Neuropsychological Measures of Pain Processing in Pain Patients and Pain Free Volunteers. A Study Using Positron Emission Tomography (PET)

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Abstract

Positron Emission Tomography (PET) has been applied to normal volunteers and patients suffering pain of various aetiologies in order to address three issues: Firstly, which areas of the brain respond specifically to painful stimuli, secondly, to what extent these areas differ across individuals according to the parameters of the stimulus and individual variability, and thirdly, the extent to which responses within these systems vary with pain pathology. Using blood flow as a marker of neuronal activity, focal cerebral responses to thermal pain were defined in normal volunteers and patients using PET and C$^{15}$O$_2$ or H$_2$O$^{15}$O. Increases in regional cerebral blood flow (rCBF) for the normal volunteers were seen in the thalamus and basal ganglia, and in the anterior cingulate, insula, prefrontal, secondary somatosensory and parieto-temporal cortices. The relative changes in these areas varied across the patient groups studied such that patients with atypical facial pain (AFP) had increased rCBF to the insula and lentiform nucleus, as for the normal volunteers, but comparatively higher flow to the anterior cingulate cortex and lower flow to the prefrontal cortex. Patients with post extraction dental pain demonstrated increased rCBF in the lentiform nucleus and thalamus only, and the rheumatoid arthritis group showed low blood flow in all areas. This variability was discussed in terms of subjects' psychological profile, social context and responses to treatment. The increased anterior cingulate response with AFP was interpreted as an attentional motivational response to pain, possibly facilitated by a lack of prefrontal control. The response patterns in both the dental pain and arthritis patients were interpreted as important adaptive responses within pain networks. The involvement of opioid systems and attention in these adaptive responses were investigated clinically and with PET.
## Contents

<table>
<thead>
<tr>
<th>Title</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>17</td>
</tr>
</tbody>
</table>

### Chapter 1: Introducing theories and mechanisms of pain processing | 18 |

- Towards a theory of pain | 18 |
- The search for the pain fibres | 18 |
- The limitations of specificity theory | 20 |
- Other theories of pain | 21 |
- Gate control theory of pain | 22 |
- Pain and emotion | 25 |
- The anatomy and physiology of pain | 28 |
- Brain systems | 30 |
- Relating the psychological and anatomical subsystems | 32 |
- Chronic pain pathology | 35 |
- Rheumatoid arthritis | 36 |
- Atypical facial pain | 38 |
- Post extraction pain | 43 |
- Conclusions | 43 |

### Chapter 2: PET Methodology, the analysis of activation studies | 45 |

- Physical principles | 45 |
- Attenuation | 46 |
- Dead time losses | 47 |
- Random and multiple events | 47 |
- Scatter | 48 |
The cameras and data management 49

(1) The CTI 931-08/12 camera 49
(2) The CTI 953B camera 50
(3) Data archiving and image transformations 51

Experimental application 52

rCBF measurement 53

Statistical analysis - The making of a Statistical Parametric Map (SPM) 57

Realignement 58

Stereotactic normalisation 59

Smoothing 60

Analysis of covariance (ANCOVA) 61

Assessment of significant change: comparison of means 63

Assessment of significant change: thresholding 64

Assessment of significant change: interpretation 65

Chapter 3: Normal variation in response to pain, groups and single case studies 67

Introduction 67

Methods 71

Subjects 71

Design 71

Apparatus 71

Procedure 72

PET data analysis - female group 74

PET data analysis - male individuals 76

PET-MRI coregistration 76

Results - group analysis 78

The comparison of rCBF changes in response to pain in the female controls 78

Results - individual studies 80
# Chapter 4: An investigation of central responses to a tonic pain stimulus

## Introduction

Methods

**Subjects**

**Design**

**Apparatus**

**Procedure**

**PET data analysis**

Results - group analysis

Questionnaire results

Results - individuals

Discussion

## Chapter 5: Cortical and subcortical responses to pain in patients suffering atypical facial pain

Introduction

Methods

**Subjects**

**Design and apparatus**
<table>
<thead>
<tr>
<th>Chapter 8: The impact of morphine on atypical facial pain and post extraction pain: A controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction 169</td>
</tr>
<tr>
<td>Methods 172</td>
</tr>
<tr>
<td>Subjects 172</td>
</tr>
<tr>
<td>Design 173</td>
</tr>
<tr>
<td>Apparatus 175</td>
</tr>
<tr>
<td>Procedure - morphine trial 176</td>
</tr>
<tr>
<td>Procedure - PET study 180</td>
</tr>
<tr>
<td>PET data analysis 181</td>
</tr>
<tr>
<td>Results 182</td>
</tr>
<tr>
<td>Pain affect and sensory ratings 182</td>
</tr>
<tr>
<td>Reaction times 182</td>
</tr>
<tr>
<td>Questionnaire scores - from the clinical trial 185</td>
</tr>
<tr>
<td>PET results 188</td>
</tr>
<tr>
<td>Questionnaire results - for the PET subjects 189</td>
</tr>
<tr>
<td>Discussion 190</td>
</tr>
</tbody>
</table>

Chapter 9: An investigation of central processing with the Stroop task and pain. A within subjects design 196
Introduction 196
Methods 201
   Subjects 201
   Design 201
   Apparatus 202
   Procedure 202
   PET data analysis 203
Results 204
   Group results 205
   Individual results 208
   Coregistration 212
   Comparing SPM with coregistration 217
Questionnaire results 218
Discussion - group 220
Discussion - individual results 223
Discussion - laterality 226
Discussion - comparing stereotaxis with co-registration 226
General conclusion 227

Chapter 10: Conclusions and future studies 229

What is the neuropsychology of pain? 229
Variation at the neurological level 230
   I. Attention and affect 232
   II. Motor control 233
   III. Avoidance learning and memory 234
The McGill pain questionnaire 239
Variation in the neurotransmitter systems 243
The contextual or societal variation 244
Conclusions and future studies 247
Appendix VII: The pain story 317
Appendix VIII: The playing cards for the modified Stroop task 319
Appendix IX: Raw data for the two PET subjects from chapter 8 320

Tables and illustrations

Table 3.1 Within group comparison for the female controls 78
Table 3.2 Within subject comparisons for the three subjects receiving pain or heat to the right hand 81
Table 3.3 Within subject comparison for subject n490 receiving pain or heat to the back of the left hand 84
Table 3.4 Within subject comparison for subject n565 receiving pain or heat to the back of the left hand 85
Table 3.5 Summary of the group and individual results 100
Table 3.6 Summary of the somatosensory responses 104
Table 4.1 Within group comparison for the application of tonic pain 112
Table 4.2 The results of the questionnaires given to each subject receiving either tonic pain or phasic pain 114
Table 4.3 Within subject comparison for subject n536 receiving tonic pain 115
Table 4.4 Within subject comparison for subjects n538 and n1027 receiving tonic pain 116
Table 4.5 Within subject comparison for subjects n1303 and n1311 receiving tonic pain 117
Table 4.6 Summary of the female group results and the tonic group and individual results 124
Table 5.1 Within group comparison of pain vs non-painful heat in the atypical facial pain patients 134
Table 5.2 the results of the questionnaires given to each atypical facial pain patient and female control 138
Table 6.1 The results of the questionnaires given to each arthritis patient and female control 149
Table A1.3 Summary of the PET data for the males and females separately
296
Table A9.1 n683 blood flow changes in response to morphine across pain and rest conditions
320
Table A9.2 n683 blood flow changes in response to pain across morphine conditions
321
Table A9.3 n843 blood flow changes in response to morphine across pain and rest conditions
322
Table A9.4 n843 blood flow changes in response to pain across morphine conditions
323
Table A9.5 Changes in blood flow in response to morphine during the rest conditions only
324
Table A9.6 Changes in blood flow in response to morphine during the induced pain conditions only
325
Table A9.7 Changes in blood flow in response to pain during the no morphine scans only
326

Figure 1.1 The direct transmission model of pain
19
Figure 1.2 Schematic diagram of the gate control theory of pain
23
Figure 1.3 A schematic representation of Leventhal's hierarchical pain pathway
27
Figure 1.4 A model for rheumatoid arthritis
37
Figure 1.5 A model for atypical facial pain
40
Figure 2.1 True and random coincidence
48
Figure 2.2 Scatter coincidence
49
Figure 2.3 2D and 3D acquisition
51
Figure 2.4 Cognitive stages constituting stimulus response reaction time
53
Figure 2.5 The single tissue compartment model
55
Figure 2.6 Smoothing
62
Figure 3.1 Pain vs heat - female controls
79
Figure 3.2 Heat vs pain - female controls
79
Figure 3.3 Pain vs heat and Heat vs pain - n463
82
Figure 3.4 Pain vs heat and Heat vs pain - n609
83
Figure 3.5 Pain vs heat and Heat vs pain - n1170  
Figure 3.6 Pain vs heat and Heat vs pain - n490  
Figure 3.7 Pain vs heat and Heat vs pain - n565  
Figure 3.8 Coregistered data from subject n490  
Figure 3.9 Coregistered data from subject n463  
Figure 3.10 Pain vs heat - individual n490  
Figure 3.11 Pain vs heat - individual n463  
Figure 3.12 Heat vs pain - individual n490  
Figure 3.13 Heat vs pain - individual n463  
Figure 3.14 Pain up and pain down - n490  
Figure 3.15 Pain up and pain down - n463  
Figure 4.1 Variability in temperature  
Figure 4.2 Pain vs heat - tonic group  
Figure 4.3 Heat vs pain - tonic group  
Figure 4.4 Pain vs heat and Heat vs pain - n536  
Figure 4.5 Pain vs heat and Heat vs pain - n538  
Figure 4.6 Pain vs heat and Heat vs pain - n1025  
Figure 4.7 Pain vs heat and Heat vs pain - n1027  
Figure 4.8 Pain vs heat and Heat vs pain - n1303  
Figure 4.9 Pain vs heat and Heat vs pain - n1311  
Figure 5.1 A causal model explaining the aetiology of atypical facial pain  
Figure 5.2 Pain vs heat - atypical facial pain  
Figure 5.3 Heat vs pain - atypical facial pain  
Figure 5.4 Females vs atypical facial pain - differences in increases in response to pain  
Figure 5.5 Atypical facial pain vs females - differences in increases in response to pain  
Figure 5.6 Development of the causal model explaining the aetiology of atypical facial pain  
Figure 6.1 Pain vs heat - rheumatoid arthritis  
Figure 6.2 Heat vs pain - rheumatoid arthritis
Figure 6.3 Females vs rheumatoid arthritis - differences in increases in response to pain 148

Figure 6.4 Atypical facial pain vs rheumatoid arthritis - differences in increases in response to pain 148

Figure 6.5 Resignation to disease 152

Figure 7.1 Pain vs heat - post extraction pain 158

Figure 7.2 Heat vs pain - post extraction pain 158

Figure 7.3 Atypical facial pain vs post extraction - differences in increases in response to pain 159

Figure 7.4 The mean temperatures chosen as non-painful hot and painful hot for each group 162

Figure 7.5 Mean scores from the Beck depression inventory 162

Figure 7.6 Mean scores for state anxiety 163

Figure 7.7 Mean scores for trait anxiety 163

Figure 7.8 Mean ratings of chronic pain from the visual analogue scale 164

Figure 7.9 Mean ratings of the acute pain from the visual analogue scale 164

Figure 7.10 Mean McGill sensory rating for the acute and chronic pains 165

Figure 7.11 Mean McGill affect ratings for the acute and chronic pains 165

Figure 8.1 Schematic representation of drug or placebo administration 180

Figure 8.2 Pain sensory ratings in atypical facial pain patients after morphine and placebo 183

Figure 8.3 Pain affect ratings in atypical facial pain patients after morphine and placebo administration 183

Figure 8.4 Pain sensory ratings in post extraction pain patients after morphine and placebo administration 184

Figure 8.5 Pain affect ratings in post extraction pain patients after morphine and placebo administration 184

Figure 8.6 Beck depression scores 185

Figure 8.7 Trait anxiety scores 185

Figure 8.8 State anxiety scores for both patient groups
before and after morphine

Figure 8.9 State anxiety scores for both patient groups before and after placebo

Figure 9.1 Pain vs heat - group

Figure 9.2 Heat vs pain - group

Figure 9.3 Stroop vs Stroop control - group

Figure 9.4 Stroop control vs Stroop - group

Figure 9.5 Pain vs heat and Stroop vs Stroop control - n1233 and n1248

Figure 9.6 Pain vs heat and Stroop vs Stroop control - n1175 and n1183

Figure 9.7 Pain vs heat and Stroop vs Stroop control - n1194 and n1246

Figure 9.8 Cingulate blood flow pain and Stroop - n1233

Figure 9.9 Cingulate blood flow pain and Stroop - n1248

Figure 9.10 Each subjects left medial hemisphere showing blood flow increases in response to pain

Figure 9.11 Each subjects left medial hemisphere showing blood flow increases in response to Stroop

Figure 9.12 Surface projections showing rCBF increases in response to pain

Figure 9.13 Surface projections showing rCBF decreases in response to pain

Figure 10.1 Circuit 1

Figure 10.2 Circuit 2a

Figure 10.3 Circuit 2b

Figure 10.4 Circuit 3

Figure 10.5 Circuit 4

Figure 10.6 Phasic pain inhibiting tonic pain

Figure A1.1 Pain vs heat - male controls

Figure A1.2 Heat vs pain - male controls

Figure A1.3 Hot vs warm - male controls

Figure A1.4 Females vs males - differences in increases in response to pain
Figure A1.5 Random group 1 vs random group 2 - differences in increases in response to pain

Figure A1.6 The differences in pain window

Figure A1.7 Variation in activation in somatosensory cortex: Pain vs heat

Figure A1.8 Variation in activation in somatosensory cortex: Heat vs pain
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Chapter 1: Introducing theories and mechanisms of pain processing

Towards a theory of pain

The traditional theory of pain, as proposed by Descartes in 1664, is generally known as 'specificity theory'. Descartes suggested that a painful stimulus transfers energy to 'threads' running through the body which opened pores in the brain and signalled pain. Thus pain was produced just as pulling at one end of a rope causes a bell, connected at the other end, to strike. Although the theory is over 300 years old it is still described in many textbooks on neurology, neurophysiology and medicine and is widely accepted by professional and lay people alike as fact rather than theory.

The modern interpretation of Descartes' 'bell pull' is summarised in figure 1.1 overleaf. Pain fibres are proposed to be stimulated and relay information to a hypothesized pain centre somewhere in the brain, a painful stimulus therefore becomes that which activates the pain centre, and pain becomes activity in the pain centre. It would seem a simple enough task to now identify pain fibres more precisely and their terminations in the central nervous system (CNS) and thus provide a number of therapeutic techniques for the many pain disorders that are known to exist. However, despite the breakthroughs in understanding and knowledge that specificity theory has provided, a definition of pain based on a direct relationship between stimulus and response has failed to resolve many of the major issues in pain research.

The search for the pain fibres

From his anatomical and physiological studies it became apparent to Johannes Müller that the brain only receives
information from the outside world via messages from the sensory nerves. He proposed a theory of specific nerve energies to produce the five classical senses - seeing, hearing, taste, smell and touch. At the time it was unclear as to whether the nerves themselves or the terminations in the brain ultimately produced the perception. Once it became clear that all nerve impulses are essentially the same, Von Frey (cited Boring⁵) extended Müller's theory to propose special sensory pathways for touch, warmth, cold and pain terminating in special centres in the brain. He assigned free nerve endings as being responsible for pain transmission based on their prolific distribution throughout the body. Later experiments demonstrated that there is indeed a relationship between receptor type and quality of experience. The free nerve endings can be grouped according to the
size of their transmission fibres. Correlative evidence exists in primates and in man that nociceptive information is transmitted via small myelinated fibres (Aδ) and unmyelinated fibres (C fibres). Generally these nociceptive neurons may respond exclusively to noxious stimuli or non-specifically, but with higher frequency, to noxious stimuli. Having defined these fibres as pain fibres, all that remained was the location of the 'pain pathway' and its termination. The spinothalamic tract has been suggested to be both 'necessary and sufficient' for the appreciation of pain in the species studied. This is at least a simplification; cutting the fibres of the spinothalamic tract (as in cordotomy) has not produced consistent reports of pain relief. However it does provide the major direct nociceptive input from the spinal cord to the brain. As a consequence, the spinothalamic tract ascending in the anterolateral cord is widely considered as the 'pain pathway'. Its primary termination, the thalamus, has been proposed as the pain centre.

