Imaging how attention modulates pain in humans using functional MRI

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Summary
Current clinical and experimental literature strongly supports the phenomenon of reduced pain perception whilst attention is distracted away from noxious stimuli. This study used functional MRI to elucidate the underlying neural systems and mechanisms involved. An analogue of the Stroop task, the counting Stroop, was used as a cognitive distraction task whilst subjects received intermittent painful thermal stimuli. Pain intensity scores were significantly reduced when subjects took part in the more cognitively demanding interference task of the counting Stroop than in the less demanding neutral task. When subjects were distracted during painful stimulation, brain areas associated with the affective division of the anterior cingulate cortex (ACC) and orbitofrontal regions showed increased activation. In contrast, many areas of the pain matrix (i.e. thalamus, insula, cognitive division of the ACC) displayed reduced activation, supporting the behavioural results of reduced pain perception.

Introduction

The behavioural–affective and sensory–discriminative elements of pain perception are reduced in situations such as war or intense excitement, via feedback information from higher-order cognitive areas (Melzack and Casey, 1968). It is found that patients report more intense postsurgical pain when they are required to attend to the pain (Miron *et al.*, 1989), and methods such as listening to music can significantly reduce postoperative pain in patients (Good *et al.*, 1999). Current research suggests that, unless the subject's attention is actively directed elsewhere, painful stimuli will take precedence over competing non-painful ones (Eccleston and Crombez, 1999). Psychological state is therefore able to modulate the perception of experimentally induced pain. Psychophysical examples of this include work by Miron *et al.* (1989), showing that directing attention to a painful stimulus increased its perceived intensity and unpleasantness compared with when subjects were asked to direct their attention away from the stimulus. Pain ratings were reduced when a cognitive task was carried out at the same time as administration of cold pressor pain (Hodes

et al., 1996). In addition, a thermal laser study found reduced human electrocortical evoked potentials when attention was diverted away from the painful stimuli (Siedenberg and Treede, 1996).

It is clear that attention can modulate pain, but our understanding of the precise cognitive mechanisms behind this remains poor. To date, attempts to identify the brain areas involved in the attentional modulation of pain have centred on the anterior cingulate cortex (ACC). The ACC has a pivotal role in executive processes, motivation, allocation of attentional resources, premotor functions and error detection (Turken and Swick, 1999). The ACC is activated by moderate to intense painful stimulation (Casey *et al.*, 1994) and PET studies have revealed large concentrations of opiate receptors in this region (Jones *et al.*, 1991). It has been suggested that attention and pain activate separate sites within the ACC (Vogt *et al.*, 1992; Davis *et al.*, 1997). Hsieh and colleagues (Hsieh *et al.*, 1995) have shown that areas of the ACC activated by painful stimulation lie in parts of the ACC adjacent to those activated by attention-demanding tasks.

During a distraction paradigm using a maze task, orbitofrontal cortical areas were found to be activated in situations of increased cognitive load, such as when the pain interfered with completion of a cognitive task (Petrovic *et al.*, 2000).

The present study addressed the functions of other brain areas that may also play a significant role. It is important that this information should be acquired if novel therapies based upon attentional manipulations are to be developed. The original Stroop Colour Word Task (Stroop, 1935) is a cognitive interference task and is used as a sensitive clinical test of executive function (Peterson *et al.*, 1999). A problem that arises when this task is used in functional MRI (fMRI) is that it necessitates speech, which produces head movements and image artefacts on functional imaging data sets. An analogue of the Stroop task developed specifically for use with fMRI is the counting Stroop task (Bush *et al.*, 1998). In this task, the subject is required to respond by a button press with the number of words presented, regardless of the word itself (speech is therefore obviated). As the counting Stroop task activates a wide network of brain regions, produces significant cognitive interference and provides on-line behavioural data, it is an ideal task to use for studies investigating the attentional modulation of pain. The hypothesis is that, during the interference condition, the painful stimulation will be perceived as less intense because of the effect of being distracted by the attention-demanding cognitive task, and that this will be reflected in corresponding modulation of the blood oxygen level-dependent (BOLD) response. This would enable us to find out which areas of the brain are involved in the lowering of pain scores by cognitive interference.

