Reduced cortical responses to noxious heat in patients with rheumatoid arthritis

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Abstract

Objectives—To test the hypothesis that patients with chronic inflammatory pain develop adaptive cortical responses to noxious stimulation characterised by reduced anterior cingulate responses.

Methods—Positron emission tomography was used to measure changes in regional cerebral blood flow (rCBF) in response to an acute experimental pain stimulus in six patients with rheumatoid arthritis (RA) in comparison to six age and sex matched controls. A standardised and reproducible non-painful and painful phasic heat stimulus was delivered by a thermal probe to the back of the right hand during six two minute periods during which time rCBF measurements were made. The effects of non-painful heat were subtracted from those of painful heat to weight the analysis towards the non-discriminatory or ‘suffering’ components of pain processing. Significance maps of pain processing were generated and compared in each group and contrasted with results obtained in a group of patients with atypical facial pain (AFP) that have been previously published.

Results—The RA patients showed remarkably damped cortical and subcortical responses to pain compared with the control group. Significant differences between the two groups were observed in the prefrontal (BA 10) and anterior cingulate (BA 24) and cingulofrontal transition cortical (BA 32) areas. The reduced anterior cingulate responses to standardised heat pain were compared with the increased cingulate responses seen in patients with psychogenically maintained pain (AFP) who had both lower pain tolerance and mood than the RA group.

Conclusions—Major cortical adaptive responses to standardised noxious heat can be measured and contrasted in patients with different types of chronic pain. The different pattern of cingulate and frontal cortical responses in the patients with inflammatory and non-nociceptive pain suggest that different mechanisms are operating, possibly at a thalamocortical level. Implications for treatment strategies for chronic pain are discussed.

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Deafferentation or ablation of anterior cingulate cortex in patients with intractable pain in addition to anxiety and depression, reduces the negative aspects of pain behaviour. Patients are still able to feel the pain but it is no longer ‘bothersome’, suggesting reduced attentional and affective responses to pain. There was no associated intellectual deficit but ‘motivation’ was frequently impaired. Local anaesthetic injection into the cingulum bundle and cingulate lesions induce analgesia in animals. Both the anterior cingulate cortex is innervated by the parafascicular and medial thalamic group of nuclei. Work by Sikes and Vogt have identified neurons in a region of anterior cingulate cortex in rabbits (area 24) that respond to noxious stimuli. Nociceptive projections to prefrontal cortex have also been identified. Nociceptive neurons in the anterior cingulate cortex have whole body receptive fields and their response may be blocked by injecting lidocaine into the midline thalamic nuclei, which are known to project to the anterior cingulate cortex in the rabbit and monkey and to prefrontal cortex. These medial thalamic nuclei are known to be nociceptive in both the monkey, and rabbit. Identification of equivalent structures in the human brain that are involved in nociceptive processing has recently been achieved using non-invasive functional imaging techniques. This has the advantage of being able to relate brain function to the actual experience of pain.

Positron emission tomography (PET) is able to provide a non-invasive method of measuring brain responses to different cognitive, sensory, and motor tasks. Previous PET measurement of regional cerebral blood flow (rCBF) in pain free volunteers have shown that the main cortical areas that are activated by a phasic thermal pain stimulus applied to the back of the right hand are the left anterior cingulate (Brodmann areas (BA) 24), right prefrontal (BA 10), anterior insula and inferior parietal (BA 40) cortices. Activation of these areas have been confirmed by other groups during phasic experimental pain, and during chronic neurgenic pain. These cortical structures have been identified as being important in the elaboration of the experience of pain. The most consistently activated region has been the anterior cingulate region recently shown to be bilaterally responsive to unilateral noxious heat stimulation.

On the basis of previous PET studies recently reviewed we have suggested that the cingulate cortex is likely to be involved in at least some of the affective components of pain processing. We have previously shown that patients with chronic pain (AFP) associated with significant depression and poor coping strategies had exaggerated anterior cingulate responses to a standardised experimental pain stimulus. On this basis we predicted that patients with RA, with definite nociceptive pain, would have diminished anterior cingulate responses. We have chosen to include the previously published data on atypical facial pain with the RA data set for ease of comparison and because it makes a direct contribution to the understanding of cortical responses in pain.