The limitations of specificity theory

The primary assumption of specificity theory is that once a nociceptive fibre is stimulated then the pain centre will react and produce the common psychological perception of pain. The fact that there are universal patterns of behaviour in response to pain, that verbal descriptions of it provide recognizable signals from one person to another concerning its presence, nature, intensity, duration, location, reference, and temporal course, is cited as evidence for the specificity of pain. However such evidence only draws on a very narrow investigation of the consequences of injury. Interpretations of injury based on a direct relationship between stimulus and pain are inadequate because they fail to account for the variable link between stimulus and pain experience. Specificity theory cannot explain why
soldiers wounded in battle rarely ask for analgesia in comparison to civilians wounded in accidents, why patients with amputations complain of pain in their 'phantom', or why cultural rituals and placebo can undermine the pain of major injury. Such observations are problematic for specificity theory and have led to a series of 'accommodations' which have generally drawn on a further Cartesian concept, the split of mind and body. The variation between injury and pain has been variously explained away as a metaphysical phenomenon beyond the boundary of real science, a distinction is made between the pain sensation itself and the individuals emotive reaction to pain. Patients who complain of pain in the absence of injury have been condemned as hysterical while those who fail to complain of pain in the presence of injury have been described as suffering from 'shock'. Words such as these have no meaning in terms of mechanism and are introduced only to preserve the dogma that each specified injury must produce an equally specific pain.

Other theories of pain

The limitations of specificity theory have led to the proposal of other theories of pain, including pattern theories. The fundamental proposal is that pain is only experienced when there is a particular array or summation of active fibres or neurons. For example, a stimulus that is only mildly painful when applied to a small area can produce considerable pain when applied over a larger area of the receptor surface. Implicit in this theory is that individual neurons are 'broadly tuned' and can respond to a variety of stimuli. This is true of wide dynamic range neurons, for example. Thus one stimulus can 'block out' another which may explain, for example, why itch and pain are never experienced together.
Pattern theories explained why a receptor could be *physiologically* specialized to receive certain sensations but still not give rise to that sensation *psychologically*. All peripheral stimuli interact as they enter the nervous system, qualitatively altering the final perception. There is no way in which a stimulus can capture and monopolise central pathways to the exclusion of other events. Specificity at the final psychological level is thus a theoretical impossibility. No neurons in the somatic projection system are indisputably linked to a single, specific psychological experience, this raises the possibility of a multi-synaptic afferent system that stands in marked contrast to the idea of a straight-through system. This idea was most clearly developed by Melzack and Wall as the *gate control theory of pain*.16

**Gate control theory of pain**

The accumulation of data problematic for specificity theory made a new theory of pain processing necessary. Gate control theory represented the necessary theoretical breakthrough for the advancement of pain research. It was a major step forward in understanding the physiological correlates of psychological interventions in pain, such as the modification of one sensation by another, and was successful in persuading investigators to relinquish ideas that were already known to be wrong but were retained for their simplicity. It shifted attention away from the peripheral nerve fibres and towards the central nervous system.

The theory proposes that pain is a result of the relative activity in small and large diameter afferent fibres: small fibre activity tends to facilitate transmission (T) cells in the spinal cord (‘opening the
Figure 1.2 schematic diagram of the gate control theory of pain. The substantia gelatinosa (SG) has inhibitory (shaded circle) interneurons connecting with transmission (T) cells. Inhibitory action can be pre synaptic, post synaptic or both. The inhibitory effect exerted by SG on the T-cells is increased by activity in the long (L) fibres and decreased by activity in the short (S) fibres. The central control trigger is represented by a line running from the large fibre system to the central control mechanisms; these mechanisms in turn project back to the gate control system. (After Melzack and Wall).

gate’), whereas large fibre activity can either facilitate or inhibit transmission (‘closing the gate’). The cells which first receive incoming afferents are arranged in the six laminae of the dorsal horn within the spinal cord. The role of these cells is to select and compute combinations of the signals which impinge on them. Some combinations sum and aid each other. Other combinations evoke inhibitions so that one input excludes the effect of the other. In general, mechanical (large fibre) stimulation at the centre of a receptive field excites the cell, increasing pain, whereas stimulation of the surrounding area inhibits the cell. These inhibitory and
excitatory interactions require the presence of interneurons. Laminae I and II (the substantia gelatinosa (SG) contain a densely packed layer of small cells which are well suited to be such interneurons and have been shown to produce T-cell inhibition.\(^\text{17}\)

A descending influence on the dorsal horn inhibitory interneurons was also included, which in turn was influenced by ascending influences, thus forming a spinal cord-brain loop. Electrical stimulation of various central structures has been shown to produce remarkable levels of analgesia. Stimulation of the periaqueductal gray (PAG) for example can produce an analgesic effect which lasts for several minutes.\(^\text{18}\) The descending analgesic system is believed to be triggered by a release of opiates in the PAG which activates cells in the nucleus raphe magnus which, in turn, send fibres to the dorsal horns and inhibit dorsal horn cells by the release of serotonin.

Recently, the gate control has been modified to account for changes that occur with long term, chronic, pain. Another reason for the collapse of specificity theory is the fact that the nervous system changes progressively with time, especially after injury. Physical changes occur such that, for example, the stimulus may remain fixed while the experience varies because peripheral nerve endings change their threshold for firing. Usually there is excitation of interneurons which increases the excitability of transmitting cells so that their receptive fields expand and may respond to low-threshold afferents as well as high-threshold afferents. This can be a major source of misery for many chronic pain patients who find that normal movement or touch triggers unbearable pain. Functional changes occur bringing the affective component of pain to dominance. This second phase of pain processing is believed to be a product of C-fibre messages because it is avoided if stimulation is restricted to Aδ fibre stimulation following C-fibre poisoning with capsaicin.\(^\text{19}\) The
sensitivity is believed to be maintained by a central mechanism because it is unaffected by anaesthetizing the affected joint following selective C-fibre stimulation.\textsuperscript{20,21}

Patients who endure this situation for a prolonged period of time develop a series of invalid behaviours and negative emotions, they often become depressed.\textsuperscript{22} It is the nastiness or unpleasantness of the pain which begins to dominate the patients life. The qualities of 'unpleasantness' comprise multiple emotional dimensions which have a complex relationship with the experience of physical symptoms.

Pain and emotion

In 1894 H.R. Marshall\textsuperscript{23} argued that pain was distinctly different from 'sensations' because of its strong negative affective quality that drives us into activity. The view that pain is simply another sensory modality is relatively recent. The development of sensory physiology and psychophysics during the twentieth century gave momentum to the concept of pain as a sensation and overshadowed the role of emotion and motivation.\textsuperscript{24} The failure of sensory models to provide a complete understanding of pain gave rise to the return of emotion to pain models. Recently debate has centred on whether emotion and pain are clearly separate and sequential or parallel processes.

Beecher (cited Leventhal\textsuperscript{25}) proposed that an emotional or reactive component is added to the primary sensory component of pain once the primary sensation becomes sufficiently strong. Such a model can explain why psychological interventions, such as imagining that a burning pain is actually the result of gentle sunshine, can reduce distress. Presumably such intervention alters the secondary emotional response in the direction of less fear and distress. However
the model fails to explain how reduction of the sensory component of pain can be achieved while leaving the emotional component intact such as when fentanyl is used as an analgesic during tooth pulp stimulation.\textsuperscript{26} Such observations can most easily be explained by an interpretation of pain that involves the parallel processing of sensory and affective components.

Leventhal's model\textsuperscript{25,27,28} suggests parallel processing of the informational and emotional aspects of the sensory experience (fig 1.3 overleaf). According to Leventhal once stimulus information passes through the gate\textsuperscript{16} it is organized and elaborated with respect to three hierarchical mechanisms in the central nervous system. Affect is considered to arise independently and virtually simultaneously with the pain experience following the same hierarchical mechanism.

The first two levels in the hierarchy are perceptual-motor processing followed by schematic processing. Both these levels are considered preconscious. Perceptual-motor processing involves the activation of an innate set of expressive motor reactions to environmental stimuli: schematic processing involves the automatic encoding in memory of the experience to produce a categorical structure representing the general informational, emotional and sensory aspects of pain experiences. These schemata are not unlike scripts\textsuperscript{29} or representative internal generalisations (RIGs).\textsuperscript{30} Despite the problem that these concepts tend towards description rather than explanation they remain a powerful influence in psychology. The script was initially intended to be an explanation for general aspects of particular behavioural patterns, such as attachment. However with such complex behaviours it became impossible to isolate general characteristics. Consequently in order to 'explain' attachment the whole behaviour became scripted. Nevertheless, the
discovery that individuals high and low in trait anxiety differ in their use of pre-attentive, attentional and interpretative mechanisms suggests a mechanism by which the expectation of a particular stimulus increases the likelihood of perceiving that stimulus within the available processing capacity. Anxious subjects automatically orient towards words that have negative emotional content in line with their internal expectations. Thus the predictive power of schemata is being realised.

At the higher conceptual level, a set of abstract rules about emotional episodes and associated voluntary responses is proposed to arise over time as a consequence of self observation and voluntary
efforts to cope with emotion provoking situations. These rules are highly variable with experience, in particular a long history of pain (chronic pain) appears to lead to a shift in emphasis from a belief in psychological factors influencing pain towards a more organic view of pain.\textsuperscript{32} This results in the patients' fears about organic damage from pain being heightened and attenuates the distress of the pain, perpetuating the whole experience.

The separation of sensation and affect is possible because it is hypothesized that they exist in separate channels which are yoked together by complex interactions. The administration of opiates appears to damp the dominant channel in any given case so that in acute pain, such as the tooth pulp stimulation described earlier, the sensory channel is inhibited and the pain is experienced as predominantly emotional.\textsuperscript{26} While administration of morphine to patients with chronic pain emphasizes the activity of the sensory channel over the affective channel and the pain is experienced as predominantly sensory.\textsuperscript{33} A similar effect can be obtained by training a subject to concentrate on the sensory aspects of a pain experience, resulting in sensory schemata being emphasized rather than pain-distress schemata and vice-versa.\textsuperscript{25}

The distinction between sensory and affective systems is reproduced at an anatomical and physiological level, and will be discussed in the following sections.

The anatomy and physiology of pain

Guyton\textsuperscript{34} classifies pain into two types: fast pain and slow pain. This classification is based on psychological and physiological observations. The psychological observation is that pain can be separated into broad categories: first pain and second pain as well as acute pain and chronic pain. Each pain type has a characteristic
pattern of description using the McGill pain questionnaire. The physiological observation is that nociceptive signals are transmitted to the brain by multiple ascending pathways, each with distinctive conduction velocities and terminations in the brain. These systems can be distinguished as basically two major systems: the phylogenetically old pathways which course medially through the brainstem, and the newer pathways which maintain a lateral course in the brainstem.

The medial pathways ascend in the ventrolateral spinal cord terminating widely in the brainstem, including the reticular formation and the periaqueductal grey matter, before projecting to the thalamus. Most fibres of the medial system pass all the way to the medial and intralaminar nuclei of the thalamus. The major projections of the medial thalamus include the prefrontal cortex, anterior cingulate cortex and the basal ganglia. The medial system is polysynaptic, transmitting impulses slowly, and exhibits only gross somatotopic organization.

The pathways which make up the lateral system pass upward to the brain through the anterolateral white matter. The lateral systems terminate predominantly in the ventrobasal complex of the thalamus with a major projection to the somatosensory cortex. However, there are also substantial terminations in the rostral reticular formation and in the medial and intralaminar group of nuclei in the thalamus. In contrast to the medial system, the lateral system consists of rapidly conducting pathways which are somatotopically highly organized.

This central dissociation of medial and lateral systems is complemented by the categorisation of fast and slow fibres. The Aδ fibres are believed to be concerned with the rapid transmission of phasic discriminative information regarding the onset, location,
intensity and duration of a stimulus bringing about responses preventing further damage. Hence the association with fast or acute pain. Whereas the C fibres are believed to signal actual peripheral damage by transmitting tonic information about the state of the organism determining the arousal and behavioural responses necessary to foster rest, thereby promoting recovery. Hence the association with slow or chronic pain. The recent developments of the gate control mechanism, reviewed earlier, appear to bear this out. However, despite the well documented involvement of the spinothalamic tract in the transmission of pain, there is surprisingly little consensus regarding the involvement of the cerebral cortex in pain processing. This has recently developed into serious controversy.

**Brain systems**

Although it is now generally agreed that many interacting areas of the brain are involved in the processing of pain, and it can be said that there is no 'pain centre', the earlier dominance of specificity theory within pain research means that experiments to uncover the location of the pain centre seem plausible. The concept of a specific pain system is the logic behind medical procedures which destroy selected peripheral nerves or pathways in the central nervous system in order to control pain. Penfield stimulated 800 areas of somatosensory cortex but found only 11 to elicit pain, despite this finding, special effort was made to place the pain centre in the somatosensory cortex. Consequently somatosensory projection areas from phantom limb pain were excised in many patients, with little effect on their pain. During neurosurgical operations many other areas of cortex were also stimulated but generally failed to produce pain. Such infrequent reports of pain led to the belief that
the pain centre was not located in the cortex but was instead a thalamic function. Thalamic neurons were thus destroyed in an attempt to abolish pain. This procedure may produce pain relief but often doesn't and can make the pain worse. Electrical stimulation of the somatosensory thalamus can sometimes relieve chronic pain, while stimulation of the intralaminal and medial thalamic nuclei can elicit intense pain during neurosurgery for chronic pain. Furthermore lesions have been placed in the cingulum bundle, frontal white matter, medial thalamus, pulvinar, amygdala, frontothalamic tracts, pituitary and hypothalamus to successfully produce pain relief. Lesions of these sites appear effective in controlling chronic pain, yet are ineffective for acute pain. Such a wide range of lesions is indicative of the widespread nature of the 'neuromatrix' underlying chronic pain, although the extent to which these lesions also produce reductions in anxiety and create a placebo effect remains largely unassessed.

Recent advances in brain imaging techniques mean that it is now possible to investigate the brain systems regulating pain information in a dynamic and non-invasive manner. These techniques all rely on measurement of regional cerebral blood flow (rCBF) in the brain. Because rCBF is the major carrier of energy for neural activities, activation of large neural networks is reflected in rCBF. The theoretical and technical background of rCBF measurements has been described in several monographs. The techniques of brain imaging used at the Hammersmith Hospital are described in the following chapter.

rCBF studies of brain processes in response to painful stimuli have provided conflicting results. Three studies have investigated continual pain stimulation. Cesaro et al report a contralateral hyperactivity in the thalamus in response to central post stroke pain,
while Di Perio et al\textsuperscript{56} have reported hypoactivity of contralateral thalamus in patients suffering unilateral cancer pain. Apkarian et al\textsuperscript{57} report a reduction in rCBF in the somatosensory cortex in response to induced cold pressor pain. Two studies have investigated phasic pain application using a contact thermode inflicting either heat or painful heat.\textsuperscript{58,59} Both studies report rCBF increases in anterior cingulate cortex. Only one reports increases in somatosensory cortex and only one reports thalamic increases.

It is as yet unclear as to why such dramatic differences in results should occur. Several possibilities arise, different types of patient may respond in different ways to their pain and subtle differences in methodology may incorporate different subsidiary pain mechanisms. For example, the terminal nature of cancer can create variable pain experiences in accordance with the phases of treatment, response, recurrence, deterioration and decline which is not characteristic of other chronic pain syndromes.\textsuperscript{60} The repositioning of a stimulus during a measurement may introduce localization circuits independent of pain processes.\textsuperscript{61} To begin the address of these possibilities it is necessary to consider the translation of the psychological perception of pain in all its complexity to the functional representation.