Painful stimulation alone activates many areas within the brain, which are often defined as the 'pain matrix' (Melzack and Wall, 1965; Tracey *et al.*, 2000). Areas activated include the somatosensory and motor cortices, the ACC, the parietal and prefrontal cortices and the insula, thalamus and cerebellum. Some of the areas identified during painful stimulation, such as the posterior parietal cortex, the ACC, dorsolateral prefrontal cortex and thalamus, are also reported as belonging to attentional networks (Peyron *et al.*, 1999). The cognitive–evaluative component of pain therefore includes attentional processes, anticipation and memory for past experiences of pain (Peyron *et al.*, 1999). fMRI is an excellent tool to study pain mechanisms in the brain. Owing to its high spatial and temporal resolution, sophisticated paradigm designs are possible, allowing individual components of the pain matrix to be characterized and dissociated. Using fMRI and a differential pain-conditioning task, Ploghaus *et al.* (2000) examined the predictions of attentional (Mackintosh, 1975; Pearce and Hall, 1980) and non-attentional (Recorla and Wagner, 1972) learning theories. Attention was manipulated by varying the degree to which painful stimulation, or its omission, was surprising or expected. The omission conditions were included in order to separate attention to the noxious stimulation site from attention-induced changes in pain perception. This accounts for the absence of activations in some areas of the pain matrix observed by Ploghaus *et al.* (2000). The present study, in contrast, examined attention-induced changes in pain perception. We therefore hypothesized that distraction will modulate regions of the pain matrix, and our analyses focused on these areas.

Material and methods
Subjects
Eight healthy right-handed volunteers (six males, two females, mean age 30 $\pm$ 9 years) were recruited. Subjects gave informed consent in accordance with full ethical approval by the Central Oxfordshire Research Ethics Committee (COREC). Subjects underwent a comprehensive verbal screen to ensure that they did not meet any exclusion criteria for MRI experimentation.

fMRI
Subjects were scanned in a 3 T human MRI scanner (Oxford Magnet Technology, Technology, Witney, Oxon., UK), using a bird-cage radio frequency coil and a reduced bore gradient coil (SGRAD Mk III; Magnex, Scientific Ltd, Yarnton, Oxon., UK). Foam padding was placed around the subject's head to minimize movement. A magnetic resonance-compatible pulse oximeter (9500 Multigas Monitor; MR Equipment Corporation, Bayshore, NY, USA) was attached to record heart rate and blood oxygen saturation throughout. Subjects wore earplugs and MR-compatible electrostatic headphones (MRC Institute of Hearing Research, Nottingham, UK) to attenuate the noise of the scanner and facilitate communication with the experimenter.

A localizer scan served as a reference for axial slice selection for functional imaging data covering the entire brain volume. Echo-planar imaging continued throughout the pain and attention paradigm and used the following parameters: echo time 30 ms, repetition time 2.5 s, flip angle 90°, field of view 256 $\times$ 256 mm, matrix 64 $\times$ 64, slice thickness 6 mm, 21 slices. A 3D Turbo Flash T_1-weighted (axial) high-resolution anatomical scan was taken for each subject using the same slice prescription as that used for functional imaging data. This was used for co-registering scans from different individuals to a common standard.

Psychophysical details
Visual stimuli
Stimuli were generated using in-house software and back-projected on to a screen (In Focus LP1000, National Projectors, Dallas, Oreg., USA) viewed by subjects wearing prism glasses. A home-built, hard-wired, MR-compatible, four-button box was used to obtain simultaneous recordings
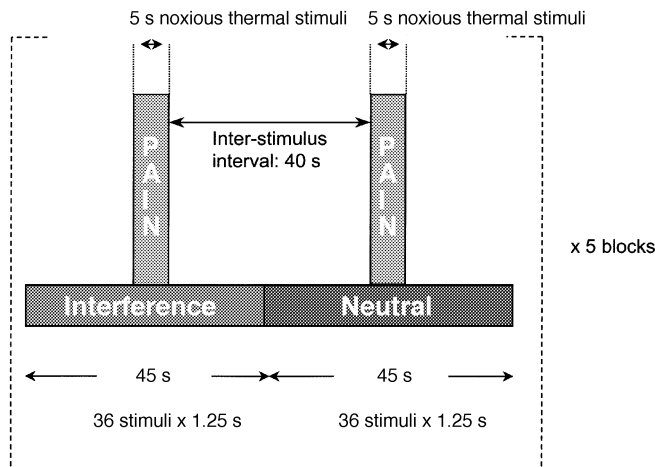
Fig. 1 The stimulus paradigm used in this study. Interference and neutral blocks of stimuli were alternated in sequence. Five blocks of each type were presented, during each of which there were 36 counting Stroop stimuli of 1.25 s duration (45 s in total). A painful thermal stimulus of 5 s duration was administered in each block concurrently with the counting Stroop stimuli. The temperature of the painful stimulus was the same across all blocks, with 40 s between each painful stimulus to prevent sensitization to the stimulus.

