FMRI of pain: an analysis of the benefits of modelling trial-to-trial pain reports.

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Background/Aims: Carefully optimized experimental paradigms and analysis methods are required for fMRI to achieve its potential as an informative biomarker for the complex psycho-physiological effects of disease and pharmaceutical agents. Any measurable variables associated with physiological, psychological, or stimulus-related factors should be assessed for their potential to be used to improve the accuracy of the trial-to-trial modelling of signal. In fMRI pain studies, pain reports can be highly varied even for constant, calibrated stimuli. Pain ratings are often recorded within sessions and are sometimes included in the modelling of fMRI signal (Davis, 1998). However, the extent to which they can be used to improve the modelling of pain-related BOLD signal activity has not been reported. The present study characterises the improvements obtained by adding pain-rating derived regressors in addition to regressors modelling stimulus intensity in an fMRI analysis.

Methods: *Design:* We analysed an event-related pain study involving 16 subjects each undergoing 6 fMRI scans (Howard, 2008). In each session, subjects received 40 thermal stimuli, ordered in a pseudo-randomised fashion and interspersed with a joystick pain-rating period that used a Visual-Analogue-Scale. 4 levels of contact-heat evoked potential stimulation were used, applied to the right forearm. The stimulus levels included a baseline of no heat, and three threshold levels: sensory detection (SDT), pain detection (PDT), and pain toleration (PTT). Sensory thresholding was performed over two visits prior to scanning using an ascending staircase method. Whole-brain scans were acquired in a 3-tesla whole body MR imaging system with a proprietary quadrature head coil (General Electric, USA). A gradient-echo EPI sequence was used. TR was 3000ms. TE was 20ms (Howard, 2008).
Statistical Analysis: A three-level mixed effects analysis was performed using FSL's FEAT GLM analysis tool (v5.98, www.fmrib.ox.ac.uk/fsl/feat5). The first level analysis modelled individual sessions and used separate regressors for each of the stimulus levels. A fifth regressor modelled the response associated with the rating period. The temporal derivatives of these regressors were included to account for variations in hemodynamic response timing. To model further variation in responses following the trial-to-trial variations in pain ratings, we added an additional regressor that modelled a linear relationship between response amplitudes and the pain ratings (recorded as values between 0 and 1). This regressor was demeaned and orthogonalised with respect to the other stimulus regressors *so that it accounted for only that variance not already modelled by the other regressors*. Second-level modelling generated cross-session effects maps for each subject. Group-level statistical maps for mean effects of interest were calculated using FLAME (Woolrich, 2004). Z-statistic images were thresholded by generating clusters with a Z>2.3 threshold and using a corrected cluster significance threshold of P=0.05. The effect of the pain-rating regressor on the signal modelling was determined by identifying regions where the additional regressor contributed significantly to the fit of the model, and by assessing changes in the outcomes of other contrasts of interest. We investigated changes in the pattern and extent of activated voxels for different contrasts to assess how the modelling could affect the interpretation of the experiment. We also assessed changes in the Z-statistic values, which indicate the statistical significance of observed effects, and are not be subject to incidental thresholding effects.

Results: The pain ratings for the different stimuli had distinct distributions, but showed considerable overlap, indicating a significant amount of variance not accounted for by the stimulus (Fig 1). The component of the ratings orthogonal to the variations in stimulus intensity had a significant correlation in the BOLD signal activity in many regions of the pain matrix, including bilateral primary sensory cortices, cingulated cortex, insula, and cerebellum (Fig 2). When compared with the results of a GLM that did not account for the pain-rating variance, other contrasts in the model increased in their extent of active voxels and average z-scores. The number of active voxels in the PTT-PDT contrast increased by a factor of 2.4 (Fig 3), while the number of active voxels in the PDT-SDT contrast increased by a factor of 4. The mean z-statistics within the activated regions increased from 1.45 to 2.70 for PTT-PDT and from 1.50 to 2.74 for PDT-SDT.
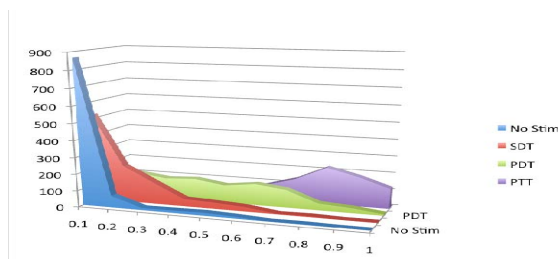

Fig 1. Histogram plot of subject ratings for the four stimulus conditions, rated between 0 (no pain) and 1 (extreme pain).
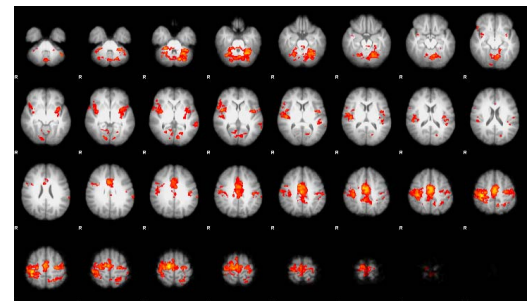

Fig 2. Brain regions where the regressor derived from trial-to-trial pain-ratings was significant.

Discussion:
These results show that there exists widespread physiological dynamics correlated with trial-to-trial variations in the pain ratings of individual subjects. The greatest improvements in modelling were found in the cerebellum and in key components of the cortical "pain matrix", confirming that these regions are highly involved specifically in processing the intensity of pain, and that the utilisation of pain ratings in the BOLD signal modelling enhances investigation of these regions. The large improvements in the extent of activated voxels in key contrasts and in the size of z-scores suggests that pain ratings should be recorded whenever feasible and included in the modelling of BOLD signal responses. Additional analysis will determine whether models accommodating a non-linear relationship between brain responses and pain ratings can further improve modelling and allow detailed analysis of the relationship between regional activity, stimulus intensity, and pain reports.

Davis KD, Kwan CL, Crawley AP, Mikulis DJ.: Event-related fMRI of pain: entering a new era in imaging pain. Neuroreport. 1998 Sep 14;9(13):3019-23.
Howard et. al. Test-retest reproducibililty of cerebral and subjective response to painful and non-pain contact-heat evoked potential stimulation. ISMRM 2008, no. 2052
Woolrich, MW. et. al Multi-level linear modelling for FMRI group analysis using Bayesian inference. NeuroImage 41:2(286-301) 2008
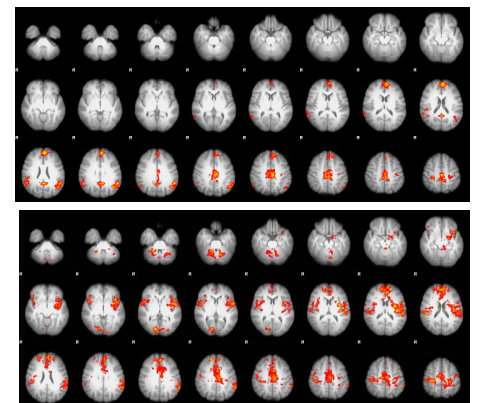
Fig. 3. (top) PTT-PDT contrast in a GLM without the additional regressor derived from pain ratings (bottom) PTT-PDT contrast with the pain ratings regressor..