Relating the psychological and anatomical subsystems

It is interesting that the rCBF increase in anterior cingulate cortex was present in both the phasic pain PET studies. Based on these two studies, Roland\textsuperscript{61} suggests that the anterior cingulate cortex could be responsible for the cortical representation of the aversive aspects of pain. This view is supported by observations of chronic pain patients following cingulotomy. Although the patients remain aware of their pain and are still able to discriminate noxious
stimuli they are no longer bothered by their pain. Furthermore, lesions of the anterior cingulate cortex of rabbits have been shown to undermine the negative reinforcing quality of a painful stimulus. These behavioural changes which result from cingulate cortex ablation may be interpreted as demonstrating the role of cingulate cortex in producing affective responses to noxious stimuli. However the anterior cingulate cortex is a functionally very heterogeneous region that can be activated by word association, the detection of visual targets and the Stroop task. Posner and Rothbart have recently suggested that the anterior cingulate cortex is the fundamental structure representing conscious attention. As virtually all rCBF measurement tasks require attentional resources this interpretation may explain the wide functional heterogeneity of anterior cingulate cortex. It also explains why pain loses its bothersome quality following cingulotomy. Presumably the patients are now able to ignore their pain as a side effect of their inability to focus attention. It is possible that the anterior cingulate is a major part of the circuitry that holds pain schemata on line. The anterior cingulate has rich connections with the temporal surface known to be important in holding information in temporary storage and to the hippocampus, which is widely held to be involved in the formation of permanent memories. Neurons in anterior cingulate cortex show a plasticity which allows discrimination between positive and negative conditioning tone stimuli. Thus cingulate cortex has the necessary properties to be a key area in attention, discrimination and avoidance. However anterior cingulotomies usually have not produced evidence for severe deficits in cognition which may be expected from the ablation of such a fundamental function as the focusing of attention and avoidance of danger. Furthermore no studies have yet directly tackled the question of dual
function in the anterior cingulate cortex in the same subject such as via the use of a cognitive task in the presence and absence of an acute pain stimulus.

The functional heterogeneity of anterior cingulate cortex and the plasticity of its neuronal structure is in contrast to the relative functional specificity of somatosensory cortex and its highly somatotopic structure. The information about painful stimuli that travels via the spinothalamic tract to excite the lateral group of thalamic nuclei interconnected with somatosensory cortex, undergoes few alterations between the spinal cord and cortex.74 Excitatory responses in monkey somatosensory cortex are generally restricted to both innocuous and noxious mechanical and thermal stimuli. Somatosensory neurons have receptive fields that are small or at least confined to one limb and always contralateral.75 Such a system is ideal for providing detailed information about the location and characteristics of particular noxious stimuli whereas projections to the medial thalamic nuclei interconnected with anterior cingulate cortex have little or no stimulus coding properties or somatotopic organization and thus are best suited for processes associated with affective responses to noxious stimuli.74

The reported variation in thalamic rCBF is puzzling as the majority of the fibres from the spinothalamic tract terminate in the thalamus. However there are also substantial projections to the rostral reticular formation, and there are liable to be many other projections which are as yet undiscovered.1 It is possible that pain information is reaching the cortex and limbic systems via routes other than the classical pain systems. Pain may also be a small portion of the total somatosensory information passing through the thalamus. In order to understand why cancer pain evoked
hypoaactivity in the thalamus while stroke hyperpathia evoked hyperactivity it is necessary to examine chronic pain in more detail.

**Chronic pain pathology**

For the vast majority of us pain is a transient experience brought about by illness or injury, which, following the proper intervention and rest, disappears. This acute short term pain has a clear functional role as both a 'warning signal' and an accompaniment to recovery to enforce stillness during recuperation. However, the functional advantage of pain from progressive arthritis, or bone cancer, or post-operative neuralgia and many other long term disorders is questionable. In these cases pain does not facilitate escape from harm nor promote recovery, indeed here the pain is the main problem and source of misery. This chronic, continuous, pain is usually destructive psychologically and socially, and may become a pain syndrome - a medical problem in its own right. The patient becomes consumed with a sense of hopelessness, helplessness and meaninglessness, and can become obsessed with the functions of his body. Usually the detrimental psychological impact of chronic pain makes the pain even worse; this connection between psychology and pain is confusing when trying to untangle cause and effect. The picture is further confused by the fact that not all chronic pain patients are alike, for example arthritis can be distinguished from cancer pain by the fact that arthritis is often described as 'aching' but cancer pain is rarely if ever described as such. The fact that both cancer pain and arthritis pain have well understood clinical aetiologies distinguishes them from chronic low back pain which has no known cause in around 70% of cases. These differences in description and aetiology are indicative of different mechanisms operating in each disorder which have implications for the
psychological and physical expression of the patients' pain. Three pain disorders are to be discussed: rheumatoid arthritis, atypical facial pain and post extraction pain.

Rheumatoid arthritis

Rheumatoid arthritis is generally described as an inflammatory disorder of the joints. The exact aetiology of the disorder is still unknown. However, it is fairly clear that in early active disease the normal synovial lining of the joint becomes swollen and hypertrophic and is then invaded by lymphocyte's and plasma cells. This invasion transforms the synovial lining into granulated tissue that destroys cartilage around the joint. This produces the first clear clinical sign for arthritis as the loss of joint space on an X-ray. Bone erosion occurs as a consequence of the lack of cartilage protection and the release of proteolytic enzymes further erodes bone and cartilage. Muscle wasting appears rapidly around the swollen joints. Subsequently, these changes may result in deformity and functional loss.

Pain is a major complaint of patients suffering arthritis, affecting around two thirds of those suffering the rheumatic form of the disease. However there seems to be no clear correlation between the advance of the disease and the pain suffered. Even during the advanced stages of the disease, when the joint is persistently inflamed indicating the presence of chemical irritants such as histamine, 5-hydroxytryptamine and prostaglandins which excite pain receptors in the bone and the joint capsule, there is a group of patients who continue to report no pain. This has led some to suggest that the pain of arthritis is mediated by the effects of stress in certain personalities, while others have suggested that psychological characteristics and attitudes to illness are more important predictors of disability and pain than the severity and
activity of the arthritis. The type of model that is being proposed is illustrated in figure 1.4 below. The model illustrates that in arthritis pain can be produced via stimulation of free nerve endings but that this is always accompanied by either inhibitory or excitatory systems originating in the CNS. The model indicates that negative coping can make pain worse, directly and indirectly. The model is clearly over simplified, it does not for example take into account changes in behaviour which can also influence the progress of the disease and the experience of pain, but it does demonstrate the potential influence of central mechanisms on the final response to peripheral injury. CNS neurons are known to change their properties as a consequence of arthritis. Thalamic and cortical neurons that normally do not respond to nociceptive inputs do so readily in arthritic animals, and they do so vigorously. It is therefore conceivable that central mechanisms can alter the final experience of pain in either the direction of increased or decreased sensation depending on the 'mind set' of the individual, and could form the basis for explaining the variation in thalamic activation seen in rCBF.

**Figure 1.4** Pain fibre excitation arises as a consequence of the chemical changes brought about during inflammation of the joint. This has a partial consequence in the perception of pain indicated by the dotted arrows. The pain is mediated by psychological factors, positive coping strategies inhibit the experience of pain, illustrated as closed circles, whereas negative strategies accentuate pain, illustrated as arrows. Adapted after Morton et al. See text for further detail.
Atypical facial pain

Atypical facial pain (AFP) is an intriguing and poorly understood clinical entity that is generally considered psychogenic in nature. It is a diffuse condition felt deep in the soft tissues and facial and alveolar bones, and can be separated into two variants: Atypical odontalgia and oral dysesthesia. Odontalgia is a continuous throbbing pain in the teeth, or extraction sites, associated with hypersensitivity to temperature and pressure in the absence of detectable underlying pathology. Dysesthesia is characterized by disturbances of taste, or more general disturbances of sensation such as the 'phantom bite syndrome', although not directly associated with pain it often progresses towards pain. Such disorders are claimed to be common, afflicting 25-45% of the general population at some time in life, and there has been an increasing awareness that the prevalence of facial pain is greater than the incidence of patient referrals would suggest.

The discomfort of AFP can vary from a dull ache to a sharp throbbing pain, is constantly present and often of many years' duration. It can affect either or both sides of the face and will occasionally wake the patient at night; commonly, it is provoked or potentiated by trauma or dental treatment. In the edentulous patient, dentures are often impossible to wear; apart from the slight facial edema (swelling) and hyperemia (increased blood flow resulting in a red appearance) of the oral mucosa, there are no other clinical signs. For the vast majority of these patients, there is an absence of objective clinical signs, and radiographic and laboratory investigations are normal.
Nevertheless a number of clinical explanations have been proposed including the loss of teeth,\textsuperscript{90} lax ligaments,\textsuperscript{91} disturbance of the sympathetic nervous system,\textsuperscript{92} and deafferentation associated with peripheral nerve injury.\textsuperscript{93} These ideas have often led to surgical procedures including the injection of sclerosing agents into the temperomandibular joint or sphenopalatine ganglion, trigeminal section, and condylotomy; no operative procedure has yet been shown to relieve the pain, and such interventions usually make the pain worse.\textsuperscript{94} More recently the role of psychological factors has been increasingly realised, and these pain disorders have been shown to be associated with a high incidence of stress and aversive life-events; these include school, work and marital difficulties, and bereavement, chronic illness in the family and financial problems.\textsuperscript{95,96,97,98} Despite initial enthusiasm about the possibility of finding a 'pain prone personality',\textsuperscript{99} there is no evidence to suggest that these disorders are accompanied by specific personality traits.\textsuperscript{100}

Several studies have attempted to find a clear relationship between depression, anxiety and pain,\textsuperscript{101} the association is strong with studies reporting up to 100\% of their pain patient sample being depressed,\textsuperscript{102} but the nature of the association remains unclear. Wade et al\textsuperscript{101} demonstrated that depression is not a significant predictor of pain-related emotional unpleasantness at any intensity level with patients reporting multiple pain complaints. Anxiety and frustration, however, were important predictors of the emotional unpleasantness of their pain. The high positive response rate (approximately 50\%) of AFP to a placebo coupled with reassurance that nothing organic is at fault suggests that anxiety regarding damage to the body may have some underlying causal role in this type of disorder.\textsuperscript{103} The type of model that is being proposed for AFP is illustrated overleaf in figure 1.5.
Figure 1.5 Pain fibre excitation occurs as a response to facial trauma or as a consequence of stress, negative cognition, personality or a combination thereof. This effect can be potentiated by social stresses. The arrows represent excitation, the circles inhibition. See text for further detail.

The model now has an additional social level not included in the arthritis model. This reflects the widely accepted role of social factors in accelerating the progress of AFP. It also shifts the balance of the model away from the traditional medical model of illness, emphasizing social and cognitive factors in the actual aetiology of the disease rather than as secondary phenomenon. This is seen by many as a point of departure for AFP from other painful disorders but there is evidence that the strict medical model also fails to explain the painful 'flare ups' in rheumatoid arthritis. It seems that there is no 'Chinese wall' between organic and psychogenic pain disorders.

The success of anti-depressants in treating AFP may suggest that depression has a causal role to play and provide a further dissociation from other pain disorders. However a number of possible modes of action have been proposed and it appears unlikely that the mechanism is dominated by alleviating depressive symptoms.
consequent to chronic pain. For example, Johansson and Von Knorring\textsuperscript{111} used zimelidine (a serotonin uptake inhibitor) in a double blind study involving 20 chronic pain patients and found superior pain relief with zimelidine despite little change in scores of depression. It is possible that depression and pain share a common biochemical mechanism which expresses itself as pain or depression depending on, as yet unknown, patient specific factors. Had tricyclics been first discovered for their analgesic properties depressives could be taking 'analgesics'. Furthermore, there is a considerable body of evidence that tricyclic antidepressants relieve pain associated with a variety of pain pathologies, including rheumatoid arthritis.\textsuperscript{112,113,114} Serotonin is known to be present in neurons projecting from the mid-brain to the rostral ventromedial medulla which is part of the 'endorphin-mediated analgesia system' and has already been mentioned as responsible for the inhibition of nociceptive messages at the dorsal horn. Further evidence for its role in the body's analgesic mechanism is that depletion of serotonin blocks the analgesic action of systemic opiates.\textsuperscript{115} This may explain the lack of response to morphine from idiopathic pain patients.\textsuperscript{33} The question of whether morphine aids idiopathic pain patients in the absence of depression is yet to be addressed.

There has been some debate as to whether psychogenic patients represent a separate clinical entity from other pain patients.\textsuperscript{116,117} Some have claimed that psychogenic and organic patients with similar complaints do not yield any significant psychological difference.\textsuperscript{118} This seems unlikely to be true, however, as important cognitions relating to pain include the patient's knowledge and beliefs about the aetiology, pathology, treatment and prognosis of the pain which has implications when there is no known pathology, in particular patients look for a cause.\textsuperscript{119,120,121} Pilowsky et al\textsuperscript{122} made
assessments of 32 patients attending a rheumatology out-patient service and compared them with 49 patients attending a pain clinic for the management of chronic intractable pain, in the absence of clear organic pathology. The assessment involved questions related to the patients experience of pain with associated anxiety and depression. Of the rheumatology group 28% claimed to be never preoccupied with ideas and concerns about disease compared with 12% of the pain clinic group. Of the pain clinic group 17% were preoccupied with thoughts of disease more than half the time as opposed to none of the rheumatology group.

Interestingly, 38% of the rheumatology patients attributed their emotional state to a psychological cause compared with 10% of the pain clinic patients who tended to blame all problems on their pain. Furthermore those attending the rheumatology clinic were quite accepting of the need for psychosocial help whereas the pain clinic patients responded to the suggestion with anxiety, discomfort and even anger.

There may be a number of explanations for these differences, including the possibility that a person who is told that no explanation can be found for her pain may take this to mean that the complaint is not believed and, as a consequence, feel constrained to insist that something physical is wrong and should be pursued. While that may be part of the explanation, another possibility is that the patient is manifesting abnormal illness behaviour, and that belief in the presence of a physical problem constitutes a psychological survival strategy.

It is not possible to come to a firm conclusion on these issues, but it is becoming increasingly clear that the distinction between 'psychogenic' and 'organic' factors is not a case of 'either/or' but rather to what extent somatic, psychological, emotional and
environmental factors are each playing a role. This is true even of pain following surgical intervention.¹²³

**Post extraction pain**

Patients who have undergone removal of an impacted lower third molar (lower wisdom tooth) usually experience severe pain in the first twelve hours following the operation, rising to maximum intensity 6-8 hours postoperatively.¹²⁴ The mechanism of the pain is not considered mysterious. Tissue trauma during the operation initiates the release of histamine, bradykinin and prostanoids. Damage to the cell membranes initiates the release of phospholipase enzymes which increases vascular permeability. This often causes inflammation as plasma leaks into the extravascular tissue and sensitization of nociceptors with subsequent perception of pain. However, as for arthritis, there is no clear relationship between the amount of tissue trauma, swelling and the level of reported pain.¹²⁵

Psychological factors such as the circumstances of the operation and the patients understanding or attention to the trauma intervene in the final perception of pain. This 'variable analgesia' been described in some detail for accident victims.¹²⁶

**Conclusions**

Pain is clearly not a straight forward mechanism but has a complex relationship to the organisms response to, and ability to cope with, stress in general. It seems clear that certain biological mechanisms come into play when an organism is faced with acute stress¹²⁷ which have probably evolved to aid and encourage recovery from injury. However it is clear that these mechanisms may not always be useful, as in the case of rheumatoid arthritis, and can create pain disorders in their own right, as in the case of AFP. The
three pain conditions reviewed were chosen to reflect that even a clearly 'organic' disorder can have a psychological component and vice versa. The fact that all the pain conditions reviewed showed variation with psychological factors demonstrates the importance of central mechanisms. The development of sophisticated techniques to monitor central rCBF means that these mechanisms can now be investigated in detail.
Chapter 2: Pet Methodology, the analysis of activation studies

Physical principles

Activation experiments using positron emission tomography (PET) are designed to detect and localise regional cerebral blood flow (rCBF) changes associated with a given behaviour or physiological process. It is generally accepted that rCBF reflects regional neural activity and rapidly responds to changes in that activity. Thus PET can in principle be used to investigate central neural changes in response to a range of stimuli, including pain stimuli, and these responses can then be compared across various chronic pain disorders as described in chapter 1.

The physical basis of PET is the localisation of the position of a positron annihilation. Positrons are sub-atomic particles emitted from the radioactively decaying nuclei of tracer substances, and have the same mass as electrons but are of opposite charge. A positron will lose its kinetic energy after travelling a mean free path of 2-3mm in tissue. During or after this movement the positron will encounter a negatively charged free electron. The result of this encounter is the annihilation of both particles and the emission of electromagnetic radiation. Coincidence detection of the two simultaneously released gamma-rays (each of 511 keV energy), which travel in approximately opposite directions (180° ± 0.5°), enables localisation of the radioactive source.