Fig. 2 Stimuli used for the counting Stroop paradigm. The counting Stroop is a distraction task in which subjects press buttons as fast and as accurately as possible to indicate the number of words presented. The neutral task contained animal words. The interference task was more complex, with incongruence between the number of words presented (required response) and the word meaning, e.g. four presentations of the word 'one' would require the subject to press button 4.

of the subjects' button-press responses and reaction times (RTs) throughout.

Noxious thermal stimuli

Thermal noxious stimuli (temperature range across subjects 50–53.5°C, duration 5 s) were administered to the dorsum of the subject's left hand using a thermal resistor (1.5 × 2 cm), designed and built in-house. This device delivered noxious stimuli with a short temperature ramp time (30–60°C in 0.8 s). It was controlled by in-house software and simultaneously measured skin temperature over the area stimulated.

Experimental design

Each subject attended one scanning session of ~45 min duration. Thermal noxious stimuli were administered to the left hand to identify the temperature to which each attributed a pain scale rating of 8 out of 10, or 'strong pain'. An outline of the timings used throughout the procedure can be seen in Fig. 1.

This study used a modified version of the Stroop task (Stroop, 1935), the counting Stroop task (Bush *et al.*, 1998). Subjects were informed that they would see sets of between one and four identical words presented on the screen as a vertical list, which would change every 1.25 s. They were asked to record the number of words presented on the screen (regardless of the word itself) using the button corresponding to the number of words presented, as quickly and accurately as possible, with strong emphasis placed on not sacrificing

accuracy for speed. In order to try to prevent subjects making the task easier by blurring the words on the screen, they were asked to verbalize the word internally once, at the same time as pressing the relevant button. The 'interference' block stimuli consisted of the number words 'one', 'two', 'three' and 'four'. During the 'neutral' blocks, the stimuli consisted of the animal names 'cat', 'fox', 'tiger' and 'frog'. Five 45-s interference blocks alternated with five neutral blocks of the same duration, starting with an interference block. Both sets of stimuli in the two experimental block types comprised words in the same semantic category and were balanced for word length (e.g. the word 'cat' is the same length as 'one' and 'frog' the same length as 'four'). For each of the five neutral and five interference blocks, the individual word stimuli were presented in pseudorandom sequence in each case, and the order of stimuli within blocks was different in all five trials for each condition. There were no congruent trials in the interference condition, e.g. there was no single presentation of the word 'one'. The reader is referred to Fig. 2, which details the presentation of the stimuli.

In the middle of each of the ten blocks, a 5-s painful thermal stimulus of constant temperature was applied to the subject's left hand at the same temperature previously rated as 8 by the subject. The visual stimuli carried on throughout and therefore four stimuli were shown whilst the pain continued. Subjects were told that they should pay attention to the task throughout but maintain an awareness of the rating they would give to the thermal stimuli, and that they would then be asked to compare pain intensity for the interference and neutral conditions at the end of the experiment using the pain scale presented during thresholding.

Statistical analysis
Behavioural data
The mean RT between stimulus presentation and button presses across interference blocks and neutral blocks was calculated across subjects and Student's one-tailed *t*-test was carried out to assess the significance of the difference between the two groups of RT means. The pain scores across subjects were analysed similarly and a one-tailed Student's *t*-test was carried out to compare the significance of the difference between the interference and neutral pain intensity scores.

Imaging data
Analysis of the fMRI images to identify regions exhibiting significant changes in BOLD signal (Ogawa *et al.*, 1992) was carried out with a multistage process using the image analysis package FEAT (www.fmrib.ox.ac.uk/fsl), an extension of MEDx (Sensor Systems, Sterling, Va., USA). The following pre-statistics processing was applied from within the FEAT package: motion correction using the SPM realign procedure (Friston *et al.*, 1995a); spatial smoothing using a Gaussian kernel of full-width half-maximum 5.0 mm; mean-based intensity normalization of all volumes by the same factor; high-pass temporal filtering (Gaussian-weighted least squares fit straight-line fitting, with high-pass filter cut-off 80.0 s). The statistical portion of the analysis was carried out from within the FEAT package using a general linear modelling

(GLM) approach (Friston *et al.*, 1995b). This allows a description of the experimental design to be made. A model is then created that is fitted to the fMRI data, indicating where the brain has activated in response to the stimuli. In FEAT, the GLM method is known as FILM (fMRIB's improved linear model) (Woolrich *et al.*, 2000, 2001). FILM uses a robust and accurate non-parametric estimate of time series autocorrelation to pre-whiten each voxel's time series; this gives improved estimation efficiency compared with methods that lack pre-whitening.

