# Threat-dependent modulation of anterior insula connectivity predicts pain

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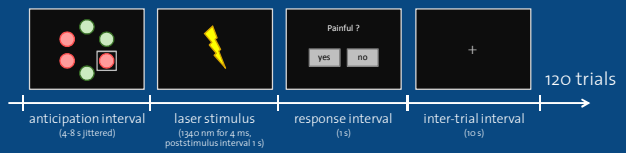
## 1 Background

The perception of pain cannot be explained in terms of afferent noxious input alone; psychological factors play an important role as well [1]. Various behavioural studies highlight the influence of anxiety, although its neural basis is unclear. Recent evidence suggests that the anterior insula and its functional connectivity within the pain network might play a key role in how pain is modulated by factors such as anxiety [2]. This leads to three questions:

1. Does the anterior insula also integrate trial-by-trial variation of anxiety?
2. How might this activity influence connectivity among pain structures?
3. Do specific differences in network activity underlie interindividual variance in the susceptibility to pain?

## 2 Experimental paradigm

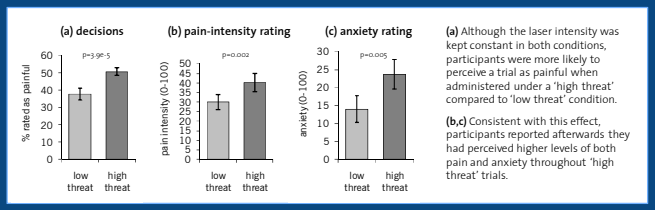
We used 3T fMRI to investigate neural activity during the anticipation and perception of pain in the context of different levels of threat-induced anxiety (2 x 2 factorial design, n=16).




On each trial, a brief laser pulse, calibrated to match the subject-specific pain threshold, was applied to one of several preselected sites on the dorsal aspect of the right foot. Prior to each pulse, subjects were told whether a site had been chosen that was **fully approved for safe stimulation** ('low threat' condition, 60 trials) or had been **approved 'with reservations'** ('high threat' condition, 60 trials). Following stimulation, subjects were prompted to indicate whether or not the stimulus had been perceived as painful. Trials lasted between 19 and 23 s each. At the end of the experiment, subjects were asked to rate the overall intensity of pain and anxiety they had experienced, separately for low- and high-threat trials.

## 3 Behavioural results

As intended by our design, trials were more likely to be perceived as painful, and subjects felt more anxious, in the 'high threat' compared to the 'low threat' condition.

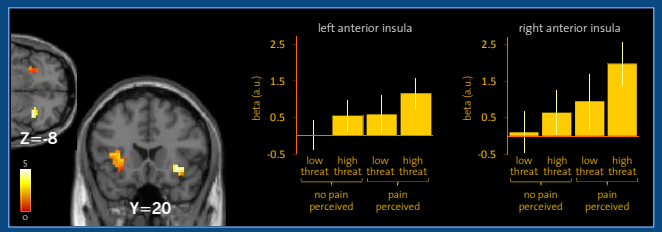



**(a)** Although the laser intensity was kept constant in both conditions, participants were more likely to perceive a trial as painful when administered under a 'high threat' compared to 'low threat' condition.

**(b,c)** Consistent with this effect, participants reported afterwards they had perceived higher levels of both pain and anxiety throughout 'high threat' trials.

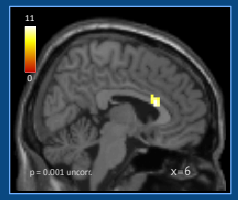
## 4 Prestimulus insula reflects both threat and pain

Regions underlying our behavioural effects should be both sensitive to threat and pain even in anticipation of a stimulus. We found that the only region implicated in both contrasts (high > low threat; pain > no pain) was the bilateral anterior insula, which was most active during anticipation whenever a 'high threat' trial was subsequently rated as painful.

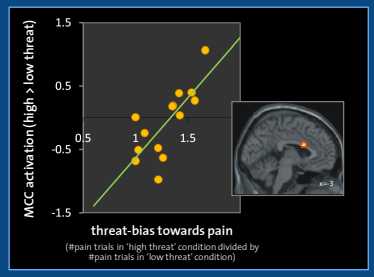



## 5 Pain modulates prestimulus connectivity with MCC

We carried out a psychophysiological interaction analysis (PPI) to investigate threat-related differences in functional connectivity of the anterior insula (psych. variable: 'high pain vs. low pain'; physiol. variable: anterior insula activity). The mid cingulate cortex (MCC) was the largest cluster of voxels whose degree of covariation with the anterior insula systematically differed across threat conditions.




## 6 MCC predicts susceptibility to pain

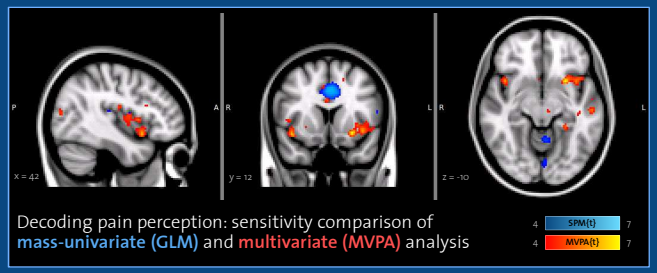



In order to further investigate the role of the MCC, we used a subject-specific indicator of susceptibility to pain under threat as a covariate in an analysis of the main effect of threat (high > low threat) during stimulation. We found that a bias towards pain was reflected by an increase in MCC activity.

## 7 Multivariate pattern analysis (MVPA)

Can pain perception be explained in terms of smooth activations alone, or is there more to be gained from considering fine-grained patterns of activity? We trained and tested a linear SVM on small searchlights (r=1) passed across whole-brain trial-wise Beta volumes, aiming to decode from activity during the decision phase whether a stimulus was perceived as painful. We compared GLM and MVPA results by thresholding the resulting group maps at p=0.001.

While the GLM-based t-contrast was most sensitive to smooth activations in cingulate cortex (blue), MVPA results favoured more subtle patterns of activity in the anterior insula (red).




Decoding pain perception: sensitivity comparison of **mass-univariate (GLM)** and **multivariate (MVPA)** analysis

## 8 Conclusions

Both the anterior insula and the MCC have previously been associated with a 'salience network' that integrates interoceptive information with emotional salience to form a subjective image of our bodily state [3, 4]. Our findings fit comfortably with this integrative notion:

1. Prestimulus activity in the anterior insula reflects trial-by-trial variations of threat and subsequent pain.
2. Prestimulus anxiety modulates the functional connectivity between anterior insula and MCC.
3. Whether this coupling leads to increased MCC activity during stimulation predicts the perception of pain.

Thus, the degree of threat-related sensitization of the pain network by the anterior insula prior to stimulation might underlie inter-individual differences in the facilitatory effect of anxiety on the perception of pain. Multivariate analyses are likely to provide further insights into information processing within the pain network.

**References**

1. Craig, A.D., 2009. How do you feel – now? The anterior insula and human awareness. *Nat Rev Neurosci*, 10(1), 59-70.
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