Detectors are placed on either side of the subject and are connected in a coincidence circuit in order to register photons in coincidence within a time window (12-25 ns). The intersection between lines connecting detector pairs defines the location of a source inside the subject.
Collection of about $\frac{1}{2}$-1 million coincident events, by a circumferential array of multiple paired detectors (100-4000) placed in one or more (7-17) rings, will allow the reconstruction of an image of a heterogeneously-distributed, positron emitting nuclide within the detector array. Using a standard computerised reconstruction algorithm, it is possible to map the spatial and temporal distribution of the nuclide. Tomographic images in one or more planes can be reconstructed in a manner similar to that used for computerized tomography (CT) and magnetic resonance imaging (MRI). An image is produced to represent the radiotracer distribution. Ideally the pixel values in the image should be directly proportional to the radioisotope concentration inside the subject.

However, quantification of the data requires corrections for the phenomena that cause systematic errors. These phenomena are:

1. Attenuation inside the subject.
2. Dead time losses.
3. Random coincidences and multiple events.
4. Scatter, where a coincidence is registered by the detectors but is due to an event where a single or multiple scattering, by one or both of the gamma rays, has occurred.

**Attenuation**

The photons emitted from the radiotracer are attenuated while they travel through tissue. A fraction of the photons are totally absorbed but a much greater fraction scatter out of the detection channel and some are detected in another channel.

The attenuation in positron emission tomography is dependent only on the total path length i.e. thickness of the subject. Thus, the attenuation correction is more accurate and easier than with single photon emission CT (SPECT) and is based on a measure of tissue
density obtained with an external ring source of positron radiation
\(^{68}\text{Ge}\) (the transmission scan) performed prior to the emission
study.\textsuperscript{130}

**Dead time losses**

Dead time losses are due to the inability of the detectors and
the electronics to register an event while a previous one is being
processed. This is clearly more significant at higher count rates.

The dead time is measured and corrected on line in modern
systems and is particularly important in studies with short-lived
isotopes such as \(^{15}\text{O}\) where the dead time can be more than 20\%. The
primary quantity used to derive dead time is the singles rate, that is
the total flux of single gamma rays striking the detectors.

**Random and multiple events**

Random events will lead to mispositioning and loss of contrast.
They are due to the finite time resolution of the detectors which
depends on the speed with which the detector records its interaction
with the gamma rays. Thus a time window is set so that events are
accepted as coincidences if the gamma rays interact within this
window. The window width is a compromise between minimising the
randoms and maximising true events.

In the scanner used, the method of correcting for randoms is to
make a modification of the coincidence circuit such that coincidences
are monitored in a 'delayed' window (one detector of the pair
delayed relative to the other) as well as the 'primary' window. The
delay is long enough (100nsec) to ensure that no true events could
occur. The random coincidences measured in the delayed window are
assumed to be equal to those in the primary window and are
subtracted on line. The time window for the scanners in this study is 12 nsec.

When three or more coincidence events are recorded in the same time window they are defined as multiples, are rejected from the acquired data on line but are used in 'dead time' correction since a fraction of the multiples is made up of true events plus random events.

![true coincidence](image)

![random coincidence](image)

**Figure 2.1** At the top is displayed the principle of true coincidence. Paired opposite directed annihilation photons are recorded almost simultaneously (coincidence detection). Underneath is displayed random coincidence. One of a pair of photons may be angled towards one detector while the other photon is angled towards another detector. Random coincidences occur when one photon from each of two separate emissions strike opposite detectors within the time-window for recording within plane coincidences.

**Scatter**

A conventional way of reducing scatter is to use inter-ring septa, these are lead collimations placed in between the detectors which prevent wide angled scattered and random coincidences, but the scatter fraction is still significant ( >10% ) and the efficiency low. The scatter fraction is defined as the ratio of the total scattered events over the sum of scattered and unscattered events.

Another way of subtracting the scatter is to use the fact that the scattered coincidences are reduced in energy. The technique
consists of only recording events which deposit energy above a lower threshold. However, this will still include some of the scattered events (and exclude some of the unscattered) due to the finite energy resolution of the detectors and so other correction methods are currently under development.

![scatter coincidence diagram]

Figure 2.2 One of a pair of photons may be angled towards one detector and the other photon may scatter towards the other detector causing scattered true coincidence. Scattered photons are of lower energy, and an energy-window on the detectors can permit rejection of the more widely scattered coincidences.

The cameras and data management

(1) The CTI 931-08/12 camera

The early studies described in this thesis were performed on the CTI 931-08/12 camera, (CTI inc., Knoxville TN, USA) at the MRC Cyclotron Unit at Hammersmith Hospital, London. This scanner consists of eight rings each of 512 closely packed bismuth germanate detectors 5.6 mm transaxial width and 12.9 mm axial height. A detector unit consists of a block of bismuth germanate cut into 32 such detectors each viewed by 4 photomultiplier tubes. From these detectors a total of 15 horizontal planes of data are acquired simultaneously, eight from direct planes from coincidence detection within the ring and 7 indirect planes from cross planes between adjacent rings. Within the detector ring are a series of 17 cm lead/tungsten septa which collimate the gamma emissions.
Transmission data are acquired using eight steel rings of diameter 65 cm each containing $^{68}\text{Ge}$ (Germanium) which decays to $^{68}\text{Ga}$ (Gallium) by electron capture with a half life of 9 months, the $^{68}\text{Ga}$ then decaying further by positron emission. The rings are moved in and out of the field of view from a shield within the gantry of the scanner.

(2) The CTI 953B camera

The later studies described in this thesis were performed on the 953B camera (CTI inc., Knoxville TN, USA) also at the MRC Cyclotron Unit. This scanner consists of 16 rings each of 384 bismuth Germanate detectors 5.6 mm transaxial width and 6.1 mm axial height. A detector unit consists of a block of bismuth germanate cut into 64 such detectors each viewed by 4 photomultiplier tubes. From these detectors a total of 31 horizontal planes of data are acquired simultaneously. The collimating septa were removed to increase the acceptance angle and hence the number of photons recorded. The inevitable increase in noise due to scattered photons is more than compensated for by the more efficient use of the administered radioactivity. Specifically the point source sensitivity is 6 to 7 times higher than with a standard camera such as the CTI 931 recording with the septa in place. In practice there is a three fold increase in useful counts over the whole brain and a five fold increase at the centre of the field of view. An advantage of this is that less radiation need be administered per scan and therefore more scans can be performed in each subject. This allows data of a quality sufficient for the identification of activated regions in the brains of individual subjects. The greater acquisition area is illustrated in figure 2.3 below.
Figure 2.3 showing increased data acquisition with the collimating lead septa removed, allowing spatial reconstruction in 3 dimensions. LOR = Line of Response.

Transmission data are acquired in similar fashion as for the 931 camera except that a rotating rod source of $^{68}$Ge is used instead of multiple steel rings.

(3) Data archiving and image transformations

All data was collected on a DEC microvax II computer and after reconstruction image files were transferred to a SUN 3/60 or SPARC workstation. Image manipulations were carried out using ANALYZE versions 4-6 image display software (BRU, Mayo Foundation, Rochester, MN, USA), and PROMATLAB (Mathworks Inc., Natick, MA, USA). Scan data were stored on magnetic tape as 16bit data. The raw sinogram data and other files were stored on optical disc. Statistical maps of significant blood flow change were then derived using statistical parametric mapping (SPM) software.
Experimental application

For each experiment a patient or subject typically undergoes a series of scans during which cerebral blood flow is measured using radio labelled isotopes. During scanning the subject performs a series of tasks which involve sensory, motor, or psychological processing. The essential elements of the task remain constant, but the complexity of the task changes in a stepwise fashion, so that the only aspect of the task which differs is that which is under investigation. Thus the input can be changed to investigate sensory processes, the output for motor processes, or the intervening cerebral computation for cognitive processes.

The fundamental basis of this approach is taken from Sternberg’s protocol for investigating simple recognition tasks. A train of successive processes or stages were proposed to constitute the reaction time taken to perceive a stimulus and recall whether it was familiar or not. These stages are illustrated in figure 2.4 overleaf. Sternberg’s proposed stages provide the basis for a method of cognitive subtraction, first applied to PET by Petersen et al. The area responsible for generating word codes was identified by asking subjects to look at a fixation point only during one scan and in another condition to look at a word. Thus, using simple subtraction of one image from another, the changes in neuronal activity associated with the activation protocol can be identified.

From the preceding description it can be seen that there are a number of requirements for a successful study. Good protocol design is essential to maximise signal and to eliminate activity from blood flow changes due to confounding cerebral activity. The
measurements of CBF must be rapid to allow repeat measurements. The number of measurements of CBF in a single subject, within the constraints of radiation dosage, current protocols and technology, is limited to 6 - 18 with each measurement being completed in 30 - 180 seconds. Although changes in cerebral blood flow can be identified in a single subject, it is common for data from a group of subjects to be pooled. Averaging images between subjects suppresses background noise and improves signal to noise ratio.

There are a number of problems with such group analyses including variations in individual brain size, shape, position within the scanner detector rings and functional anatomy, differences in global flow between subjects, the relationship between global and local changes and systematic intersubject differences in neurophysiology. These problems are dealt with in the framework of statistical parametric mapping, an approach developed by Dr. K.J. Friston and his colleagues in the MRC Cyclotron Unit.136,137

**rCBF measurement**

In all studies at the Hammersmith rCBF was measured using the positron emitter oxygen 15 to label CO₂ (C₁⁵O₂), which is inhaled over two minutes, or to label H₂O (H₂¹⁵O) which is infused over two
minutes.\textsuperscript{138} (Inhalation of \textsuperscript{15}O results in the brain signal from \textsuperscript{15}O due to carbonic anhydrase in the lungs, use of \textsuperscript{15}O directly is preferable as it can be monitored more precisely.) \textsuperscript{15}O in nitrogen was synthesized from the \textsuperscript{14}N(d,n) \textsuperscript{15}O reaction by the bombardment of nitrogen (containing 1\% CO\textsubscript{2}) by 9.5 MeV deuterons at 30 mA. Impurities were removed by an aneil catalytic furnace absorber at 800\textdegree{}C. Activity was measured in a copper spiral within a high pressure ionisation chamber. Radiochemical purity was confirmed by gas chromatography. Typically the product was 99.5\% pure with contaminates being \textsuperscript{15}OO, \textsuperscript{15}O\textsubscript{2} and \textsuperscript{15}O. The product was delivered to the patient as a continuous supply by means of plastic tubing and a standard oxygen mask. On inhalation of \textsuperscript{15}O\textsubscript{2}, water in blood is labelled with oxygen 15 by the in vivo exchange between CO\textsubscript{2} and water. Direct infusion of \textsuperscript{15}O\textsubscript{2} can be used in preference to \textsuperscript{15}O\textsubscript{2} inhalation, using a similar process of production of \textsuperscript{15}O\textsubscript{2} as for that of \textsuperscript{15}O\textsubscript{2}. \textsuperscript{15}O\textsubscript{2} in nitrogen is synthesized from \textsuperscript{14}N(d,n) \textsuperscript{15}O\textsubscript{2} reaction by the bombardment of nitrogen (containing 1\% O\textsubscript{2}). Following the removal of impurities, as before, the radiochemical is mixed with 5\% hydrogen in a palladium catalytic furnace at 200\textdegree{}C. The \textsuperscript{15}O is delivered to the patient via an intravenous drip.

The use of \textsuperscript{15}O as a tracer has several advantages over other tracers such as \textsuperscript{15}O.\textsuperscript{139} Both labelled water and carbon dioxide are relatively simple to produce, the short half life of \textsuperscript{15}O (2.1 minutes) allows for repeat measurements during one scanning session, the partition coefficient of water is less dependent on pathology than other tracers, such as \textsuperscript{15}O, and \textsuperscript{15}O\textsubscript{2} inhalation and \textsuperscript{15}O\textsubscript{2} infusion are convenient and safe to administer.

The data acquired in a PET study need to be expressed in terms of some physiological, biochemical or pharmacological process. This is done using a model to formulate a mathematical description of the
biological process being measured in terms of the temporal and spatial fate of the tracer, such that the parameter of interest can be derived. A single tissue compartment model may be used to describe the fate of $\text{H}_2^{15}\text{O}$ (figure 2.5 below). Two basic methods for measuring rCBF with $\text{H}_2^{15}\text{O}$ and PET are the steady-state and build-up techniques; both involve the continuous inhalation of $\text{C}^{15}\text{O}_2$ or infusion of $\text{H}_2^{15}\text{O}$.

In the steady state technique, it is assumed that the fractional extraction and tissue : blood partition coefficient of $\text{H}_2^{15}\text{O}$ are unity. Therefore, at equilibrium, when the concentration of $\text{H}_2^{15}\text{O}$ in arterial blood and tissue is constant, the inflow of $\text{H}_2^{15}\text{O}$ is equal to that lost by diffusion into the venous blood and by physical decay. If the physical decay constant were small (long half life), the concentration of tracer in the tissue would be proportional to distribution volume; flow information would be lost. However, when the decay constant is large (short half life - that of $^{15}\text{O}$ is 2.1 minutes) tissue tracer concentration becomes proportional to flow, and the equilibrium equation can be solved for rCBF if the activities of tracer in arterial blood and tissue are measured via blood samples from the radial artery.

\[\text{INPUT} \quad \text{OUTPUT}\]

\[
\begin{align*}
\text{Blood Flow} \times \text{Arterial Concentration} \times \text{Fractional Extraction} & \quad \Rightarrow \quad \text{VOLUME OF TISSUE} \quad \Rightarrow \quad \text{Physical Decay} \\
\text{Blood Flow} \times \text{Tissue Concentration} \times \text{Tissue: Blood Partition Coefficient.} & \quad \Rightarrow \quad \text{Physical Decay}
\end{align*}
\]

Figure 2.5. The single tissue compartment model to measure rCBF using continuous inhalation of $\text{C}^{15}\text{O}_2$ or infusion of $\text{H}_2^{15}\text{O}$. The $\text{H}_2^{15}\text{O}$ distributes throughout the tissues and tracer is lost by diffusion back into the blood and by physical decay. At equilibrium, the input balances the output, which forms the basis of the operational equation to calculate rCBF.
artery. rCBF is measured in terms of volume of blood per volume of
tissue per minute, expressed as ml/dl/min.

This technique has some disadvantages. The time needed
before the steady-state is reached is about ten minutes (i.e. 5 half
lives), resulting in a slow method and an inefficient use of the total
radiation received by the subject; the method is less sensitive at high
flow rates, and has a low temporal resolution.

One way to overcome these limitations is to use a continuous
inhalation of $^{15}$O$_2$ or infusion of $H_2^{15}$O for all or part of the study
period but, in contrast to the steady state method, to commence
scanning from the start of the inhalation or infusion, thereby
recording the tissue build-up and retention or washout. By
performing multiple serial scans during the build up phase it is
possible to measure both rCBF and the volume of distribution of
water. The mathematical principles underlying the build-up
technique are complex, and have been described in detail by
Lammertsma et al$^{140,141}$; they are briefly summarised below.

The single tissue compartment model is described by the
following differential equation (from Lammertsma et al),

$$\frac{dC_t(t)}{dt} = [F \times C_a(t)] - [(F/V_d + \delta) \times C_t(t)]$$

where $C_t(t)$ is the regional tissue concentration of $H_2^{15}$O, $F$ is the rCBF,
$C_a(t)$ is the arterial concentration of $H_2^{15}$O, $V_d$ is the volume of
distribution of water, and $\delta$ is the decay constant of $^{15}$O.

Several assumptions are made in the equation: that water is
freely diffusible; that the activity in the arterial fraction contributes
negligibly to the PET signal; that venous and tissue concentrations are
only negligibly different; and that both rCBF and the volume of
distribution of water are constant during the measurement period.