Figure 1  Scheme of component of processes leading to handicap and the different components of disease related behaviour that may contribute to it.
Cortical responses to pain

RA. The normal control group is common to both data sets and has also been previously published.22

Methods
We examined the cerebral responses to the non-discriminatory components of phasic thermal pain, exactly as previously described21-22 in a group of six female patients with active RA according to American Rheumatism Association criteria (mean (SD) age 62 (12.2): disease duration 4–30 years, Ritchie assessment of disease activity (mean (SD))33 (22): current global VAS pain score (mean (SD)) 53 (53) and compared their responses in the presence of ongoing arthritic pain with a group of pain free normal volunteers (mean (SD) age 54.7 (9.3): results previously published22). There were no significant differences between mean ages for the three groups. All patients with RA had involvement of the metacarpophalangeal joints, but none of the patients had active synovitis under the area of skin stimulated during the PET studies. Anxiety and depression were assessed using the Spielberger state/trait self evaluation questionnaire,27 and Beck Depression Inventory (BDI),28 before scanning. All subjects were familiarised with a pain visual analogue scale and the McGill pain questionnaire22 used during the scan to assess their arthritis pain and the experimental pain. Previously published psychophysics data from a group of female patients with AFP22 of comparable age (54.2 (8.4) are included for reasons stated above.

The PET results in the AFP group will be discussed together with the RA group results.

Before the scans, temperatures that, when applied to the back of the right hand, were reproducibly experienced as non-painful hot or painful hot were established for each subject using a thermal stimulator (Somedic: thermotest Type 1). The thermal stimulator delivers a reproducible ramp of increasing heat to the back of the hand via a water cooled thermode, which is either painfully or non-painfully hot at its peak, after which it returns to baseline. Throughout the experiment the heat stimuli are delivered as phasic stimuli (4 per min). The painful hot temperatures were determined by the patients according to which temperatures they felt confident of being able to tolerate throughout the experiment for each two minute rCBF measurement period. These were carefully selected so as to be sure that no reflex withdrawal might occur. The tolerability of the stimulus was an important aspect of the study as the patients were lying in the scanner for approximately two hours. Suppression of normal reflex withdrawal was therefore intrinsic to the design of the experiment. During scanning a reproducible phasic thermal stimulus was delivered via a contact probe to the back of the right hand every 15 seconds. The site of the probe was not moved at any stage during the course of each trial and none of the subjects moved during the rCBF measurements. The phasic stimulus was delivered for two minutes during which time rCBF was measured by PET (CTImodel 931-08/12 Knoxville) using inhalation of C15O2. This procedure was repeated six times, three times using tolerably painful heat and three times using non-painful heat as determined before the PET experiment. The order of the painful and non-painful stimuli was chosen so as to be as unpredictable as possible. The subjects were not told the total number of stimulations or the proportion of each type of stimulus before the scan, to minimise anticipation. However, this would only be effective for the first stimulus of each two minute period of stimulation, after which the subject would quickly realise which type of stimulus they were receiving. So it seems likely that there would be time during each two minute period of stimulation for some implementation of intensity dependent cognitive strategies.

To compare the effects of painful and non-painful thermal stimulation within and across the groups the following procedures were implemented: correction for head movement between scans; reorientation into a standardised stereotactic anatomical space; and a correction made for global changes in blood flow between scans. Finally, a statistical comparison of blood flow distributions between stimulus conditions and groups was performed to identify sites of significantly changed rCBF.29 These comparisons yield a statistical parametric map (spm) of significant change or difference in rCBF. Each of these procedures allows the compression of all the results to be assimilated into a single data set represented within standardised stereotactic space of Talairach.30 The latter has become a standard convention to allow different research groups to compare their results objectively and to provide an anatomical template for these type of functional results. The number of patients analysed in these studies is generally accepted as appropriate given the power of the statistical methods (spm), with approximately a million values (voxels) of data compared six times for each subject. The statistical power within a small group of patients is therefore

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z score</th>
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<td>Medial frontal (area 32)</td>
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<td>Inferior parietal (area 40)</td>
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<td>0</td>
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<tr>
<td>Thalamus</td>
<td>L</td>
<td>-18</td>
<td>-18</td>
<td>12</td>
<td>3.406</td>
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</tbody>
</table>

Table 1 Significant increases in regional cerebral blood flow responses to the suffering and intensity components of pain (painful heat—non-painful heat) in patients with AFP (with active RA and normal controls) (all Z scores denote a significant increase in rCBF)
Patients with RA demonstrated significantly reduced cortical and subcortical responses to experimental pain compared with controls (table 2) including reduced dorsolateral prefrontal (DLPF) (BA 10) and anterior cingulate (BA 24) and cingulofrontal transition cortical (BA 32) responses.

Subsignificant responses in the areas showing a significant increase in rCBF in the normal controls (contralateral insula cortex, lentiform nucleus and thalamus, anterior cingulate area 24 and ipsilateral cortical responses in prefrontal area 9 and inferior parietal area 39/40) are just detectable and illustrated in figure 2.