The study was designed in a factorial way. Two explanatory variables were proposed to model each subject's fMRI time-course data on a voxel-by-voxel basis. The explanatory variables were the Stroop condition and the painful stimulation, and were modelled within the GLM, both independently and as interactions between the two variables. Each explanatory variable resulted in a parameter estimate image. This estimate indicates how strongly that waveform fits the fMRI data at each voxel; the higher it is, the better the fit. Areas showing a significant positive interaction between variables are more active, as measured by the fMRI signal change, when the pain and Stroop conditions occur simultaneously than would be predicted by the simple addition of the responses to both stimuli alone. In contrast, the negative interaction indicates a reduction in activity during simultaneous presentation of stimuli. To convert from a parameter estimate to a *t*-statistic image, the parameter estimate is divided by its standard error, which is derived from the residual noise after the complete model has been fitted. The *t* image is then transformed into a *Z* statistic, an 'activation map', by standard statistical transformation.

A fixed-effects group cluster analysis (a second-level analysis) was carried out on the subjects' activation maps to produce representative group results. Four contrasts were formed. The first compared interference blocks with neutral blocks, the second compared pain with non-pain, the third reported the positive interaction between pain and interference and the fourth looked at the negative interaction between the pain and the interference task. The thresholding parameters used for the fixed effects analysis were a *Z*-score threshold of 2.0 and a probability value of $P = 0.05$ for cluster significance (Worsley *et al.*, 1992; Friston *et al.*, 1994; Forman *et al.*, 1995).
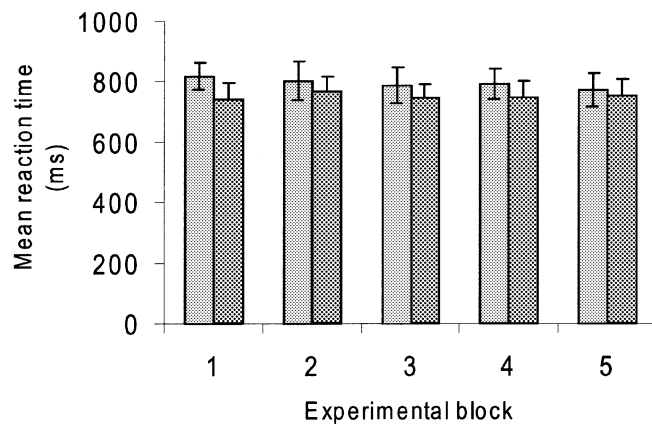
Fig. 3 Mean RTs by experimental block for both interference (light grey) and neutral (dark grey) tasks. The mean RT for the interference task was significantly increased compared with the mean RT for the neutral task ($P = 0.0008$). ANOVA revealed no significant practice effects with time.

Quantification of pain modulation by distraction
The inclusion of interactions in the model for the fMRI signal provides the flexibility to identify those voxels in which the

Table 1 *Positive interaction*

Brain region	Laterality	Talairach coordinates	Mean Z	Maximum Z
Orbitofrontal cortex	L/R	18, 44, 2	2.31	3.80
Perigenual cingulate	L/R	–10, 32, –2	2.25	3.05
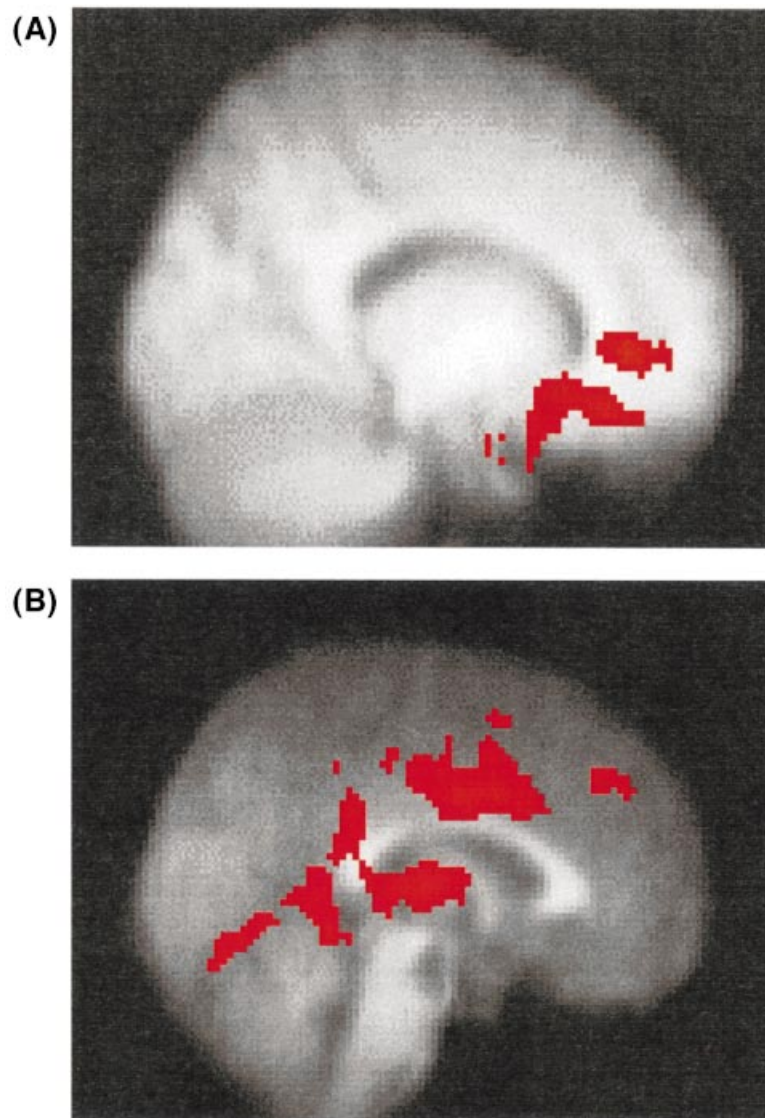
Fig. 4 (**A**) Perigenual cingulate activation associated with the positive interaction. The explanatory variables of the Stroop task and pain were modelled within GLM independently and as a non-linear interaction between the two variables. The positive interaction reveals areas that are more active when pain and Stroop are occurring simultaneously than would be predicted by the simple addition of the responses to both stimuli alone. (**B**) Midcingulate activation associated with the negative interaction. The negative interaction reveals areas that are less active when pain and the Stroop task are occurring simultaneously than would be predicted by the simple addition of the responses to both stimuli alone.