It should be noted that a PET scan does not provide
instantaneous tissue concentration but the integral over a scan.
However, by performing multiple scans (frames) and monitoring the arterial concentration of $\text{H}_2^{15}\text{O}$, it is possible to calculate absolute rCBF on a pixel-by-pixel basis using standard linear least squares fitting procedures. However, the measured arterial blood curve from the radial artery will be delayed and dispersed compared to the cerebral arterial blood curves; a mathematical correction for this is employed.

Arterial measurements can be excluded altogether from the procedure if a comparison study is being done, making absolute values of rCBF unnecessary and thus avoiding a sometimes difficult and disturbing arterial cannulation. This is possible because for the range of rCBF observed in the human, rCBF and regional $\text{H}_2^{15}\text{O}$ tissue activity are nearly linearly related, that is, any increase in rCBF entails an increase in the amount of radioactivity recorded from that region.

**Statistical analysis - The making of a Statistical Parametric Map (SPM)**

The statistical analysis of PET images representing different physiological function involves two major operations. First is the need to compare like images with like images. This is overcome by the realignment of the images and normalisation of the data set into a standard stereotactic space. The second operation relates to the size of the data set. Fox and Mintum pioneered the analysis of PET images using change-distribution analysis which reduces rCBF change to a distribution of change foci described by location and magnitude. The magnitude was normalized to global flow by dividing the regional values of cerebral blood flow by the whole brain mean. Subtraction images (stimulus minus control states) were created, and then stereotactically re-orientated and averaged. Physiological responses
were identified by differentiating outliers from background noise by intensity.

In the technique developed by the Hammersmith group the contribution of changes in global flow to regional flow changes has been dealt with using analysis of covariance (ANCOVA). An rCBF map is calculated across subjects for each of the series of stimuli. This results in average rCBF maps for each stimulus associated with an estimate of variance across subject. Rather than examining for outliers to describe physiology, these maps can then be subjected to formal statistical comparisons which generates statistical maps of rCBF change known as statistical parametric maps (SPMs). The rest of this chapter describes the individual steps which result in the formation of the SPM.

Realignment

The final aim of a study is to compare different scans on a pixel by pixel basis. To do this the images must be in the same position so as to ensure the pixels coincide. One way to achieve this is to ensure the subject does not move. A number of approaches have been employed to minimise head movement: each subject had an individually moulded head support made from polyurethane within a polystyrene shell. This supports the patient comfortably whilst minimising movement and ensures that after movement the subject returns to their original position.

Even in these conditions of comfort, to remain still over two hours or more is a demanding task. Automated Image Registration (AIR) software has been specifically developed to correct for head movement between scans. AIR consists of an algorithm which calculates the ratio of one image to another at each voxel (cubic pixel) in the brain and then aligns the two images such that the variance of
this ratio is minimised across all voxels. This technique is now fully automated, rapid, does not rely on external markers, and has been validated using phantom studies.\textsuperscript{144}

**Stereotactic normalisation**

The aim of normalisation of brain images is to co-register homologous loci from different subjects. It is assumed that there is a close relationship between structural and functional anatomy at the level of the spatial resolution of PET. This space is defined by the atlas of Talairach and Tournoux,\textsuperscript{145} the international standard for communicating PET results.

The differences in position of CBF images are dealt with first by using an image analysis software package (Analyze version 6, BRU, Mayo Foundation, Rochester, MN)\textsuperscript{133} to establish the position of the image within the data set in x and y dimensions and then centring the image by simple translation. In addition at this stage the images are displayed in three planes. The degree of roll (rotation about the intercommissural (AC-PC) line) and yaw (rotation about the z-axis) was corrected by eye using considerations of symmetry. The intercommissural line is then identified, and the image translated and re-orientated for gross deviation in pitch around that line. The AC-PC line can be established on the CBF images by identifying four landmarks: the ventral aspect of the anterior corpus callosum; the ventral aspect of the posterior corpus callosum; the ventral aspect of the thalamus; and the occipital lobe. Linear regression can then be used to fit the intercommissural line to these points, an approach which has now been automated.\textsuperscript{136,146}

The anterior-posterior extent of the volume image is identified using a threshold (one third the image maximum). 15 coronal sections through this image were sampled proportionately and then
compared with a standard template obtained from the brains of ten normal volunteers. Using a least squares technique the position of best match was obtained for each of the 15 templates and this was used to estimate the position of the intercommisural plane by a linear regression. Images were then re-orientated to be parallel with the AC-PC line. An estimate was made of the position of the vertex and the distance between this point and the AC-PC plane was used to calculate a vertical scaling factor.

Having re-orientated the images of CBF, the images have to be resized, rescaled, and resliced to correspond to the human brain atlas of Talairach and Tournoux. This process may be considered to have two separate components, corresponding to differences in size and differences in shape.

Differences in size are dealt with by a simple proportional resizing relating the width and length of the data set to the idealised data set. Differences in shape are managed by a more complex non-linear resampling technique. A final transformation matrix is calculated for the individual CBF images for each subject.

Smoothing

Image noise propagated through the reconstruction process is randomly distributed and has high frequency. Signal is not randomly distributed and has high or low frequency. Smoothing of the high frequency components of the image therefore increases the signal to noise ratio at the expense of losing some of the signal.

Despite the anatomic standardisation there will still be differences in gyral and functional anatomy between subjects. These small differences mean that identification of an increase in cerebral blood flow is less reliable. The impact of this topographic variability is reduced by smoothing the image in 3 dimensions (x, y, and z) with
a Gaussian filter of 10 pixels (20 mm) - Full Width Half Maximum (FWHM). This smoothing increases the spatial extent of each activation focus, and the probability that these foci will overlap, thus making them easier to detect in a group of subjects. This is shown diagrammatically in figure 2.6 overleaf. The degree of smoothing has been determined both on theoretical and empirical grounds.

Analysis of covariance (ANCOVA)

The changes in local cerebral activity have two components: global or whole brain region independent change, and local or regional change. It has been shown that the increase in focal activity due to cognitive, sensory or motor activations is independent of global activity. Consequently ANCOVA can be used to analyze the data. In this situation rCBF is regarded as the dependent variable, and global flow is the covariate. For every pixel within the data set, a regression line is calculated which describes the relationship between regional flow and global flow for each subject across all the conditions. The data set can then be examined to see whether or not the observed value deviates from the predicted value. Thus a map is generated for each condition which contains the mean observed minus predicted values with the associated error variance. This map is normalised to the mean global CBF of 50ml/100ml/min. Pixels at which the adjusted rCBF do not exceed 36ml/100ml/min are not analyzed further on the assumption that they represent white matter or cerebral spinal fluid (CSF).
Figure 2.6 Individual subjects A, B, C & D all have a small activation focus which although within the same area of the image do not overlap. When a mean image from all four subjects is created, this focus may be identified only if the images are smoothed.
Assessment of significant change: comparison of means

The maps generated as described above can then be compared using a two tailed paired t test on a pixel by pixel basis. The adjusted condition means are compared using a weighting or contrast. The null hypothesis is that the two conditions are identical, and therefore the sum of this weighting is zero. The mean images of cerebral blood flow are then added as specified in the weighting and the mean blood flow and error variance calculated for each pixel. The mean ±sd for each pixel within the weighted image is normally distributed, and should include zero within its range. The pixels which do not contain zero within the mean ±sd are statistically significant and do not fulfil the null hypothesis.

These significant pixels are then displayed as a statistical parametric map. This map is created by displaying the brain in three projections: sagittal, coronal and transverse. Each pixel in the whole brain set is displayed along the 'line of sight' on to each of the three projections. In order to locate a pixel its position must be examined in each of the projections. The data can also be displayed onto drawings of cortical surfaces or onto a series of transverse planes which greatly aid interpretation. The direction of the weighting specifies whether statistically significant increases or decreases are displayed.

Statistical maps represent images of the significance of change rather than the magnitude of change, allowing brain regions to be compared qualitatively in terms of relative significance. The distinction between images of change size and images of change significance relates to regional differences in the variability of cerebral activity. Significance has two components, namely, the size of the difference and the error variance associated with that
difference. SPMs therefore are functions of both the size and reliability of change.

**Assessment of significant change: thresholding**

Traditional levels of significance are derived for single comparisons. At the P<0.05 level of significance there is a one in twenty chance of a false positive occurring. If twenty comparisons were made, then by chance one of them would be significant, giving the false impression of a positive result. When two complex images are compared, hundreds of comparisons are made and many will reach conventional levels of significance. One solution to this problem is to calculate how many comparisons would expected to be significant by chance in a data set this size. If there are more significant comparisons than would be expected by chance then the conclusion that there was a difference between the two images would be justified. A simple \( \chi^2 \) test can test for the significance of the excess. In the SPM package this is called ‘omnibus’ testing because it provides an overall comparison between all the pixels in two images. The test shows that the images are significantly different but does not allow one to specify exactly where these differences lie.

The selection of an appropriate level of significance is confounded by the large number of pixels in a PET image and the multiple comparisons made. Thus, to reject the null hypothesis, that no change has occurred due to experimental manipulation, a threshold adjustment must be made for the number of comparisons made. One approach to this problem is to use a Bonferroni type of correction. This method was developed to correct for false positives when multiple comparisons are made, although it has been shown empirically that an omnibus threshold of \( p=0.001 \) effectively protects against false positives.\(^{132} \) However these techniques are valid only
for the total number of independent comparisons made rather than the absolute number. Within the PET image, neighbouring voxels are not truly independent, partly for physiological reasons and partly because the image has been smoothed. (Thus a plane 100 voxels by 100 voxels with a FWHM of 10 voxels will represent 100 effectively independent measurements despite constituting 10,000 voxels). The adjustment made depends on the SPMs smoothness. Smoothness can be determined empirically and can be used to calculate a threshold required to identify significant foci.

**Assessment of significant change: interpretation**

Interpretation of the SPM image depends on the hypothesis posed prior to data acquisition. The null hypothesis can be constructed in a number of different ways dependent upon the research question to be asked. A distinction should be made between using the SPMs as an image of significant change and using them to identify foci of significant change, because this will affect the criteria set for the rejection of the hypothesis.

The simplest null hypothesis is one which is topographically constrained and states that there has been no change in rCBF at a single specified brain location. Because of the smoothness present in the SPM it is rarely necessary or possible to pick an exact pixel. Only the data from this single cerebral region should be presented with a threshold of $p<0.05$ applied at that region. Other research questions may either pose a single null hypothesis relating to the profile of the activation, or may pose multiple null hypotheses about each pixel. The threshold for each of these varies. In practice when a single null hypothesis is proposed about the profile of activation then the threshold is usually $p<0.001$, with no correction for multiple
comparisons. The collective nature of the significant data should be emphasised.
Chapter 3: Normal variation in response to pain, groups and single case studies

Introduction

PET has provided convincing and consistent evidence for the importance of the cortex in pain processing in man.\textsuperscript{58,59} Different results from different centres has generated debate as to the precise function of different areas in acute pain response.\textsuperscript{61,148,149} Talbot et al\textsuperscript{58} have demonstrated increases in somatosensory cortex activity in response to pain using PET and argue that it has a fundamental role in the appreciation of acute pain stimuli. In contrast, Jones et al\textsuperscript{59} have reported no changes in the somatosensory region and suggest the somatosensory cortex to be involved in temporal and spatial localization. This suggestion is supported by Apkarian et al\textsuperscript{57} who have reported decreases in somatosensory cortex activity in response to pain using SPECT. There are a number of points which need to be addressed.

Several differences are apparent in the methodology used by different researchers. Both Talbot and Jones have favoured a phasic heat stimulus applied with a metallic probe, the temperature peak set to be either painful-hot or non-painful hot. Differences between Jones' and Talbot's methods relate to the positioning of the stimulus. Jones applied his heat probe to the same position on the back of the subjects' right hand while Talbot minimised the risk of tissue damage by moving the probe between six points along the forearm. In contrast to both Jones' and Talbot's method, Apkarian has used a tonic heat stimulus applied with a water bath set to either a painful-hot or tepid temperature. These differing methodologies may account for the different outcomes in the three experiments.
A phasic stimulus is advantageous because it allows for regular application of a more intense heat pain stimulus with minimal risk of tissue damage. A phasic pain stimulus is not any hotter than that applied tonically but is applied to a smaller area of tissue and the subject is less likely to adapt or habituate to it. In contrast to tonic heat, phasic heat rises suddenly and sharply so that the subjects are unable to control it by distraction and thus the final psychological experience is more precisely painful. However phasic stimuli has been criticised as being most unlike many problematic chronic pains which are better modelled by a continual tonic stimulus (although many chronic pains are intermittent such as trigeminal neuralgia and rheumatoid arthritis), and the phasic pains necessarily introduce an element of non-painful input to the painful stimulus because of its on-off nature which can be eliminated with a continuous tonic stimuli.

Talbot's stimulus differs from Jones' in that it provides the subject with more variable information regarding localization and will contain less effects of habituation. It is as yet unclear what effect these differences may have on the subsequent cortical localization of pain. Talbot's experiment also differs from Jones' in that they used more subjects, more runs and allowed a lower Z-score for significance.

All studies so far have concentrated on pain application to the right side of the body and left cortical responses have thus been interpreted as 'contralateral'. However it is possible that all such pain responses irrespective of the side of the body to which they are applied are lateralised to the left cortex. This would be consistent with the general function of the left brain to be associated with language and the intricate engagement of pain and language. Lateralization to the left seems especially likely for the anterior
cingulate cortex, reported in both PET studies. The anterior cingulate is known to be involved in the emotional processing of chronic pain\textsuperscript{152} and has been shown to elicit vocalization when stimulated.\textsuperscript{153} In contrast to the somatosensory cortex, the anterior cingulate is very poorly somatotopically organized, only around 50\% of cingulate nociceptive neuron units studied show a preference for ipsilateral and contralateral stimulation.\textsuperscript{154} Thus, cingulate cortex is less likely to be lateralised on the basis of somatotopic organization and the left cingulate may constitute a specialized area for affective pain analysis.

Implicit to the debate surrounding these variable responses is the question of individual differences. It is plausible that the position of the somatosensory cortex may not be constant from one individual to the next as has been shown with regard to visual area V5.\textsuperscript{143} Such variability is problematic when dealing with a number of subjects that have to be grouped for statistical purposes, and is compounded by the inherent difficulty of isolating somatosensory cortex from adjacent cortical structures.

Thus the studies reported here were undertaken with several aims. One was related to the appropriateness of using a phasic stimulus in the investigation of chronic pain. (A study of tonic pain stimulation is reported in the following chapter). Clearly if the projections of phasic pain do not consistently correspond to the medial pain system then the relevance of a phasic stimulus to chronic pain must be questioned. Preliminary studies with the 953B (3d) camera affords a comparison of inter-individual response and group response measured with the 931 (2d) camera, thus a second aim was to determine the extent to which results obtained from single subjects are representative of the conclusions drawn from studying groups. Co-registration of selected individuals' PET results with their own high resolution MRI image allowed the examination of variation.
in sulcal and gyral anatomy in areas of interest and to relate this variability to the position of pain response as defined by PET results. A third aim was to determine whether changes in the area of the somatosensory cortex occur below our chosen threshold for significance. Finally, the use of both right sided and left sided pain stimulation allowed the investigation of lateralisation in pain response.

The possibility of differences between individuals due to gender differences and age is discussed in appendix I. The males for that comparison come from the previous study of pain processing by Jones et al and followed a slightly different experimental procedure. Jones' study included a further baseline condition (warm), hence the experimental conditions used with the females from this series of work are not entirely similar. Moreover, the question of male female differences is not a priority purpose of this thesis, nevertheless, given the recent prominence that male/female differences in response to pain has received, and the mix of male and female results in this thesis beginning with this chapter, it was considered important to address this issue. The results from a gender analysis are therefore considered away from the main body of the text in an appendix. In summary, the results indicate that any sex differences are slight and difficult to differentiate from differences due to chance effects. Such differences are not further investigated in this chapter as the males and females were here scanned using different cameras and there is, as yet, no mechanism for quantitative comparison between cameras.
Methods

Subjects

Six female volunteers (mean age 54.6 s.d. 9.3) were scanned using the 931-08/12 (2D) camera and five male volunteers (mean age 24.4 s.d. 6.1) were scanned using the 953b (3D) camera. All 11 volunteers were right handed.

Permission to carry out these studies was obtained from the ARSAC-UK (Administration of Radioactive Substances Advisory Committee, UK) and the Research Ethics Committee of Hammersmith Hospital. The patients' fully informed signed consent was obtained prior to each procedure.