**Behavioural measures**

Table 3 shows the results of the questionnaires given to all the RA patients and the controls and in addition includes some unpublished results from a group of patients with AFP whose cerebral responses to noxious heat have been previously published. It also includes the temperatures chosen as painful hot and non-painful hot and heat tolerance. The control group chose significantly higher temperatures for painful hot (mean PH 47.6°C) than the RA group (mean 46.3°C; \( t = 3.0; p < 0.01 \)) and the AFP group (mean 45.2°C; \( t = 2.1; p < 0.05 \)). There was no significant difference between the temperatures chosen by the AFP and RA group.

Both the AFP (mean (SD) PT 42.9 (1.4)) and the RA (mean (SD) PT 46.4 (1.6)) group had significantly lower heat pain threshold than the control group (\( t = 4.73; p = 0.01 \) and \( t = 2.66; p < 0.05 \) respectively). Heat pain threshold was also significantly less in the AFP group (mean 42.9°C) than the RA group (mean 46.4°C; \( t = 3.15; p < 0.05 \)).

There were no significant differences between the groups for heat pain tolerance although the difference between the AFP group (46.9°C), and the RA (46.6°C) and control groups (49.1°C), approached significance (\( t = 2.48; p = 0.09 \) and \( t = 2.35; p = 0.07 \) respectively).

Of the remaining measures, there were no significant differences in heat pain. PET

In the normal control group (previously published\(^\text{13} \)) there was a significant response to the suffering components of acute experim- ental heat pain in the periaqueductal grey in the brain stem, lentiform nucleus and anterior cingulate cortex (area 24) opposite to the side of stimulation and dorsolateral frontal cortex (area 10), medial frontal cortex (area 32), and inferior parietal cortex ipsilateral to stimulation of the right hand (table 1). In patients with AFP significant increases in rCBF were also seen in anterior cingulate cortex but not in prefrontal cortices, but the cingulate responses were significantly greater in the AFP group (table 1; previously published\(^\text{14} \)).

**Results**

**PET**

In the normal control group (previously published\(^\text{13} \)) there was a significant response to the suffering components of acute experim- ental heat pain in the periaqueductal grey in the brain stem, lentiform nucleus and anterior cingulate cortex (area 24) opposite to the side of stimulation and dorsolateral frontal cortex (area 10), medial frontal cortex (area 32), and inferior parietal cortex ipsilateral to stimulation of the right hand (table 1). In patients with AFP significant increases in rCBF were also seen in anterior cingulate cortex but not in prefrontal cortices, but the cingulate responses were significantly greater in the AFP group (table 1; previously published\(^\text{14} \)).

**Table 2** Significant differences in regional cerebral blood flow responses to the suffering and intensity components of pain (painful heat—non-painful heat) between the group of patients with active RA and normal controls (all Z scores denote an increased response in the control group compared with the RA group). Z scores indicate the normal deviate for each location.

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates</th>
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<tr>
<td>Prefrontal cortex (area 10)</td>
<td>Female controls versus rheumatoid arthritis R 26 40 12 3.190</td>
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<tr>
<td>Cingulofrontal transition cortex (area 32)</td>
<td>R 18 32 16 2.990</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate cortex (area 24)</td>
<td>L -12 2 40 2.690</td>
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</table>

See Table 1 for details of coordinate system.

![Figure 2](http://ard.bmj.com/AnnRheumDis/firstpublishedas10.1136/ard.56.10.601) on 1 October 1997. Downloaded from http://ard.bmj.com. Jones, Derbyshire
Table 3 Results of the questionnaires given to each patient with RA and AFP and for the female controls reported previously.

