On the complexity of the BOLD response to painful heat, relationship of the response with self-assessment of pain and implications for fMRI sensitivity to analgesic treatment

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Introduction: The complexity of the experience of pain is reflected in the functional MRI BOLD response to painful stimuli [1-3]. Several publications reported on a biphasic BOLD response composed of an early phase closely locked with stimulus time, and a late phase which some have suggested is related to self-assessment of pain (Chen 2002). In a placebo controlled study of painful heat, the GLM approach was used to generate quantitative measures and address the issue of sensitivity of these endpoints to Buprenorphine treatment (BUP); with a focus on endpoints related to early, stimulus-locked, and late phase modeled by self-assessment.

Methods: The study was a placebo-controlled 2-way cross-over design conducted in healthy male volunteers (n=12). Each subject was scanned on two days at least two weeks apart (allowing for compound washout) in a randomized sequence with either Placebo or a clinically efficacious dose of BUP, 2 mg, administered sublingually. Acute painful heat stimuli were applied to the dorsum of the left foot 75 min after dosing. Subject-specific threshold temperatures (mean, std. dev., 46.4 ± 2.5°C) were pre-selected that yielded a 7/10 pain rating. Each stimulus was applied in 7 consecutive cycles in on/off fashion (on/off = 15s/25s). Whole brain images (64x64x41 matrix, 3.5x3.5x3.5 mm^3 resolution) were acquired using an EPI sequence (TR/TE=2500/30ms). Subjective Visual Analog Scale (VAS) ratings of pain were continuously recorded for each subject during the fMRI experiment. FSL was used to perform General Linear Model analysis [FSL (4)]. The first-level design matrix consisted of two regressors: the applied stimulus temperature and the reported VAS time courses. These regressors were demeaned and the VAS regressor was orthogonalized with respect to the stimulus regressor so that it modeled only the variance not already explained by the stimulus regressor [5] For each regressor, mean z-scores were calculated for several Regions-of-Interest (ROIs) believed to constitute the pain processing network. The ROIs included Insula, Thalamus, Putamen, Anterior cingulate Cortex, and Primary Somatosensory Cortex.

Results: Figure 1 shows second level, mixed-effects, GLM contrast maps (paired t-test design) depicting regressor-specific BOLD responses. A substantially larger effect can be observed in the S1 area.

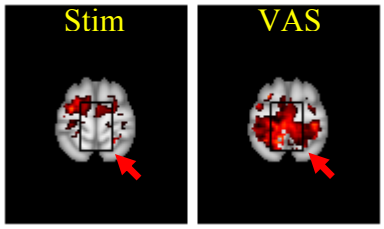

Figure 1: Second level, mixed-effects, paired t-test, maps for the contrast Placebo>BUP for stimulus- locked (left panel) and VAS-locked (right panel) BOLD responses around the Primary Somatosensory Cortex area (red arrow). Note considerably larger effect of treatment on the VAS regressor.

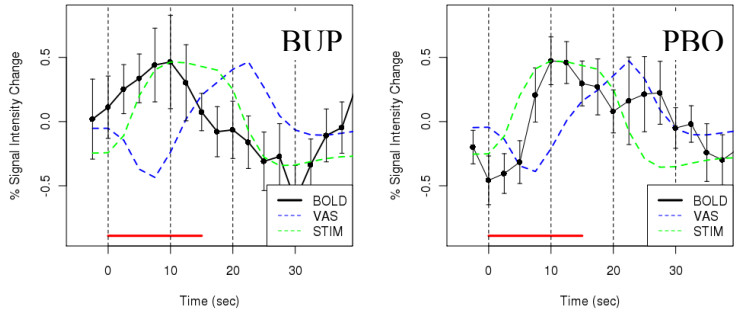

Figure 2: Example of peri-stimulus plots from S1 for a subject following BUP (left panel) and Placebo (right panel) administration. Plots are overlaid with associated Stimulus and VAS regressors. Green horizontal line represents duration of stimulus.

Figure 2 shows an example of the average BOLD response in S1 to painful heat stimulation and associated regressors for a single subject following either placebo or BUP administration. On the placebo run, two phases of the BOLD response are clearly depicted; the first phase peaks around 10s after stimulus onset and the late phase peaks around 25s.

Figure 3 shows standardized BUP treatment effect sizes for multiple regions of interest and for self-assessment.

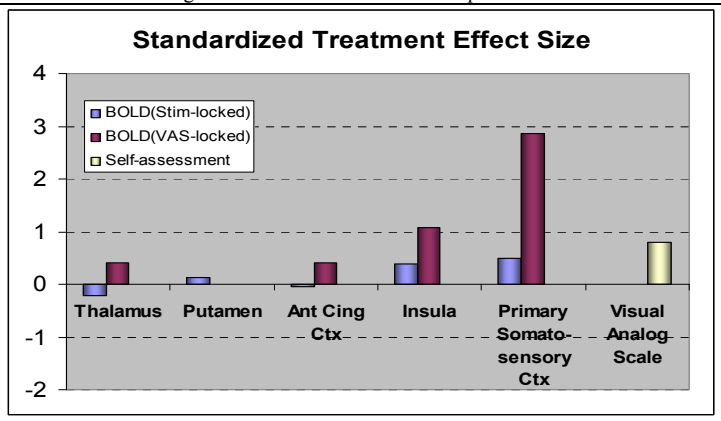

Figure 3: Standardized BUP effect sizes on BOLD (Stim-locked and VAS-locked) and Self-assessment endpoints.

Conclusion: The GLM approach allows for detailed quantitative analyses of the complex BOLD response to pain. Summary fMRI endpoints associated with self-assessment were found to be much more sensitive to BUP treatment than stimulus locked responses. These results also suggest that studies using fMRI in conjunction with continual VAS ratings are considerably better powered (require smaller sample sizes) than those using self-assessment alone.

References: [1] Chen 2002, [2] Upadhyay 2009, [3] Tseng 2009; [4] Smith (FSL); [5] Duft 2009