activation in response to painful stimulation is increased (positive interaction) or decreased (negative interaction) by the interference condition. Similarly, the examination of such interactions reveals the effects of pain on the activation in attentional areas.

Using this model, the magnitudes of fMRI signal responses to the painful stimulus in the interference and non-interference condition were identified. These responses are described here as parameter estimates from the model fitting, in arbitrary units, representing the fMRI signal changes. Having manually defined regions of interest of the pain matrix from anatomical scans, the mean values of the parameter estimates (fMRI signal changes) were calculated

over these regions. This provided a measure of regional pain activity during the two different cognitive load conditions. A group mean activity across subjects was thus established, allowing a test of significance between the interference and neutral conditions (paired *t*-test) to be carried out for each brain region.
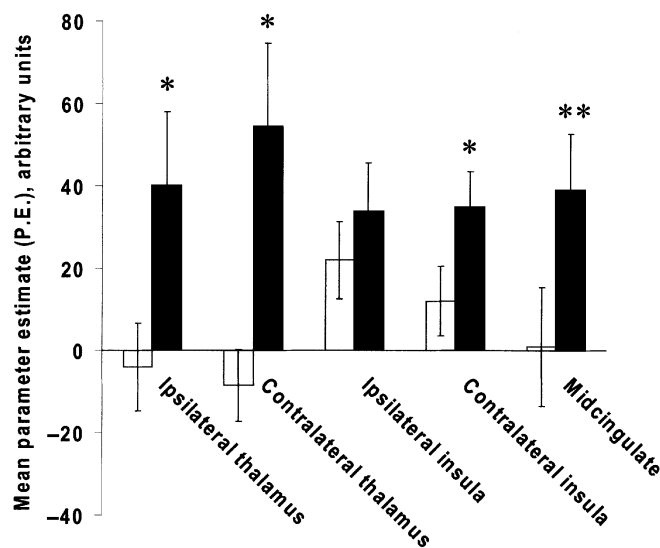
Results
Behavioural results
For the counting Stroop task, the overall mean RT for all interference blocks was significantly greater than the mean

Table 2 *Negative interaction*

Brain region	Laterality	Talairach coordinates	Mean Z	Maximum Z
Insular cortex	L	–36, 6, 0	2.34	3.78
Cerebellum	L/R	8, –78, –16	2.36	3.25
Thalamus	L/R	2, –14, 12	2.44	3.71
Medial/superior temporal gyrus	L	–54, –10, 0	2.27	3.48
Hippocampus/caudate	L	–26, –34, 6	2.17	2.83
Midcingulate	L/R	–4, –20, 32	2.38	3.60
Posterior cingulate	L/R	0, –36, 28	2.17	2.70
Midcingulate/premotor cortex	L/R	6, –2, 50	2.29	3.40

Fig. 5 Mean parameter estimates within key areas of the pain matrix during painful stimulation in the interference task (white) and the neutral task (black). The group results show mean ± 1 SEM regional activation, and significance levels are indicated for $P < 0.05$ (*) and $P < 0.005$ (**). The parameter estimate is the factor by which the linear signal model is scaled to best fit the fMRI time-course data. Parameter estimates are measured in arbitrary units and are proportional to fMRI signal changes. The ipsilateral thalamus, contralateral thalamus, contralateral insula and midcingulate all showed a significant drop in pain activation during the distracting interference condition compared with the neutral condition.

