

Midazolam Anxiolysis Revealed Using FMRI

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Introduction

Pain is a subjective experience that involves both sensory and affective components. The emotional effects of chronic pain are often reported as more disabling than the pain itself. In the healthy individual, learning to recognize signals of pain allows painful events to be avoided. However, such learning can cause fear and anxiety in chronic pain patients [1]. Functional neuroimaging studies of pain tell us that the pain experience is mediated by a network of brain regions. Recent imaging studies have begun to dissect different neuroanatomical aspects of the conscious experience of pain. In particular, regions involved in the expectation or anticipation of pain have been identified as being similar to those associated with pain, although during anticipation Ploghaus *et al* [2] showed that it shifted rostrally in the anterior cingulate cortex (ACC) and insula.

Benzodiazepines are clinically effective anxiolytics, their effects being mediated by α_2 gamma-aminobutyric acid (GABA) receptors. The present study performs a neuropharmacological dissection of functions associated with anticipation to pain compared to those associated with pain itself using FMRI. This is important not only for improving our understanding of brain activity associated with anticipation of pain but also because such an approach may provide novel drug targets for the treatment of anxiety.

Methods

Eight male volunteers aged 25±5 years (mean ±SD) underwent gradient-echo echo-planar imaging on two occasions at 3T (Varian Unity Inova) (TR=2.5s TE=30s, in-plane resolution 4x4 mm, twenty-one 6 mm thick axial slices covering the whole brain, 223 volumes). T1 weighted structural scans were also acquired for image registration. Before each scan, thermal stimulus (5s duration) temperatures were adjusted to two different levels: one eliciting a moderate/strong pain and the other warm but not painful. Thermal stimulation was provided by a home-built device (2x1.5cm) attached to the back of the left hand. Shortly preceding each scan the subject received an intravenous bolus of either 30 µg/kg midazolam or saline vehicle (crossed-over across sessions). During scanning volunteers were presented with a thermal conditioning paradigm [2] designed to dissociate pain from its anticipation. Coloured lights of variable duration (5-15 s) signalled either the painful hot or a non-painful warm stimulus. Seven stimuli of each type, warm or painful were administered in a pseudorandom order. Subjects learned the association between colour and stimulus type. Comparison of the period preceding painful and warm stimulation allowed activity associated with anticipation to pain to be identified. A similar conditioning paradigm has shown midazolam to reduce reported anxiety associated with painful thermal stimulation [3].

FMRI data were analysed using FEAT, (FMRI Expert Analysis Tool [4]). Pre-processing included motion correction, spatial filtering (FWHM=5mm) and high-pass temporal filtering (Gaussian weighted straight line fitting, cutoff above 75s). General linear modeling of the data was performed to identify significant blood oxygen level dependent (BOLD) signal changes during the painful (P) compared to the non-painful warm (W) stimulation (P-W) and during the anticipation to pain (AP) compared to the period of anticipation to warm (AW) stimulation (AP-AW). Using FEAT, a second level mixed effects analysis was performed to identify group-representative activity associated with pain (P-W) and anticipation to pain (AP-AW) in the saline and midazolam conditions. Furthermore, in the principal regions defined by significant activity in the P-W and AP-AW conditions, the BOLD signal change under saline was compared with the corresponding signal changes under midazolam.

Results and Discussion

Volunteers were able to recall the relationship between the colour of the light and the temperature of the stimulus at the end of each scan. Volunteers reported stimulus intensity ratings after each scan on an 11-point combined thermal-pain intensity numerical rating scale: warm and painful hot scores were 4.6±0.3 and 8.4±0.2 for saline sessions and, 4.1±0.2 and 7.7±0.2 for midazolam sessions respectively (mean±SEM). The reported intensity of the painful stimulus was significantly less ($P<0.05$) during midazolam than saline.

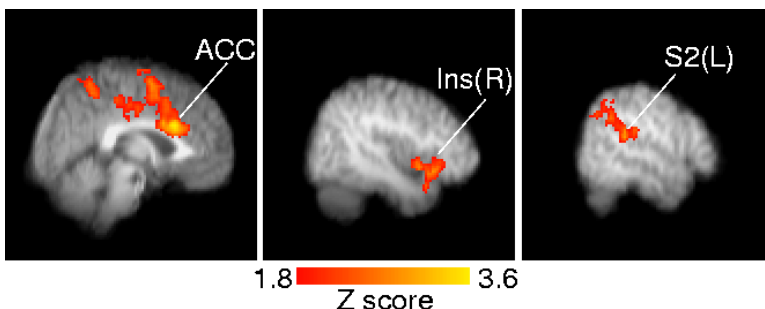


Fig. 1. Representative activity from anticipation to pain (saline condition) generated by a mixed effects analysis of 8 subjects. The condition AP-AW (anticipation to warm subtracted from anticipation to pain) is shown. Statistical thresholding was performed at the group level with $Z>1.8$ and a cluster significance threshold of $P<0.05$.

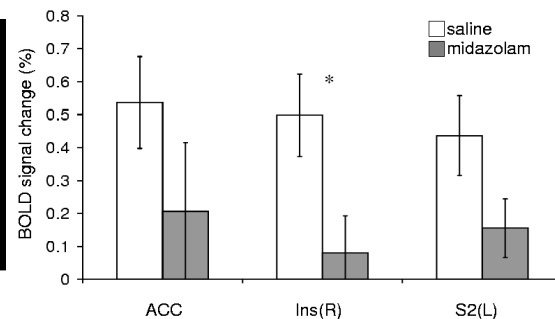


Fig. 2. BOLD signal changes arising during anticipation to pain (AP-AW) within regions of interest showing anticipatory activity during saline administration: anterior cingulate cortex (ACC), contralateral insular cortex (Ins), ipsilateral secondary somatosensory cortex (S2). Mean and standard errors are shown for the placebo (saline) and midazolam conditions.

Under saline administration, a pattern of pain-related (P-W) activity was observed that coincides with the previously reported pain matrix [5] including bilateral ACC, bilateral anterior and posterior insula, bilateral thalamus, contralateral motor cortex, contralateral primary sensory cortex, brainstem, cerebellum, prefrontal cortex and superior temporal gyrus. Under midazolam administration those regions plus some additional areas were observed (frontal areas, secondary sensory cortex and Brodmann area 40). Direct paired comparison of the midazolam and saline conditions at the group level (both voxel-wise and using the region of interest approach) showed no significant drug induced differences in pain-related activity.

Under saline administration the following regions were active during anticipation to pain (AP-AW): bilateral ACC, contralateral (right) insula (extending into inferior frontal gyrus and superior temporal gyrus) and ipsilateral (left) S2/posterior insula. Following midazolam administration, none of these regions reached a statistically significant level of anticipatory activity. In these three principal regions, defined by activity during the saline condition, the anticipatory related signal was decreased during midazolam administration. The contralateral (right) insular region showed the most significant drug-induced reduction in anticipation-related signal change ($P<0.01$). The anterior cingulate and secondary somatosensory cortical regions showed trends towards significance ($P<0.10$ and 0.07 respectively). The observed pattern of anticipatory activity is broadly in agreement with previous reports of activity in the ACC and insular cortex [2,6,7].

Our data suggests a selective pharmacological modulation of the anticipatory component of the pain experience. It is unlikely that the observed drug-modulation of brain activity arises from general haemodynamic effects of midazolam because the modulation of anticipatory activity was observed in regions overlapping with those also active during the pain condition, the brain activity for which was not affected by the drug. We demonstrate that pharmacological challenges can be used to dissect brain activity associated with different components of the pain experience.

References

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