the BOLD response in the analysis, to process the data of noxious electrical stimulation (NES) of the hindpaw in rat models of incisional and inflammatory pain.

METHODS: Adult Sprague Dawley rats received trauma in the right hindpaw by a surgical incision[3] (n=6) or injection of 200µl Complete Freud's Adjuant (CFA) (n=6). A control group (n=6) received only anesthesia to compensate for the possible side effects of surgery. fMRI images were acquired 24h later on a 9.4T Bruker Biospiec with a GE EPI sequence (TR/TE:1000/18ms, 12-13 slices, 1.2mm thick, FOV 30*30mm^2, Matrix 80*80, 600 averages) under anesthesia with medetomidine. NES (2ms, 9Hz, 5mA) was applied to the injured hindpaw in a block design paradigm of 10s stimulation and 20s rest. The fMRI data were processed in SPM8, using two design matrices: The standard analysis model of a boxcar, here named as linear model (LM), assuming constant equal canonical responses for each second of stimulation, and a second model (nonlinear model: NLM), assuming different canonical responses to each second of 10s stimulation, in order to identify possible deviations from the standard response profile. The first design matrix consisted of two regressors (one for 10s stimulation and 20s rest block), while the second one included eleven regressors (each second of the stimulus presented with a separate regressor, and one for the 20s rest). The individual activation maps in SPM were calculated for the contrast of first stimulation in the design (10s in LM and 1s in NLM) with uncorrected p-value<0.01, and were compared with that of a simple t-test as model-free reference analysis (MATLAB script, p<0.01). Quantitative ROI analysis was carried out on activated regions using either a t-test, or the SPM hemodynamics function, or the Marsbar toolbox of SPM8. The percent signal changes of BOLD were calculated and averaged over the stimulation cycles and all animals in a group. Group-analysis (uncorr. p-value<0.05) of the data was done using a T2-weighted template.[4]

RESULTS: Group analysis of the sham animals showed that NES induced activation in the pain matrix (Fig. 1), including contralateral activation of primary somatosensory cortex (S1), ipsilateral activation of the cerebellar nucleus (Cb) and bilateral activation in several brain regions, cingulate cortex (Cg), medial septal nucleus (MS), lateral septal area (LSD), retrosplenial cortex (RSC), thalamus (Tha), hypothalamus (HTh), periaqueductal gray (PAG), hippocampus (Hc), and brachium of the inferior colliculus (BIC). However, the LM analysis showed only sporadic activation of the S1 region in the pain models, while the simple t-test showed activation and pronounced signal changes, which differed from the expected HDR (Fig. 2). This pattern was similar to biphasic response seen in human studies. The additional degrees of freedom provided by NLM analysis enabled detection of these deviations in signal profile and allowed for fitting a HDR to the data. Deviation of the canonical HDR was observed in averaged time courses of the BOLD response in both pain models in ROIs in S1 (Fig. 3a). This difference of profiles resulted in larger cluster sizes of BOLD activation in S1, if calculated with the NLM analysis (Fig. 3b). Since this deviation from the standard HDR occurred in other regions of pain matrix as well, the NLM analysis (Fig. 3c) detected a larger number of activated regions in the pain matrix of the pain models.

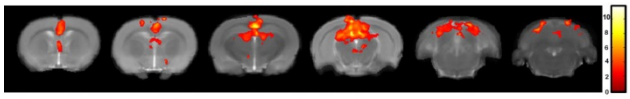

Figure 1: BOLD activation pattern for the sham group after group analysis using NLM and contrast of 10s stimulation vs rest (uncorr. p<0.05)

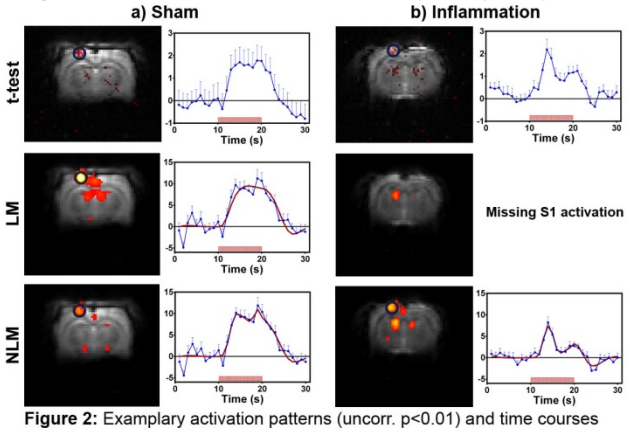

Figure 2: Examplary activation patterns (uncorr. p<0.01) and time courses from ROIs in S1, determined by t-test (p<0.01), LM and NLM for a sham (a) and inflammatory animal (b). The red curves on time course graphs show the fitted HDR. The red bars under the time courses show the stimulation period. LM fails to show the activation in the pain models.

DISCUSSION: The activation maps of NLM were presented here using the contrast of the first second of stimulation, so that the immediate response to pain onset could be emphasized. The flexibility of NLM enables depiction of different contrasts and mirrors the time course of BOLD signal change. The present study demonstrates the importance of accounting for response variations in analysis model, in order to fit the actual shape of the BOLD response to painful stimulation in rat models of incision and inflammation. Extracting the full information from the BOLD time course may help in generating new or modifying present theories of pain processing.

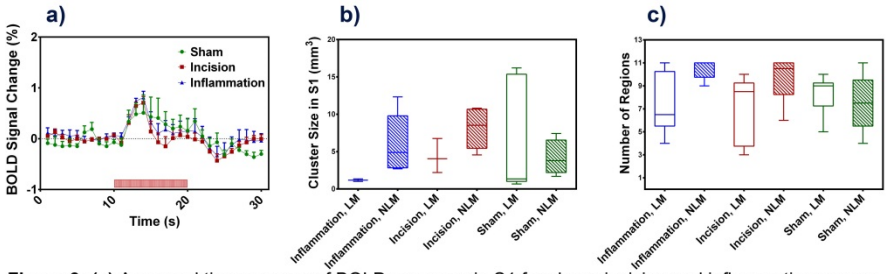

Figure 3: (a) Averaged time courses of BOLD response in S1 for sham, incision and inflammation groups (Mean ± SEM n= 6). The red bar under the time courses indicate the stimulation period. **(b)** Cluster sizes of the activations in S1 detected by LM and NLM for each group (n=6) **(c)** Total number of activated regions from 11 expected regions of the pain matrix detected by LM and NLM (for each group, n=6)

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