RT for all neutral blocks (interference blocks, mean ± standard error of the mean RT 794 ± 55 ms; neutral blocks, mean RT 748 ± 52 ms; $P = 0.0008$, Student's t-test). This is displayed graphically in Fig. 3.

There was no indication of practice effects. A one-way ANOVA (analysis of variance) showed that there was no significant difference in RTs over time from blocks 1 to 5 (neutral blocks, $P = 0.998$, $F = 0.0317$; interference blocks, $P = 0.986$, $F = 0.087$). Pain intensity ratings were significantly lower during the interference blocks than during neutral blocks (interference blocks, mean intensity 6.6 ± 0.2; neutral blocks, mean intensity 7.3 ± 0.3; $P = 0.006$, Student's t-test).

Functional imaging results

The group analysis for the counting Stroop task alone showed activation in areas reported previously (ACC, medial frontal gyri, premotor and primary motor cortex, inferior temporal gyrus and superior parietal lobule) (Bush *et al.*, 1999). The group analysis for noxious thermal stimulation confirmed that the subjects showed activation in all brain regions associated with the pain matrix (Peyron *et al.*, 1999). Areas activated in our study were consistent with this typical activation resulting from noxious stimulation and included the insular cortex, bilateral thalamus, anterior cingulate and sensory cortex. These findings confirm the validity of our modelling and its capacity to dissociate pain and Stroop activations within the brain.

Group analysis for the positive interaction (see Material and methods) revealed activity in bilateral orbitofrontal cortex and bilateral perigenual cingulate. Table 1 shows the areas activated in this contrast together with the Talairach coordinates for these areas. The cingulate activation is illustrated in Fig. 4A.

Group analysis for the negative interaction revealed activation in areas including the contralateral insula, midline cerebellum, medial thalamus, left superior and medial temporal gyri [Brodmann area (BA) 21/22], contralateral hippocampus/caudate, bilateral posterior cingulate cortex, bilateral midcingulate and midcingulate/premotor areas (for areas activated together with their corresponding Talairach coordinates, see Table 2). The midcingulate activation is illustrated in Fig. 4B.

The group results (mean ± standard error of the mean) of regional activation or signal changes in the pain matrix during the interference and neutral conditions are illustrated in Fig. 5. The ipsilateral thalamus, contralateral thalamus, contralateral insula and ACC all showed a significant drop in pain activation during the distracting interference condition compared with the neutral condition. This is discussed more fully below in the Discussion.

Discussion

It is well known that distracting attention from a painful stimulus reduces pain perception (Miron *et al*., 1989), although the exact neuronal basis for this modulation remains an enigma. fMRI is an ideal method with which to investigate the brain regions implicated in this modulation. Petrovic and colleagues (Petrovic *et al*., 2000) found decreased visual analogue scale pain scores when subjects performed a maze task at the same time as receiving painful stimuli compared with subjects in the pain alone condition. The intensity and the affective nature of the painful stimulus were reduced when attention was directed away from pain compared with when subjects focused on it (Miron *et al*., 1989), highlighting the profound effect of psychological state on the perception of experimental pain.

Our experimental results showed decreased behavioural pain ratings whilst subjects were occupied in a more distracting cognitive interference task than when they were performing a neutral, less demanding task. These ratings were obtained as an average rating at the end of the experiment for pain perceived during the interference task and pain perceived during the neutral task. Pain ratings obtained during an experiment are optimal, since they negate the need for subjects to remember average pain intensities. However, during complicated cognitive paradigms it is not always desirable to introduce other confounds, such as rating pain during baseline blocks between Stroop conditions, as this may invalidate the fundamental Stroop task itself.

We believe that we minimized any potential bias in reporting pain intensities in this experimental paradigm through the use of naive subjects and careful attention to the instructions given to participants. Future studies could benefit and reduce any bias still further by carrying out one non-imaging session in the scanner, where pain would be rated during the cognitive paradigm or where subjects would carry out the paradigm on the bench outside the scanning environment.