Design

All subjects were compared in their response to an intermittent ramp of both painful and non-painful heat stimuli. Thus the within subject variable was pain vs non-pain. A non-painful hot stimulus was chosen as a baseline to control for the temporal and somatotopic localisation components of the painful stimulus.

A range of dependent variables were investigated: pain quality as measured by the McGill pain questionnaire (appendix II) and pain intensity as measured by a visual analogue scale (VAS - appendix III); the regional cortical responses as measured by PET was the main dependent measure for all subjects. As for all the PET studies reported, changes in blood flow were used as a measure of change in synaptic activity.127

Apparatus

The stimulus for both hot and painful hot conditions, was produced by a Marstock thermal threshold stimulator (Somedic:
thermoelectricType 1)\(^{155}\) which delivers reproducible intermittent ramps of increasing heat to the skin via a water-cooled peltier probe.

The visual analogue scales (VAS) and the McGill scale were either displayed using the Macintosh Hypercard™ system or presented verbally between rCBF measurements.

Scans for the group study were obtained with a PET scanner; CTI model 931-08/12 Knoxville, U.S.A. whose physical characteristics have been described elsewhere.\(^{156}\) Data were obtained for single subject analysis with a PET scanner; CTI model 953B Knoxville, U.S.A., with the inter-detector collimating septa removed to increase the acceptance angle and hence number of photons recorded. As described in chapter 2, the increase in noise is compensated for by the more efficient use of the administered radioactivity.\(^{130}\) Consequently data can be produced of a quality sufficient for the identification of activated regions in the brains of individual subjects.

**Procedure**

Anxiety and depression were assessed using the Spielberger state/trait self-evaluation questionnaire (appendix IV),\(^{157}\) and Beck Depression Inventory (BDI - appendix V),\(^{158}\) prior to scanning. All subjects were then familiarised with the pain visual analogue scale and the McGill pain questionnaire\(^{35}\) used during the scan.

Prior to the scans temperatures which when applied to the back of the hand, were reproducibly experienced as non-painful hot or painful hot were established for each subject using the thermal stimulator. This was done via the Marstock method. The probe was placed onto the back of the subjects' hand which was to be stimulated during the scan, i.e. the right hand for all six female volunteers and three of the male volunteers, and the left hand for the remaining two male volunteers. Two control switches are wired
in parallel to the thermal stimulator, the subject held one and the experimenter the other. Once the subject was happy that he or she could press the switch to operate the machine, the experimenter began the first ramp of heat. The subject was instructed to switch the heat off as soon as it became just perceptibly painful. This was repeated six times. After the sixth time, without moving the probe, the subject was asked to leave the heat increasing until it became no longer tolerable. It was stressed that the machine would switch off at 50 °C and that the subject was not expected to reach such a high temperature. This was repeated three times giving a total of nine measures.

The first three measures were discarded to account for habituation, the next three recordings were averaged to give a measure of pain threshold and the final three recordings were averaged to give a measure of pain tolerance. In general, the temperature which was to be used during the scan as non-painful hot was taken as 2 °C below threshold and the temperature to be used as painful-hot was taken as 2 °C below tolerance. These temperatures were confirmed as either non-painful or painful hot by the subject and adjusted when necessary.

Each subject was positioned in the scanner so that the axis of the scanner was approximately parallel to the glabellar-inion line, which in turn is parallel with the line between the anterior and posterior commissures (AC-PC line). A transmission scan was performed using an external ring source of positrons to provide an image of regional tissue density for the correction of emission scans for tissue attenuation effects.

Each subject underwent six or twelve sequential scans of pain then heat or heat then pain over the course of a single two hour or three hour session, each scan providing measurements of relative
regional cerebral blood flow (rCBF) during application of either heat or pain. In each subject rCBF was measured by recording the distribution of cerebral radioactivity following inhalation of the freely diffusible positron emitting $^{15}$O-labelled tracer, carbon dioxide ($C^{15}O_2$) (931 scanner) or venous infusion of $H_2^{15}$O (953B scanner). Any increase in rCBF entails an increase in the amount of radioactivity recorded from that region.$^{128,137,143}$

Each thermal stimulus was commenced 5 seconds prior the start of the scan. Subjects were warned prior to the start of each stimulation but were not told whether the painful or non-painful temperature was to be applied. The two stimuli were alternated from scan to scan, to avoid any possible order effects, the series commenced with non-painful hot in half the subjects and painful-hot in the other half. Each scan lasted two minutes, during which time an intermittent and precisely reproducible ramp of increasing heat was applied to the back of the hand every 15 seconds. During the time of stimulation the lights were dimmed and silence maintained in order not to contaminate the sensory input. After each measurement verbal confirmation was obtained that subjects had experienced the stimulus appropriately as non-painful hot or painful hot. Where applicable, McGill responses and VAS scores for the retrospective acute pain were recorded.

*PET data analysis - female group*

As the female data was collected from scanner 931 (2d), the signal was too low for single subject analysis and therefore the female subjects are grouped together. The following describes the procedures undertaken in order to analyze the female group of six subjects. (For more detail see chapter 2).
The object of the analysis of these studies was to compare changes in blood flow between the different stimulation conditions so that the effect of increasing heat intensity without pain could be contrasted with the effect of painful thermal stimulation and vice versa. To make this comparison the following procedures were carried out using statistical parametric mapping (SPM software, MRC cyclotron unit, UK) and interactive image display software (Analyze, Biomedics Research Unit, Mayo Clinic) on a SPARC 2 workstation (SUN Microsystems Europe Inc., Surrey, UK). All calculations and matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York, USA).

Correction for head movement between scans was carried out by aligning them all with the first one, using Automated Image Registration (AIR) software specifically developed for the purpose. Each re-aligned set of scans from every patient was reorientated into a standardised stereotactic anatomical space. A correction was made for global changes in blood flow between scans. These two procedures allow flow values for each stimulus condition to be pooled across subjects. Finally a statistical comparison of blood flow distributions between conditions and groups was performed to identify sites of significantly changed regional flow.

The AC-PC line was identified directly from the PET image and the data transformed into the standard stereotactic space of the stereotactic atlas of Talairach and Tournoux. In order to increase the signal to noise ratio and accommodate variability in functional anatomy, each image for the group comparison was smoothed in X, Y and Z dimensions with a Gaussian filter of 20mm (FWHM). Differences in global activity were removed following a pixel by pixel analysis of covariance.
The differences between one condition and another were assessed with the appropriate contrast (weighting of the 6 condition means) using the t-statistic. This analysis is performed for each pixel and the resulting set of t-values constitutes a statistical parametric map (SPM(t)).

The significance of each SPM(t) was assessed by comparing the observed and expected pixels above a specific criterion (p<0.001). The threshold of omnibus p<0.001 was chosen because empirical studies with phantoms have shown that this threshold protects against false positives. The area of the somatosensory cortex was further investigated using a constrained search with the lowest available threshold of p<0.05 (Z=1.645).

**PET data analysis - male individuals**

As the male subjects were scanned using the newer 953B (3d) camera, signal is sufficient to obtain data from single individuals. A procedure similar to the one described above was used for analyzing the pattern of rCBF change in individual subjects except the differences between one condition and another were assessed using the weighting from the 12 condition means and the smoothing was reduced to a filter of 10mm (FWHM).

The search for areas of significance was conducted in the same manner as above with an omnibus threshold of p<0.001 to investigate the whole brain for significant change in response to pain.

**PET-MRI coregistration**

For two of the individual subjects (n463, age 22 and n490, age 31) an MRI was obtained using a 1 Tesla Picker HPQ Vista system using an RF spoiled volume acquisition that is relatively T1 weighted to give good grey/white contrast and anatomical resolution (TR 24
ms; TE 6 ms; non-selective excitation with a flip angle of 35°; field of view in plane 25 x 25 cm; 192 x 256 in plane matrix with 128 secondary phase encoding steps oversampled to 256; resolution 1.3 x 1.3 x 1.5 mm; total imaging time 20 min). After reconstruction the MR images were also aligned parallel with the intercommissural line, and interpolated to yield a cubic voxel size of 1.00 x 1.00 x 1.00 mm, which permitted coregistration with PET images.

For the coregistration of SPM and MR images the steps of image realignment to the intercommissural line and anatomical standardization were omitted. However the subsequent filtering, followed by ANCOVA and the generation of a thresholded SPM(t) were identical. The SPM(t) was then coregistered with the subjects own MRI scan. Such superimposition allowed us to determine the position of the region of maximal rCBF change in relation to the gyral and sulcal pattern of that brain.
Results - group analysis

The comparison of rCBF changes in response to pain and heat in the female controls

Pain vs Heat

The left half of table 3.1 shows the areas of increased rCBF in response to painful hot as compared to non-painful hot in the group of six female volunteers. It can be seen that there is increased rCBF in the contralateral lentiform nucleus, insula and anterior cingulate and ipsilateral frontal areas 32 and 9, region of the periaqueductal gray (PAG) and inferior parietal area 40. A further increase in rCBF can be seen within the region of the contralateral primary somatosensory cortex at 24 mm to the ac-pc line (fig. 3.4). This change was only significant at the lowest available level of significance (p<0.05; Z>1.645).

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Table 3.1 Within group comparison for the female controls, see appendix VI for the abbreviations.
Figure 3.1 Data averaged from the group of six females. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six females. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The areas showing significant increases in blood flow are the region of PAG, lentiform nucleus, insula, and prefrontal, parietal and anterior cingulate cortices.

Figure 3.2 A, as for figure 3.4, B and C with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are hippocampus, and posterior cingulate, occipital and parietal cortices.
Heat vs pain

The right half of table 3.1 shows the areas of significant decrease in rCBF in response to pain. These were seen in midline occipital cortex (area 19), hippocampus, posterior cingulate cortex and parietal cortex.

The detail of table 3.1 is reproduced in figures 3.1 and 3.2 which show these focal activities as SPMs at the appropriate levels in the brain.

Results - individual studies

The comparison of rCBF changes in three male subjects receiving pain or heat to the right hand

Pain vs heat

From table 3.2 overleaf it can be seen that n463 shows a clear contralateral thalamic, caudate and premotor rCBF increase, however these increases are only sub-significant in n609 and n1170. The ipsilateral increase in parahippocampal gyrus (PHG) for n463 can be seen as a sub-significant change in n1170, there is no evidence of any increase in this region for n609. n609 shows extensive ipsilateral increases in lentiform nucleus, insula, temporal, prefrontal and premotor cortex and primary somatosensory cortex. Contralateral increases are only observed in insula and anterior cingulate cortex, these contralateral increases can be seen subsignificantly in both n463 and n1170. Increases in the region of PAG only reach significance in n1170, but can be seen sub-significantly in n463, there is no evidence of any change in n609. n1170 also showed contralateral increases in Lentiform nucleus, there were no significant ipsilateral increases for this subject.
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Table 3.2 Within subject comparisons for the three subjects receiving pain or heat to the right hand.

**Heat vs pain**

Decreases in rCBF did not reach significance for n463, both n609 and n1170 showed significant decreases in inferior parietal cortex, this region was just below significance for n463. Anterior cingulate, posterior cingulate, inferior parietal and temporal cortex and hippocampus showed decreased rCBF in either n609 or n1170.
The detail of table 3.2 is reproduced in figures 3.3, 3.4 and 3.5 which show these focal activities as SPMs at the appropriate levels in the brain.

Figure 3.3 Data from subject n463 experiencing stimuli to the back of the right hand. A. The SPM(t) values derived from the formal pixel-by-pixel comparison of the adjusted mean blood flows and variances for each of the two conditions, pain is contrasted with heat on the left and heat with pain on the right. B. The orthogonal projections of the statistical comparison at a threshold of p<0.001 (Z threshold 3.09). The colour scale below reflects the Z value of each pixel in the SPM(t) images only. The areas showing significant increases in blood flow are PHG, thalamus, caudate and premotor area 6. There are no significant decreases for this subject.
Figure 3.4 Data from subject n609, A and B are as above. The areas showing significant rCBF increases are lentiform nucleus, insula, temporal area 21, prefrontal area 44, premotor area 6, somatosensory cortex and anterior cingulate cortex. Significant decreases can be seen in hippocampus, inferior parietal area 39 and anterior cingulate cortex. The centre of each of these changes is significant at a p<0.001.

Figure 3.5 Data from subject n170, A and B are as before. The areas showing significant rCBF increases are the region of PAG and lentiform nucleus. Significant decreases can be seen in temporal, inferior parietal and posterior cingulate cortex. The centre of each of these changes is significant at a p<0.001.
The comparison of rCBF changes in three male subjects receiving pain or heat to the left hand

Pain vs heat

Tables 3.3 and 3.4 show the areas of significant increased and decreased rCBF in response to pain delivered to the back of the left hand of two subjects, n490 and n565. Both subjects n490 and n565 show a remarkable number of ipsilateral changes in response to the pain stimulus; both subjects show increased rCBF in ipsilateral PAG, insula, prefrontal cortex and anterior cingulate cortex. In addition

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Table 3.3 Within subject comparison for subject n490 receiving pain or heat to the back of the left hand.
### Table 3.4 Within subject comparison for subject n565 receiving pain or heat to the back of the left hand.

n490 shows ipsilateral thalamus and caudate, and subject n565 ipsilateral inferior parietal cortex and extensive temporal cortex. Contralateral increases for n490 were only seen in anterior cingulate and caudate, while for n565 changes were more widespread including anterior cingulate, temporal, insula, lateral premotor, inferior parietal, frontal and somatosensory cortex.
The detail of table 3.3 and 3.4 is shown as SPM images in figures 3.6 below and 3.7 overleaf.

Figure 3.6 Data from subject n490 experiencing pain to the back of the left hand. A and B are as before. The areas showing significant increased rCBF are PAG, lentiform nucleus, insula, thalamus, caudate, prefrontal areas 46 and 9 and anterior cingulate cortex. The areas showing significant decreased rCBF are insula, posterior cingulate, anterior cingulate, frontal (area 32), and inferior parietal cortices. The centre of each of these changes is significant at a p<0.001.
Heat vs pain

rCBF decreases were seen in both subjects in occipital cortex (area 19). No further overlap is apparent for the two subjects. n490 had decreases in contralateral temporal (area 21), posterior cingulate (area 31), prefrontal (area 10) and inferior parietal cortices (areas 39 and 40) and in ipsilateral PHG. n565 had bilateral decreases in orbital frontal cortex (area 11) and hippocampus and contralateral decreases in prefrontal (area 44) and inferior parietal cortex (area 39).

Figure 3.7 Data from subject n565 experiencing pain to the back of the left hand. A and B are as before. The areas showing significant increased rCBF are temporal cortex areas 20, 21, 22 and 38, PAG, prefrontal areas 47, 45 and 10, insula, anterior cingulate cortex, inferior parietal areas 39 and 40 and frontal area 32. The areas showing significant decreased rCBF are orbitofrontal cortex area 11, hippocampus, prefrontal area 44, inferior parietal area 39 and occipital area 19. The centre of each of these changes is significant at a p<0.001.
PET - MRI coregistration

Figures 3.8 and 3.9 show the medial surface through the anterior cingulate, thalamus and PAG for the two male subjects n490 and n463 who received left and right sided stimulation respectively. Below is a horizontal slice cut at the level of the PAG. Both subjects show an rCBF increase in the PAG which confirms the impression of a PAG activation from the SPM image(figures 3.3 and 3.6). In addition n490 shows a remarkable rCBF increase across anterior cingulate cortex which is in contrast to the very tiny increase in n463. Both subjects show a thalamic rCBF increase which is stronger in n490.

Figures 3.10 and 3.11 show a series of horizontal slices through the two brains. n490 shows a bilateral increase in insula, a strong ipsilateral thalamic increase which concentrates in the medial thalamic nuclei, ipsilateral lentiform nucleus, bilateral prefrontal cortex (left sided area 46, right sided area 9) and extensive anterior cingulate cortex. These areas compare well with those reported from the SPM{t} analyses, the only area missing in the SPM being the contralateral prefrontal cortex which was just below significance on the SPM. In the higher coregistered slices it can be seen that there is an increase in the bilateral premotor cortex (area 6) with spread over supplementary motor area (SMA) and primary motor cortex (MI). These changes are shown in more detail as surface renderings in figure 3.14.