<table>
<thead>
<tr>
<th>Condition/questionnaire</th>
<th>AFP group (SD)</th>
<th>RA patients (SD)</th>
<th>Female controls (SD)</th>
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<tbody>
<tr>
<td>NPH °C</td>
<td>39.5 (1.8)</td>
<td>41.1 (1.39)</td>
<td>44.8 (1.90)</td>
</tr>
<tr>
<td>PH °C</td>
<td>45.2 (2.8)</td>
<td>46.3 (1.32)</td>
<td>47.6 (0.73)</td>
</tr>
<tr>
<td>Threshold °C</td>
<td>42.9 (1.4)†*</td>
<td>46.4 (1.6)†*</td>
<td>47.9 (1.31)</td>
</tr>
<tr>
<td>Tolerance °C</td>
<td>46.9 (1.8)</td>
<td>48.6 (1.8)</td>
<td>49.0 (1.1)</td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td>16.0 (10.0)†*</td>
<td>6.5 (2.07)†*</td>
<td>4.8 (5.04)††</td>
</tr>
<tr>
<td>State anxiety</td>
<td>23.0 (16.4)†*</td>
<td>9.0 (2.6)†*</td>
<td>13.7 (8.33)</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>27.3 (16.0)</td>
<td>15.8 (6.32)</td>
<td>13.3 (5.39)</td>
</tr>
<tr>
<td>PVas-Ac</td>
<td>62.8 (30.4)</td>
<td>46.7 (21.4)</td>
<td>68.3 (18.1)</td>
</tr>
<tr>
<td>McGill sensory-Ac</td>
<td>0.20 (0.12)</td>
<td>0.18 (0.06)</td>
<td>0.26 (0.15)</td>
</tr>
<tr>
<td>McGill affective-Ac</td>
<td>0.11 (0.21)</td>
<td>0.07 (0.09)</td>
<td>0.18 (0.21)</td>
</tr>
<tr>
<td>PVas-C</td>
<td>47.6 (12.8)*</td>
<td>29.6 (13.4)*</td>
<td>—</td>
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<tr>
<td>McGill sensory-C</td>
<td>0.28 (0.06)</td>
<td>0.11 (0.08)</td>
<td>—</td>
</tr>
<tr>
<td>McGill affective-C</td>
<td>0.14 (0.10)</td>
<td>0.06 (0.06)</td>
<td>—</td>
</tr>
</tbody>
</table>

PH: The temperatures delivered as painful hot in degrees Celsius and NPH: the temperatures delivered as non-painful hot during scanning. BDI = Beck depression inventory. McGill sensory-Ac = McGill sensory score for the induced acute pain. McGill affective-Ac = McGill affect score for the induced acute pain. PVas-Ac = Visual analogue score for the induced acute pain. McGill sensory-C = McGill sensory score for the patients own background pain. McGill affective-C = McGill affect score for the patients own background pain. PVas-C = Visual analogue score for the patients own background pain.

Significant differences are denoted in the text and are denoted by * or †. Where there is only a significant difference between two groups these symbols are denoted singly. Where there is a significant difference between two groups and a comparator group the latter is expressed as a single symbol and the two other groups that are different from it as a double symbol.

Discussion

The relation between pain, impairment of function, disability, and subsequent handicap is likely to be complicated (fig 1). To understand these relations it is necessary to understand some of the mechanisms contributing to the elaboration of the experience of pain.

The hypothesis that at least the anterior cingulate responses to noxious stimuli should be modified during inflammatory pain has been substantiated. The extent of the reduction of the cortical and subcortical responses seen in the RA group has not been previously observed, although reduced anterior cingulate and prefrontal responses have also been observed in patients with acute inflammatory dental pain. Although it is not possible to determine the level at which the cortical responses in RA are modified, the possible anatomical and physiological basis for this modulation requires further clarification.

Noicceptive projections from the medial thalamic nuclei to prefrontal, insula, and cingulate cortices appear to be involved in both chronic and acute pain processing. These structures are generally considered part of the so-called ‘medial pain system’, concerned with emotional, evaluative, and motivational responses to pain. Anterior cingulate lesions are also known to result in antisocial and sometimes psychotic behaviour. The anterior cingulate is therefore involved in the integration of a number of higher functions including the assignment of emotional significance to sensory inputs, vocalisation, response selection, attention, mood, and social behaviour consistent with the concept of a role in the integration of cognition, affect, and response selection. In this context and in view of its consistent involvement with pain processing, it is the most likely cortical area to demonstrate adaptive mechanisms in patients with chronic pain associated with different behavioural responses. Patients with RA have been shown to develop their own cognitive strategies for dealing with their pain, which probably have some influence on cortical responses to noxious stimuli within and distant from the joint.

The differences between the results in this RA group and those obtained in patients with AFP require more detailed discussion. The AFP group had a lower pain tolerance and chose a lower painful temperature for experimental stimulation during scanning but demonstrated a substantial increase in anterior cingulate responses with reduced prefrontal responses. The RA group chose slightly lower temperature for their painful hot stimulations than the control group. However, this is an unlikely explanation for the reduced cingulate responses in the RA group because the AFP group chose a lower PH temperature than the RA group, which resulted in an increased anterior cingulate response.

It is probable that the reductions in response to noxious stimuli in the anterior cingulate cortices observed in RA are related to modulation of behavioural responses to pain that are well documented in patients with RA. The two main behavioural differences between the AFP group and the RA group were that the AFP patients were significantly depressed and suffered from severe pain in the absence of any demonstrable noxious input. This does not exclude a source of noicceptive input, but if they do exist it seems more probable that the dominant mechanisms are persevered hyper-attentional and affective responses to noxious and non-noxious inputs, and that the converse is the case with the RA group. Both attention and pain have been shown to be processed in adjacent networks within the cingulate cortex.