Painful stimuli take precedence over non-painful ones unless a concerted effort is made to direct attention elsewhere. It is thought that frontal regions, including the orbitofrontal cortex, play a key role in modulating pain processing during attentional manipulation paradigms (Miron *et al*., 1989; Davis *et al*., 1997; Derbyshire *et al*., 1998; Peyron *et al*., 1999; Petrovic *et al*., 2000; Ploghaus *et al*., 2000). Peyron *et al*. (1999) suggest that an intensity coding matrix (anterior insula, SII, contralateral thalamus) is overlaid on an attentional matrix (bilateral thalami, posterior parietal and prefrontal cortices, anterior cingulate gyrus). Although the pain matrix is well characterized, studies to date have not entirely clarified the nature of its modulation by attention, leading to a drop in perceived pain intensity. Our experiment combined high-field fMRI with a novel attentional paradigm ideally suited for functional imaging (Bush *et al*., 1998). To look at this in detail, our imaging data were analysed with the GLM (Friston *et al*., 1995*b*), a sophisticated analysis tool able to discriminate interactions between competing events, such as central activation attributable to painful stimuli or to performing the counting Stroop task.

We shall limit our discussion to the positive and negative interactions, as they reveal specifically how attention modulates pain activation, and vice versa. Figure 5 shows the dramatic ability of cognition and, more specifically, attention, to reduce the BOLD signal directly in response to the same painful stimulation in areas known to be involved in pain processing, such as the insula, thalamus and midcingulate.

Negative interactions

Insula

The insular cortex is involved in the intensity encoding of painful stimuli (Peyron *et al*., 1999), interacting with the autonomic nervous system and playing a role in somatosensory processing (Coghill *et al*., 1999). The area receives input from the spinothalamically activated posterior thalamic nuclei and has links with the amygdala, the temporal pole, the hippocampus, the premotor cortex, the prefrontal cortex and the ACC. Decreased activation in this area is therefore consistent with decreased reported pain intensity.

Thalamus

The medial thalamic nuclei have been found to show increased activation as a result of painful stimulation (Tracey *et al*., 2000). Studies documenting increased populations of nociceptive neurones in the medial intralaminar thalamus lend credence to its role in the transmission and processing of noxious stimuli (Kwan *et al*., 2000). The relative decrease in activation found in this study could reflect reduced processing of the noxious stimuli, resulting in lowered perception of pain. Peyron *et al*. (1999) found bilateral increased activation when subjects attended actively to noxious stimuli, supporting the results of existing research (Portas *et al*., 1998). If attention is distracted away from the stimuli, one might expect to find a relative fall in activation, as was found in our study.

Hippocampus

There is evidence to suggest that the hippocampus has a role in pain processing (Lathe *et al*., 2001). For example, Wei *et al*. (2000) demonstrated that the amplitude of excitatory postsynaptic potentials of hippocampal CA1 pyramidal cells is positively related to the intensity of nociceptive stimulation. Ploghaus *et al*. (2000) demonstrated that hippocampal responses to pain vary as a function of attention. In this study, attention to the noxious stimulation site was manipulated directly by varying the degree to which painful stimulation, or its omission, was surprising or expected. The hippocampus was activated whenever a mismatch between pain expectation and experience led to increased attention. The present finding

shows that the hippocampus is activated when attention is not distracted away from the pain, which is consistent with the observation by Ploghaus *et al*. (2000) that the hippocampus is activated during attention to the noxious stimulation site.

Midcingulate

The ACC has a variety of specialized subdivisions processing cognitive, sensory and motor information (Devinsky *et al*., 1995). Further subdivisions of the ACC (Bush *et al*., 2000), based on function, neuronal projections and cytoarchitecture (Devinsky *et al*., 1995), include a caudal 'cognitive' division (midcingulate), BA 24b′, 24c′ and 32′, and a rostral 'emotional' division (perigenual cingulate) (BA 24a–c, 32, 25, 33). The midcingulate sends projections to the lateral prefrontal cortex (BA 9/46) and the premotor and supplementary motor areas. It forms part of a distributed attentional network and is activated by cognitively demanding tasks such as the Stroop task (Devinsky *et al*., 1995).

During cognitively demanding tasks, an increase in signal in the midcingulate occurs and, interestingly, a decrease in signal is observed in the perigenual cingulate at the same time (Drevets and Raichle, 1998; Whalen *et al*., 1998). This phenomenon is reciprocal: the perigenual cingulate is able to inhibit and decrease activation in the midcingulate (Drevets and Raichle, 1998; Whalen *et al*., 1998). In other experiments, the midcingulate shows increased activation during cognitively demanding tasks but is 'deactivated' by intense emotional states (Bench *et al*., 1992) and in the anticipation of pain in the laboratory (Drevets *et al*., 1995).