In general n463 shows similar increases to n490 only much weaker. There is a clear response in the PAG, bilateral thalamus (more lateral than n490), right prefrontal area 9 and right anterior cingulate cortex. There is also a small increase in SMA but none in somatosensory cortex. Again, these areas are close to those reported in the SPM, however the PHG reported in the SPM is seen in the coregistration images to be just anterior to the hippocampus and
Figure 3.8 Data from subject n490 in which the MR images, shown on the left, have been coregistered and superimposed with the SPM(t) images on the right. A medial slice through the left hemisphere is depicted with a horizontal slice corresponding to the level of the PAG below. The SPM(t) images share a common colour scale for their pixels' Z values, indicated on the right. There is increased rCBF in the anterior cingulate cortex, thalamus and PAG.

Figure 3.9 Data from subject n463 in which the MR images, shown on the left, have been coregistered and superimposed with the SPM(t) images on the right. The images depicted are as above. There is increased rCBF in the anterior cingulate cortex, thalamus and PAG.
Figure 3.10 Data from subject n490 in which the MR images and SPM\(t\) images have been coregistered and superimposed. Horizontal slices at 4mm intervals are depicted, parallel with the AC-PC plane. The SPM\(t\) images share a common colour scale for their pixels' Z value indicating increased rCBF, shown on the right. Strong ipsilateral responses can be seen in the insula, thalamus and lentiform nucleus. The insula response is also evident contralaterally. Bilateral prefrontal and anterior cingulate increases are clearly visible superior to the corpus callosum.

Figure 3.11 Data from subject n463, displayed as above. Small increases in rCBF can be seen in bilateral thalamus, prefrontal cortex and anterior cingulate cortex.
lateral to the amygdala, the centre of this increase is in the posterior nuclei of the thalamus.

rCBF decreases in response to pain are shown in figures 3.12 and 3.13. n490 shows decreases in right orbitofrontal cortex (area 11), right amygdala, right prefrontal area 10, temporal area 21, posterior cingulate cortex (area 31) spreading to occipital cortex, and the frontal eye fields (area 8). There are a number of discrepancies with the SPM(t) analysis. The SPM area reported as frontal area 32 is not confirmed with the coregistration. The SPM report of inferior parietal cortex has a low Z score on the coregistration (Z < 3). The report of decreased rCBF in the PHG from the SPM cannot be confirmed from the coregistration images, there is an area active in that region but it is not clear whether it is posterior thalamus, a blood vessel or PHG.

n463 shows only slight decreases. However there is an interesting decrease in the region of the primary somatosensory cortex which is compared with the increase seen in n490 and examined in more detail in figures 3.14 and 3.15. From these two figures it can be seen that the rCBF decrease on the left cortical surface of n463 lies on the post central sulcus in the primary somatosensory cortex. n490 shows an increase in the right (contralateral) primary somatosensory cortex and an ipsilateral decrease.
Figure 3.12 Data from subject n490 in which the MR images and SPM(t) images have been coregistered and superimposed. Horizontal slices at 4mm intervals are depicted, parallel with the AC-PC plane. The SPM(t) images share a common colour scale for their pixels' Z value indicating decreased rCBF, shown on the right. Decreases in rCBF are evident in right orbitofrontal cortex, amygdala, Wernicke's area, posterior cingulate cortex and the frontal eye fields.

Figure 3.13 Data from subject n463 displayed as above. No significant decreases are apparent for this subject although small changes are detected in right orbitofrontal and prefrontal cortex and left somatosensory cortex.
Figure 3.14 Data from subject n490 in which the MR images have had the scalp removed to reveal the surface of the brain. Surface projections are shown from above, the left and the right with the coregistered and superimposed SPM(t) images indicated in red. Increased rCBF in response to pain is shown above, decreases shown below. The colour scale is arbitrary.

Figure 3.15 Data from subject n463 displayed as above.
Discussion - group

Before discussing the results further two cautions are warranted. First, although the subjects were not warned which stimulus they were about to receive it is unlikely that the subjects anticipated pain throughout the heat application. Each application consisted of either 8 (using the 931 (2D) scanner) or 11 (using the 953 (3D) scanner) ramps of heat or pain. The stimuli were always constant within a given scan, thus, following the first two or three stimulations, it is likely to have been clear to the subject whether he or she was receiving pain or heat. Consequently, the measure of pain response is liable to include anticipation of pain and arousal whereas the measure of heat is not. Hence it is important to consider the results of experiments investigating anxiety when interpreting these results.159,160,161 Much of the research regarding anxiety concerns trait anxiety, associated with long term personality disorder, rather than state anxiety and is therefore not directly relevant to the situation here. Long term mood disorders are known to correlate with changes in biological function that are not known to occur during the transient mood disorder. For example, it is likely that frontal-lobe hypoactivity, observed in depressed patients,162 is a result of long term biochemical deficiency rather than a transient mood change. Furthermore anxiety is mostly regarded as a temporal or hippocampal phenomenon,159,160 and these areas are not often active in pain studies, interestingly the hippocampus showed a decreased rCBF in this study. A PET study of anticipation of painful electric shock, i.e. anticipatory anxiety similar to that present here, without any experience of pain did not show increased blood flow in areas associated with pain such as the anterior cingulate cortex or somatosensory cortex.163
The second caution relates to the fact that many of the interpretations placed on regional findings with PET are based on animal studies and what is known about patients undergoing craniotomy after a short-acting anaesthetic. It should be emphasised that these various other techniques are entirely different from PET both from the point of view of experimental design, the volume of the brain that can be sampled, spatial resolution and the type and number of subjects studied. Differences are therefore bound to emerge. Furthermore, negative results do not necessarily exclude any response as a region of small increase surrounded by a large region of decreased flow or no change is not likely to be detected.

The areas of activation highlighted in the comparison of pain with heat for the group included the main projections of the medial pain system and thus emphasise the importance of this system in the processing of the non-somatotopic elements of an acute pain stimulus.

The interpretation of the response in the PAG is difficult given the fundamental involvement of this area in pain analgesic mechanisms.\textsuperscript{164} It is possible that analgesic mechanisms are triggered automatically to damp certain ascending nociceptive information.\textsuperscript{126} This process is partially mediated by the release of 5-HT.\textsuperscript{165} This suggestion is supported by the fact that PAG also responds to a hot, non-painful, stimulus as reported in appendix I.

The activity in the insula is intriguing in light of recent evidence to suggest that loss of this area results in virtual total loss of appreciation of pain\textsuperscript{166,167} but not a complete loss of sensory perception. For example, the patients with insula damage had little difficulty in identifying objects placed in their hands with eyes closed, and responses to non-noxious temperatures was not significantly changed. With the exception of one patient showing
slight deterioration of roughness discrimination, these case studies emphasise that pain discrimination can be severely impaired while general somatotopic functioning remains intact.

The significance of the response in the contralateral lentiform nucleus is uncertain. Lentiform nucleus is most often associated with planned action\textsuperscript{168} and movement,\textsuperscript{169} thus the increased lentiform rCBF observed here may relate to an alerting or priming mechanism for movement as has been observed in primates,\textsuperscript{170} and can be seen as an ancillary pain mechanism related to escape behaviour. Alternatively it may relate to a nociceptive specific response which has been observed in the caudate nucleus-putamen and globus pallidus of the rat\textsuperscript{171} and may explain how damage within the striatal complex leads directly to the experience of pain.\textsuperscript{172} It is known that electroacupuncture has the effect of increasing the concentration of leu-enkephalin within the striatum of the rat which increases pain threshold,\textsuperscript{173,174} while in the striatum depletion of dopamine can undermine some aspects of morphine associated analgesia\textsuperscript{175} depletion of serotonin can enhance morphine associated analgesia.\textsuperscript{176} Thus disruption of the neurotransmitter system within the striatal complex may reduce or enhance pain perception depending on which neurotransmitter has been affected. In addition to the nociceptive specific responses within the striatum, there are several basal ganglia-thalamocortical circuits, each with different functions, including 'limbic' responses.\textsuperscript{177} The medial thalamic nuclei project onto the striatum and innervate the putamen and caudate.\textsuperscript{178} Thus, pain specific information may be passed directly from the thalamus to lentiform nucleus where it may be finally processed as pain or modulated as part of a motor program before relaying to higher cortical centres.
A response in thalamus was expected. The lack of a thalamic response in the female group is puzzling and not consistent with Jones' previous report, though it is consistent with Talbot et al. As the thalamus carries all sensory information to the cortex it is possible that this area shows a smaller relative increase in blood flow with pain as compared to heat and is thus more difficult to detect than other areas, a suggestion which receives empirical support from the results reported in appendix I. In addition, the activation of ipsilateral prefrontal cortex and anterior cingulate cortex is consistent with activation of medial thalamic nuclei.

Activation of frontal areas is interesting in the context of earlier reports of relief of suffering in advanced cancer by prefrontal lobotomy. Such an operation rendered the patient indifferent to his chronic pain despite acute pain perception and general somatotopic discrimination remaining intact. However the operation also had far more traumatic implications for the patients' personality and social functioning which have proved difficult to explain. Shallice has proposed a theoretical model which views these dysfunctions as the outward sign of a disorder of a central control system. The theory states that part of the regulating function of the frontal lobes is to supervise switches in attention. Patients with frontal lesions are proposed to have lost their cognitive supervisory attentional system that directs behaviour away from stereotyped responses. This theory is powerful because it enables the explanation of the behaviour of patients with prefrontal lesions as the result of perseveration of a well learned task, a direct consequence of the failure of supervisory attention. The patients thus become indifferent to pain because their attention is being accessed by the more fundamental organising principles of everyday life, i.e. they are highly distractable.
Surgical lesions of cingulate cortex and/or the cingulum bundle have produced similar reports of indifference to previously intractable chronic pain, leaving general somatotopic perception and localization intact, but have generally not repeated the devastating changes in personality produced by lobotomy. The specific alleviation of the ‘bothersome’ qualities of chronic intractable pain directly implicates cingulate cortex in affective responses to noxious stimuli. Animal models of chronic pain also show a significant involvement of cingulate cortex. Lidocaine injections into the cingulum bundle significantly reduce responses to hindpaw injections of formalin. Gabriel et al have shown that rabbits with anterior cingulate lesions fail to pair a previously learnt noxious stimulus with a conditional tone stimulus, thus cingulate lesions disrupt the prediction and avoidance of the noxious stimulus. The anterior cingulate cortex has a functional similarity with prefrontal cortex in that it also has a profound involvement with attention. As mentioned in chapter 1, the anterior cingulate cortex is activated in many PET studies but is particularly notable when demands are specifically placed on attention such as when a large number of targets is presented; during conflict blocks of the Stroop task; and during most tasks that involve detection of target visual stimuli. Thus the anterior cingulate activation can be interpreted as both an attentional and nociceptive phenomena while the parietal response could be an orienting response.

In summary, the group result emphasizes the importance of the projections of the medial pain system. The activation of somatosensory cortex was only significant at a very low threshold which is generally not accepted as significant using PET. However, a more detailed discussion of somatosensory response is included in appendix I and elsewhere. Of the other activated areas, each has a
potential fundamental involvement in pain processing but must also include ancillary mechanisms such as anticipation and attention.
In order to gain an insight into the amount of variability in pain response and to summarise the results of this chapter, table 3.5 above summarises all the regions of rCBF increase and decrease seen
in the group and single subjects. For the sake of simplicity the side of the response is not included in the table.

The regions listed in bold in the table are those areas which produced a response in more than half of the individual subjects. All of these areas were significant in the group as well. Only inferior parietal area 39 showed a significant decrease in blood flow in more than half the individual subjects, this area is italicised in the table and showed no evidence of a decrease in the group. The possibility that these differences between the group and the individual subjects is sex related is discussed in appendix I.

The PAG is a tiny structure which lies anterior to the cerebellum in the brain stem. The small size of this structure and its proximity to many other structures including red nucleus, hippocampus, and hypothalamus as well as cerebellum, mean that it is not possible to be sure of its activation in the SPM results. However, the fact that the PAG is clearly coregistered in subjects n463 and n490 (below significance in n463), allows for greater confidence in naming this structure on the SPM(t) of individuals and the group. As noted above, the PAG is often implicated within the descending analgesic system in animals\textsuperscript{189,190,191} and has been used as part of the chronic pain analgesic regimen in man.\textsuperscript{192,193} It is seen as being central to a network of structures involved in descending analgesia which consists of insular cortex, amygdala, nucleus accumbens, dorsal raphe nucleus, hypothalamus, reticular formation and thalamus.\textsuperscript{194,195,196,197,198,199} The increase in rCBF seen in PAG in this experimental protocol is consistent with the concept of a continual pain suppressing mechanism which constantly inhibits transient and unimportant inputs, and which increases its activity in response to stressful input such as pain,\textsuperscript{200} or pleasurable input such as sexual stimulation.\textsuperscript{201}
In general, Table 3.5 emphasizes the consistency of those areas seen in the group across the individuals. Lentiform nucleus, prefrontal cortex, insula, and anterior cingulate cortex are all active in at least three of the five individual subjects at a significant level. However, there is a large variation within other regions. The regions that responded in only one or two individuals include PHG, thalamus, caudate, medial frontal cortex (area 32), inferior parietal cortex (area 40), temporal cortex, and somatosensory cortex. This could represent misinterpretation of the data, peculiarities of the individual, or variation within the methodology. For example, the combined activation of temporal area 22 (Wernicke's area), parietal area 40, and prefrontal area 45 (bordering Broca's area) in n565 suggest activation of the 'articulatory loop' i.e. internal verbalisation. This subject also had an anterior cingulate activation much more anterior than normal, closer to the vocalization section of cingulate. Also, n463 did not show any of the commonly activated areas and hence this subject's activation profile may represent an alternative pain processing network or, less dramatically, be emphasizing a smaller aspect of the network such as motor response.

These increases in rCBF were mostly confirmed with the coregistrations and other areas shown to be present at a subsignificant level. A clear activation in PAG is evident for n463 but is below the level of significance as is this subject's anterior cingulate activity. However, increases in the PHG reported from the SPM(0) turned out, on closer inspection with the MRI, to be the posterior section of the ipsilateral thalamus. Discrepancies between MRI coregistration and SPM may be expected to occur in the brain stem region where there are many small clusters of important nuclei. Caution in interpreting these changes from the SPM is therefore
called for. This same problem was found when examining the decreases in rCBF in the PHG region with the MRI from n490.

**Somatosensory area in individuals: the pattern of gyri and sulci and the variation in activation**

As can be seen from the two surface projections of the coregistered subjects the position of the somatosensory cortex in subject n490 is approximately 4mm posterior to that of subject n463. This small variation is important because the somatosensory cortex is flanked by motor cortex (areas 4 and 6) anteriorly and by inferior parietal cortex (area 40) posteriorly making localization of SPM responses difficult. From the SPM in figure 3.6 (subject n490) it can be seen that there are two subsignificant increases at 40mm to the ac-pc line within the region of the somatosensory cortex. In the absence of the MRI, using just the SPM results, this increase was interpreted as an inferior parietal response. MRI is thus an important tool in understanding pain responses in somatosensory cortex.

Unfortunately, as both increases and decreases in rCBF occur in the somatosensory region in response to pain, the PET data itself cannot be used as a reliable indicator of the somatosensory region. Thus, unlike the previous investigation of area V5,143 the measure of gyral variation in somatosensory cortex using pain will remain largely subjective, and so will not be speculated on further.

The variation in somatosensory CBF indicates the possibility of variable somatosensory response in accordance with the intensity of the pain as compared to the heat. This was investigated in appendix I. In summary, appendix I suggests that the somatosensory cortex may compromise some of the quality analysis of a stimulus in order to more clearly localise the stimulus as it becomes painful. This process may be carried out via surround inhibition, a well known
phenomenon in other sensory modalities, and could appear on the PET scan as a decrease in rCBF. From this theory both subject n463 and n490, who had a pain window of 4°C and 5°C respectively, should have shown an rCBF decrease in response to pain. However, subject n490 showed a clear increase on the MRI in the contralateral somatosensory cortex and n463 showed a decrease. This result does not support the theory presented in appendix I. Table 3.6 below shows the results from the other subjects studied. As can be seen, the somatosensory cortex shows a general trend towards rCBF increase regardless of temperatures chosen. These increases can be considered significant as the result of a constrained search (see chapter 2 and appendix I). Nevertheless, the group result would still not have been reported as significant by Talbot et al, and the individual results mostly fall in the central pain window of appendix I and are therefore liable to give a less robust and more variable signal.