It is interesting that the two patient groups did not rate the affective components of either their ongoing or experimental pain any differently. This may reflect a lack of sensitivity of the subcomponents of the McGill scale in small numbers of patients or that we are wrong in our assumptions about the effect of affect on pain processing. This becomes important to our understanding of inflammatory pain. The development and selection of changed attentional and affective responses underpin the positive coping strategies that are well developed by people who suffer from RA. It has been suggested that some patients with AFP may ‘overvalue and obsess about their pain’. Patients with chronic pain including AFP and fibromyalgia tend to have increased attention to pain, poor coping strategies, and different pain belief systems with a predominance of catastrophising seen more commonly in patients with high distress and depression levels. It therefore seems probable that the differences in the anterior cingulate response between the AFP and RA groups are because of differences in processing of affective and attentional components of nociceptive processing, which may also be related to changed response selection. Larger longitudi-
nal studies are required to determine which of these components are the main determinants of the differences in anterior cingulate responses. The DLPF cortex has been implicated in normal supervision of attentional processes, depressed mood (areas 9, 46),\textsuperscript{44} willed actions (areas 46, 10),\textsuperscript{44} and response inhibition.\textsuperscript{45} The reduced prefrontal responses to a standardised experimental pain stimulus would seem to occur with all types of chronic pain studied so far. There are extensive reciprocal connections between dorsolateral prefrontal cortex including areas 9, 46, and 10\textsuperscript{46} to anterior cingulate cortex in primates. Recent studies in monkeys suggest that area 9 of prefrontal cortex is involved in inhibition of attention to a particular task\textsuperscript{47} when the animal is required to make a shift in attention from one task to another. In this context it is interesting that Hsieh et al, have shown that prefrontal responses to pain are critically dependent on the psychological state of the subject. If they are pre-conditioned by a painful stimulus and know when to expect the painful stimulus there are reduced rather than increased prefrontal (ventromedial) and cingulate responses.\textsuperscript{48} This result was attributed by the authors to the acute stress of the injury and to the general stress which accompanies pain. Thus, the pain of the injury makes the pain much less bothersome, but also attributed by the authors to the acute stress which accompanies pain.

Responses to nociceptive stimuli within the anterior cingulate motor areas have been recently reported\textsuperscript{49} and may be related to response inhibition, together with areas of prefrontal cortex. Premotor planning, including inhibition, is likely to be highly modified bynoxious inputs in patients with RA. Electrophysiological studies in monkeys have implicated the dorsolateral prefrontal cortex in either deciding not to move or suppression of motor execution.\textsuperscript{50}

The neuropharmacological basis of the differences of cortical responses to pain are not known, but indirect evidence implicates the endogenous opioid system. Substantial changes in opioid receptor binding consistent with cortical opioid peptide release during inflammatory pain have been shown in patients\textsuperscript{51} and animals with arthritis.\textsuperscript{52} Mice with the enkephalin gene mutated to block metenkephalin production demonstrate significantly increased supraspinally mediated behavioural responses to noxious heat.\textsuperscript{53} In patients with RA pain the region specific changes in in vivo opioid receptor binding were mainly in the prefrontal, anterior cingulate, and temporal cortices.\textsuperscript{54} Cognitive coping strategies for dealing with cold pressor induced pain are less effective after administration of the opiate antagonist naloxone.\textsuperscript{55} Morphine analgesia modifies anterior cingulate, prefrontal, and insula cortical function,\textsuperscript{56} suggesting that opiates may preferentially modify the cortical projections of the medial thalamic nuclei. This is consistent with the finding that morphine does not effect pain localisation but makes the pain much less bothersome, suggesting the modification of affective, attentional or even stress responses.

The results of this study clearly show a striking reduction in frontal and anterior cingulate cortical responses during inflammatory pain, which is distinct from previously reported increased cingulate responses in patients with psychogenically maintained pain. This suggests that different physiological and psychological mechanisms are operating to modify responses to noxious stimulation in these two types of pain and may have some relevance to the development of more effective therapeutic strategies.

We are most grateful for the MRC support that we received enabling us to carry out these studies, in addition to support from the BMA (Doris Hillier Award) and the Violet Richards Charity. We are also particularly grateful for the encouragement of Professor Terry Jones (MRC CU) in the pursuit of this work and to Professor Brent Vogt (Bowman Gray School of Medicine, Winston-Salem, North Carolina) for his very helpful comments on an earlier draft of this manuscript.

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