A relative decrease in activation compared with what would be expected from the simple sum of activation in the pain and Stroop conditions was found in the midcingulate. This could explain the fall in pain intensity scores reported by subjects, as it is known to be involved in the affective component of pain processing (Rainville *et al*., 1997). In addition, the reduction of midcingulate activation probably occurs via reciprocal inhibition due to the increased perigenual cingulate activation found in our study (see below, Positive interactions).

The midcingulate region of the ACC is commonly activated in all pain studies. It is involved in attentional processes common to attention and pain (Davis *et al*., 1997; Kwan *et al*., 2000). In addition, increased activation in rostral parts of the ACC is thought to reflect anticipation or orientation to the painful stimulus, whilst pain itself leads to activation in the midcingulate region (Ploghaus *et al*., 1999).

Positive interactions

Orbitofrontal cortex

The orbitofrontal cortex (BA 10, 11) is a heterogeneous prefrontal region with strong links to the hippocampus and other medial temporal lobe structures, the posterior cingulate cortex, the retrosplenial cortex, the sensory areas (SI and SII), the amygdala, the thalamus and the insula. These connections point to possible involvement in context-dependent memory and pain processing roles. In addition, the orbitofrontal cortex contains neurones responsive to negative emotional stimuli, and studies have shown that electrical stimulation of the orbitofrontal and medial prefrontal cortices results in analgesia in both primates and non-primates (Oleson *et al*., 1980; Thorpe *et al*., 1983). Increases in orbitofrontal activation were found during the modulation of laboratory pain in situations of increased cognitive load (Petrovic *et al*., 2000). There is a negative correlation between experimental pain intensity ratings and activation of the orbitofrontal cortex; thus, lower activation in this area occurs with higher pain ratings (Derbyshire *et al*., 1997). In our study, we found increased activation of the orbital frontal cortex as subjects rated pain lower, thereby confirming these earlier findings. The increased activation in the orbitofrontal cortex as a result of increased cognitive load during the interference Stroop task may inhibit, e.g. the insular cortical, parietal or midcingulate areas, leading to diminished perception of pain intensity and reduced pain ratings by subjects.

Perigenual cingulate

Our study found a relative increase in activity in the perigenual cingulate compared with what would be predicted by adding the signal increases in the pain and the Stroop condition together. This indicates a synergistic effect of pain and the Stroop task on this area, leading to more activation in the perigenual cingulate when pain and Stroop interference occur together, perhaps accounting for the reduced midcingulate activation occurring (see above) via the reciprocal inhibition observed in previous studies.

The perigenual cingulate has links with the nucleus accumbens, the amygdala, the anterior insula, the hippocampus, the orbitofrontal cortex and the periaqueductal grey. Other studies have shown that associated limbic areas show decreases in activation alongside the perigenual cingulate when this area is inhibited by the midcingulate (Shulman *et al*., 1997). Interestingly, in our study, the negative interaction observed in the midcingulate was reflected in a corresponding decrease in activation in the contralateral hippocampus and insular cortex.

This experiment focused on the ability of cognition—specifically, distraction of attention whilst subjects engage in a cognitively demanding task relative to a less demanding neutral one—to reduce the subjects' perception of the intensity of painful thermal stimuli. This is reflected in the modulation of key regions that are known to be involved selectively in thermal pain processing. Pain, however, is a multiplex of cognitive and sensory attributes that could also interact and be modulated by attention (or distraction). We can therefore only interpret our results as an interaction between the level of attention (or distraction) and painful *thermal* stimuli. Future studies to extend our observations

will investigate the ability of attention to modulate other painful stimuli that are non-thermal and any corresponding brain activation changes, thereby controlling for these potential other components of our painful stimulus.

Conclusions

Significantly lower pain intensity scores were reported whilst subjects were engaged in the more cognitively demanding interference Stroop task than in the neutral condition. This experiment used functional neuroimaging to look closely at the neural correlates of this phenomenon. The reduced perception of painful stimuli applied during the interference task compared with those felt during the neutral task was accompanied by reduced activation in some key components of the pain matrix, including the insula, midcingulate and thalamus. In conjunction with this, the perigenual cingulate and orbitofrontal regions involved in cognitive tasks and attention were found to show increased activation during cognitive interference coupled with pain. We should like to build upon the results of this acute experimental pain study to characterize the modulation of chronic clinical pain by cognitive modulation of attention. Our results suggest which brain areas might be subject to modulation and specific hypotheses can now be generated and tested. A greater knowledge of the central neural components orchestrating the modulation of pain by attention is vital if we are to continue to make informed choices in the selection of cognitive behavioural strategies for the alleviation of pain within the clinical arena.

Acknowledgements

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