Chronic arthritis pain modulation by a cyclooxygenase-2 inhibitor: An fMRI-pharmacological study

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INTRODUCTION

Earlier we have shown that chronic complex regional pain syndrome pain (neuropathic) seems to be a prefrontal condition. In this study we present preliminary data on brain responses to chronic arthritis pain (inflammatory) and the effect of a COX-2 inhibitor in modulating pain processing.

METHODS

• One patient suffering from chronic arthritis was tested. Prior to scanning, the patient was trained to use the finger-span device to rate magnitudes (fig. 1).

• In the scanner the patient rated 1) spontaneous pain in the absence of external stimulation (baseline) using the finger-span device, 2) rated fluctuations in pain during application of random series of external mechanical stimuli (stimulus pain rating) to the painful joints, and 3) the length of a bar that fluctuates in time in a pattern derived from their own ratings of pain (visual control signal).

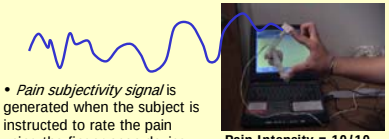
•The patient stopped analgesic medications for 24 hours. He was scanned prior-, 1 and 3 hours after ingesting one dose of COX-2 inhibitor (200 mg Celebrex).

• Pain and visual ratings are used to calculate vectors used to search for brain activity (BOLD signal) and to control for contaminants (fig. 2).

•BOLD responses are determined using FSL software (fmrib, Smith et al. 2001).

RESULTS

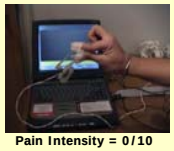
1 On-line Signal For Pain Subjectivity And Visual Control.



• *Pain subjectivity signal* is generated when the subject is instructed to rate the pain using the finger-span device.

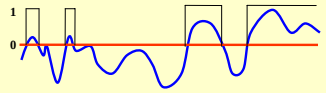
Pain Intensity = 10/10

• *Visual control signal* is generated when the subject is instructed to follow a recorded pain rating projected on a screen using the finger-span device.



Pain Intensity = 0/10

2 Vectors And Covariance Matrices.



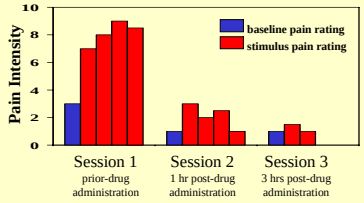
• *A binary vector (P_s)* for high - low ongoing pain upon external stimulation is generated.The mean value of stimulus pain rating signal is calculated. Pain ratings having a value larger and smaller than the mean are designated by 1 and 0, respectively

•*A binary vector (P_b)* for high – low spontaneous ongoing pain is generated.The mean value of pain subjectivity signal is calculated. Pain ratings having a value larger and smaller than the mean are designated by 1 and 0, respectively.

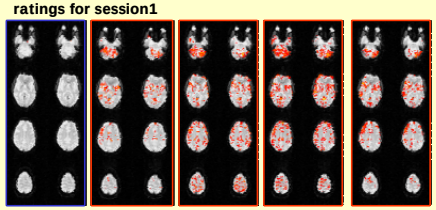
•*A binary vector (V)* for visual control is generated from the visual control signal in a similar fashion to P_s. BOLD responses to V control for motor component.

•*A second control vector (S_s)* is generated by inverting in time the original stimulus pain rating. This vector has the same statistical properties as P_s but does not correlate with the pain experience. S_s is used to subtract non-specific activations.

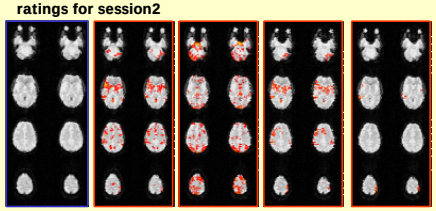
3 Pain intensity ratings and brain activity are significantly reduced after administration of drug



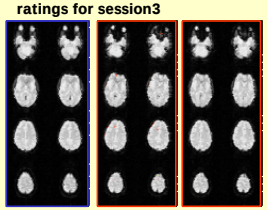
•**Activity maps for the baseline and stimulus pain ratings for session1**



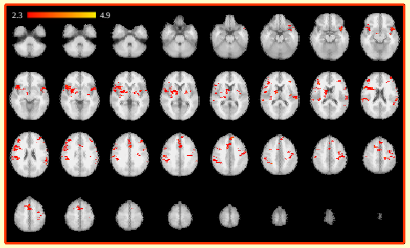
•**Activity maps for the baseline and stimulus pain ratings for session2**



•**Activity maps for the baseline and stimulus pain ratings for session3**



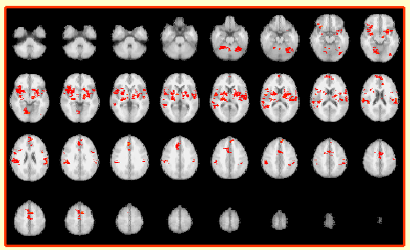
4 Activity map for the group average of stimulus pain ratings - controls (P_s - P_b - V - S_s) for Session 1



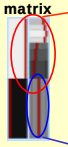
•Left SI/MI regions are activated, which corresponds to the right hand used for ratings since this comparison also identifies the times where the rate of hand movement rate is maximal. Multiple anterior cingulate areas are activated as well as, bilateral SII, anterior insula, and thalamus.

•NOTE: The group average for sessions 2 and 3 separately did not yield any significant brain activity.

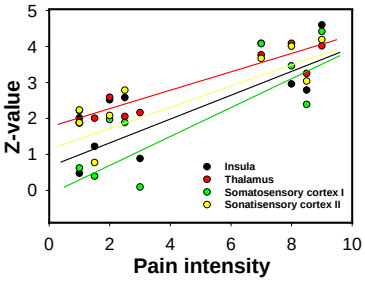
5 Activity map for the group Average of all stimulus pain ratings –controls for all 3 sessions with their respective mean pain intensities as covariates



Design matrix



•The group average of all stimulus pain ratings - controls for all 3 sessions (P_s - P_b - V - S_s) with their respective mean pain intensities as covariates exhibit activity in anterior cingulate, bilateral SII, anterior insula and thalamus is tightly correlated with the pain intensity.



The Z-values of P_s for all sessions plotted against pain intensity. Activity in all areas exhibit a high correlation to mean pain rating (Insula, R=0.73; thalamus, R=0.82; SI, R=0.64; S II, R=0.71).

CONCLUSIONS

• Results in one subject indicate that stimulus related arthritis pain activates brain regions identified in acute painful stimuli in normal subjects, underlying regions innervated by spinothalamo-cortical pathway.

• A single clinical dose of a COX-2 inhibitor, reduced the pain ratings by 50% 2 hours after administration, and decreased brain activity to below threshold in all areas identified initially.

•Contrasting these activations in a population of chronic arthritics or neuropathic pain conditions, should reveal brain circuitry differences between inflammatory and neuropathic chronic pain conditions.

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