<table>
<thead>
<tr>
<th>Region</th>
<th>rCBF Increases</th>
<th>rCBF Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female group</td>
<td>Female group</td>
</tr>
<tr>
<td>S1,2,3</td>
<td>n463 n469 n565</td>
<td>n463 n490 n609</td>
</tr>
<tr>
<td></td>
<td>s s √ s</td>
<td>s</td>
</tr>
<tr>
<td>Temp Diff °C</td>
<td>2.8 4.0 5.0 4.2 4.5 2.5</td>
<td>2.8 4.0 5.0 4.2 4.5 2.5</td>
</tr>
</tbody>
</table>

Table 3.6 Summary of the somatosensory responses. Each tick indicates a significant SPM change (increase or decrease) in blood flow at the p<0.001 level for each subject or group. An 's' indicates SPM change below the p=0.001 threshold. Only contralateral changes are indicated. The lower row shows the temperature difference between the painful hot and non-painful hot stimulation for each subject or group (averaged).

The fact that the female group and subject n1170 both showed subsignificant increase in the somatosensory area consistent with their tight pain windows indicates some support for the hypothesis. This will be returned to when considering further individual studies later.
The laterality of pain response

Classical anatomy\textsuperscript{203} indicates that the pain pathways decussate at the level of the spinal cord such that left sided stimulation is represented in the right cortex and vice versa. This is widely reflected in anatomical studies of the spinothalamic tract.\textsuperscript{39} However the role of neural input representing the ipsilateral body surface is uncertain. A number of studies have indicated significant ipsilateral projections\textsuperscript{204,205} and have demonstrated that descending analgesia is preferentially mediated ipsilaterally.\textsuperscript{206,207} Of the nociceptive units in area 24 of the rabbit showing a preferential response to either ipsilateral or contralateral noxious stimulation 45\% had a greater response to ipsilateral stimuli.\textsuperscript{154}

Thus the large number of ipsilateral responses in the individuals studied here could represent either a previous underestimation of ipsilateral projections, which may vary with the stimulus parameters,\textsuperscript{208} or a lateralisation of pain response in some structures possibly relating to the processing of affect as suggested in the introduction. This latter hypothesis seems less likely given that subject n609 receiving right sided stimulation produced considerable right (ipsilateral) responses while the two subjects receiving left sided stimulation both showed considerable left (ipsilateral) responses. If function was lateralised then it would be expected that responses would remain predominant in one hemisphere regardless of the side of stimulation.

Right sided stimulation will remain the norm for the majority of this thesis, consistent with most previous work, stimulation of the left side will be returned to in the final experimental chapter.
Chapter 4: An investigation of central responses to a tonic pain stimulus

Introduction

From chapter 3 and appendix I it can be seen that the somatosensory cortex has a variable response to pain which may be dependant on the exact parameters of the 'cognitive subtraction'. When the temperature of the non-painful hot stimulation was much lower than the temperature of the painful hot stimulation the resulting subtraction (PH-NPH) included a non-nociceptive component and rCBF decreases in somatosensory cortex were observed. This non-nociceptive component was reduced as the temperature of the non-painful stimulation approached pain threshold and rCBF increases in somatosensory cortex were observed. This variability in temperature is illustrated in figure 4.1 overleaf. As the variability in the final subtraction image is due to the use of a ramp of heat which runs from a non-painful temperature to a painful temperature it can be eliminated via the use of a consistent, i.e. tonic, stimulus. Such an approach should reveal a consistent increase in rCBF in the somatosensory cortex in accordance with the discussion in appendix I. However, previous research with a tonic stimulus has shown precisely the opposite effect, namely rCBF decreases in the somatosensory region. It is therefore possible that there are additional differences between tonic and phasic pain which may produce a variable CNS response.

Of the reported differences between phasic and tonic stimulation, the most consistent are the greater unpleasantness of tonic stimulation and the resistance of phasic stimulation to morphine analgesia. These differences emphasise the similarity of tonic stimulation to the clinical entity of chronic pain
Figure 4.1 Four ramps are illustrated from a painful hot (PH) scan and from two possible non-painful hot scans. Non-painful hot A (NPHA) breaches the no pain barrier and approaches pain, non-painful hot B (NPHB) does not breach the no pain barrier and only approaches pain threshold. Thus the subtraction PH - NPHA there will be no non-painful component whereas in PH - NPHB there will be a residual non-painful component in the final subtraction image.

disorder. It is argued that there is an artificiality associated with brief pain stimuli and inferences drawn from them to naturally arising human pain. However, the type of phasic stimulus discussed is usually electrocutaneous which consists of extremely brief pulses (<100 msec pulse-width) and the type of tonic stimulus used is normally cold pressor. Hence these past findings are not strictly comparable with the studies here as our phasic stimulus has a pulse-width of 15 seconds and our tonic stimulus was chosen as hot in order to remain consistent with previous research and the use of painful hot phasic stimuli.

Thus it is unclear whether our phasic stimulus is comparable to the experience of chronic pain disorders such as AFP and clinical pains such as post extraction pain. However, it is clear from chapter 3 and other published work that the medial areas most often
implicated in chronic pain disorders are activated in PET studies using a phasic painful stimulus similar to that used here.

The aim of this study was twofold: firstly to investigate whether the variability of response within the somatosensory cortex is caused by the variability within a phasic pain application; and secondly to investigate whether involvement of medial systems in the processing of a tonic pain stimulus is any different from that of phasic pain. Implicit to this second aim is to establish firmer grounds for using phasic stimuli in the investigation of pain disorders.
Methods

Subjects

Six male volunteers (mean age 29 s.d. 11) were used for the following study of tonic stimuli. Permission to carry out the studies was received as before. In addition, the questionnaire data from ten subjects (six female and four male) from chapter 3 were used as comparison with the questionnaire data collected for this chapter.

Design

All subjects were compared in their response to a continuous stimulus of either hot water or painfully hot water creating the usual within subject variable of pain vs non-pain. In addition to the main dependent measure of cortical response, pain quality was also measured via the McGill pain questionnaire and by a visual analogue scale. In order to counterbalance any ordering effects half the subjects began scanning with a painful scan while the other half began with a non-painful scan.

Apparatus

The stimulus for both the hot and non-painful hot conditions was produced by a water bath which was designed and constructed at the Hammersmith Hospital for this experiment. The bath consisted of an immersion heater, temperature gauge, a circulation fan and a rubber glove which allowed the subject to insert his hand horizontally into the water bath.

The McGill and VAS were presented verbally following two of the painful stimulation scans. Depression and anxiety were measured prior to scanning using the Beck depression inventory and the Spielberger evaluation questionnaire respectively.
Scans were obtained with PET scanner; CTI model 953B with the septa removed.

**Procedure**

Prior to the scans, water temperatures which with the right hand immersed via the glove were reproducibly experienced as non-painful hot or painful hot were established for each subject using the water bath apparatus. For the painful hot stimulation, it was ensured that the subject experienced pain within two minutes of putting their hand into the bath and that the pain did not become unbearable over a five minute period. Using an initial temperature of 50 °C, the temperature was adjusted up or down accordingly. For the non-painful hot stimulation an initial temperature of 40 °C was confirmed to be consistently hot or warm without becoming painful for each subject. Thus, as for the phasic studies, each subject experienced the stimuli they were to receive prior to the beginning of the scan.

Positioning in the scanner and transmission scan were carried out as before and were followed by the subjects positioning of the right hand into the water bath. Once a comfortable position was achieved, the dynamic scans began.

Prior to each scan the bath was heated or cooled to the appropriate temperature and confirmed as either non-painful hot or painful hot by the subject. Each scan lasted 2 minutes 45 seconds, during which time the subject continuously experienced either pain or heat in their right hand. After each measurement verbal confirmation was obtained that the subjects had experienced the stimulus appropriately and, where applicable, McGill responses and VAS scores were recorded. During the interscan period, the subjects hand remained in the rubber glove but was able to rest on a metal bar above the water.
**PET Data analysis**

The object of the analysis of these studies was to compare changes in blood flow between the different stimulation conditions so that the effect of continual heat intensity without pain could be contrasted with the effect of continual painful thermal stimulation. As before the following procedures were carried out; correction for head movement and global changes between scans, stereotactic positioning and comparison of the twelve condition means at a p<0.001. The images were smoothed in X, Y and Z dimensions with a Gaussian filter of 10mm (FWHM).

These procedures were carried out for both the group and the individuals separately.
Results - group analysis

<table>
<thead>
<tr>
<th>Region</th>
<th>Co-ordinates x</th>
<th>Co-ordinates y</th>
<th>Co-ordinates z</th>
<th>Z-score</th>
</tr>
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<td>(BA 44)</td>
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<td>(BA 46/10)</td>
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<tr>
<td>Parietal Cx</td>
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Group - right sided changes

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<th>Co-ordinates y</th>
<th>Co-ordinates z</th>
<th>Z-score</th>
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<td>Insula</td>
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<tr>
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<td>Parietal Cx</td>
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<td>16</td>
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<td>A. Cingulate</td>
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Group - left sided changes

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<th>Co-ordinates z</th>
<th>Z-score</th>
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<tbody>
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<td>-64</td>
<td>4</td>
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<tr>
<td>P. Cingulate</td>
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<td>-64</td>
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<td>Occipital Cx</td>
<td>-26</td>
<td>-70</td>
<td>24</td>
<td>3.191</td>
</tr>
</tbody>
</table>

Table 4.1 Within group comparison for the application of tonic pain. Changes shown are significant at P<0.001 (Z>3.09)

Pain vs heat

The left hand side of table 4.1 shows the rCBF increases seen in response to painful hot water as compared to non-painful hot water. Bilateral increases can be observed in insula and parietal cortices (area 40), contralateral increases in lentiform nucleus and anterior cingulate cortex and ipsilateral increases in prefrontal cortex (areas 44, 46 and 10). These increases are illustrated as SPM(t) in figure 4.2.

Heat vs pain

The right hand section of table 4.1 shows the rCBF decreases in response to pain. Decreases are evident in bilateral occipital cortex (areas 17, 18 and 19) and in contralateral posterior cingulate cortex (area 31). In addition to the above there is a decreased rCBF in somatosensory cortex which is significant at a p<0.01 (z=2.33). These changes are illustrated as SPM(t) in figure 4.3. From figure 4.3 it can
Figure 4.2 Data averaged from the group of six males. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six males. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The colour scale below reflects the Z value of each pixel in the SPM(t) images only. The areas showing significant increases in blood flow are lentiform nucleus, insula, prefrontal areas 44, 46 and 10, parietal areas 39 and 40 and anterior cingulate cortex.

Figure 4.3 A, as for figure 4.2., B, C and D with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are occipital cortex areas 17, 18 and 19 and posterior cingulate cortex area 31. In addition there is a subsignificant decrease in somatosensory cortex.
be seen that there are additional rCBF decreases in temporal cortex (area 22) with a Z-score of approximately 2.

**Questionnaire results**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Tonic Group (SD)</th>
<th>Phasic Group (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>3.6 (2.41)</td>
<td>4.9 (5.06)</td>
</tr>
<tr>
<td>State Anxiety</td>
<td>10.6 (5.54)</td>
<td>13.7 (8.12)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>14.6 (6.35)</td>
<td>15.9 (5.39)</td>
</tr>
<tr>
<td>PVAS</td>
<td>55.5 (15.2)</td>
<td>60.5 (19.3)</td>
</tr>
<tr>
<td>McGill Sensory</td>
<td>0.29 (0.11)</td>
<td>0.28 (0.13)</td>
</tr>
<tr>
<td>McGill Affective</td>
<td>0.12 (0.07)</td>
<td>0.18 (0.18)</td>
</tr>
</tbody>
</table>

Table 4.2 shows the results of the questionnaires given to each subject receiving tonic pain for this study and phasic pain for the studies reported in chapter 3. There is no significant difference between the groups on any of the reported measures.

Table 4.2 shows the results of the questionnaires given to all the subjects (2 of the male subjects from the prior experiment were excluded because of their poor English) prior to the scanning and in between scans. To determine a measure of the sensory intensity of the induced pain, all the descriptors within the sensory categories of the MPQ were summated by rank value and then divided by the highest possible score. This scoring method yielded values ranging from 0 to 1 with a score of 0 indicating the subject did not select any adjectives from any of the sensory categories and a score of 1 indicating the subject selected the highest ranked word in each category. This same procedure was used to obtain a quantitative measure of affective descriptors. These values were averaged for all three of the acute pain applications on the 931 camera and for three (every other pain scan) of the pain applications on the 953 camera.

From table 4.2 it can be seen that there is very little difference between the two groups. No differences reached any level of significance. Qualitative differences revealed by the McGill will be discussed in the final chapter.
Results - individuals

Pain vs heat

Tables 4.3, 4.4 and 4.5 show the individual subject responses. The left hand side of each table indicates rCBF increases in response to the tonic pain stimulus. n536 showed considerable increases in rCBF in response to the tonic pain. These increases were ipsilateral in the anterior cingulate (area 24 spreading towards prefrontal area 10), temporal, insula (bordering with lentiform nucleus), somatosensory and prefrontal cortices and contralateral in the region of PAG, orbital, temporal, occipital, parietal association and primary motor cortices. Figure 4.4 illustrates these increases as SPM{t}. n538

<table>
<thead>
<tr>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
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Table 4.3 Within subject comparison for subject n536 receiving tonic pain or heat to the right hand.
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Table 4.4 Within subject comparison for subjects n538 and n1027 receiving tonic pain or heat to the right hand.
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Table 4.5 Within subject comparison for subjects n1303 and n1311 receiving tonic pain or heat to the right hand.

also showed a wide range of rCBF increases. Significant increases can be reported in ipsilateral prefrontal cortex (area 10), caudate and a widespread area incorporating the border of anterior cingulate, frontal area 32 and the frontal eye fields (area 8). Contralateral changes can be seen in the region of the PAG, hippocampus and
orbital frontal (area 11), occipital (area 19), prefrontal (areas 42, 44 and 10), anterior cingulate and lateral and medial premotor (area 6) cortices. The insula shows bilateral increase. These increases are illustrated as $\text{SPM}(t)$ in figure 4.5 and shows additional subsignificant increases in inferior parietal cortex (area 40) and somatosensory cortex.

$n_{1025}$ showed no significant changes at the $p<0.001$ level. Figure 4.6 shows the subsignificant changes as $\text{SPM}(t)$. Increases can be observed in bilateral prefrontal cortex (area 10), thalamus and anterior cingulate cortex spreading towards frontal area 32.

$n_{1027}$ showed ipsilateral rCBF increases in anterior cingulate cortex, insula, occipital cortex (area 18) and medial premotor cortex which bordered somatosensory association area 5. Contralateral increases were significant in temporal cortex (area 22) and inferior parietal cortex (area 40). These increases are illustrated as $\text{SPM}(t)$ in figure 4.6.

$n_{1303}$ showed mostly bilateral increases in insula, prefrontal cortex (areas 42, 43, 44 and 45) and inferior parietal cortex (area 40). In addition there was increased rCBF in ipsilateral caudate and prefrontal cortex (area 10) and contralateral thalamus and anterior cingulate. These increases are shown as $\text{SPM}(t)$ in figure 4.8.

$n_{1311}$ showed significant increased rCBF in ipsilateral prefrontal cortex (area 10) and inferior parietal cortex (area 40). There was a contralateral increase in temporal cortex (area 21). Anterior cingulate cortex showed bilateral increases. These increases are shown as $\text{SPM}(t)$ in figure 4.9
Heat vs pain

The right side of tables 4.3, 4.4 and 4.5 show the decreases in rCBF for the above subjects. These decreases are illustrated as SPM(t) to the right of the subjects' increases in figures 4.4 to 4.9.

n536 showed bilateral decreased rCBF in inferior parietal and posterior cingulate cortices, ipsilateral in temporal cortex and contralateral in hippocampus, occipital cortex and primary somatosensory cortex.

n538 showed only ipsilateral decreases in temporal (area 21), posterior temporal (area 37) bordering inferior parietal (area 39) and occipital (area 19) cortices. Subsignificant decreases can be seen in the region of the contralateral somatosensory cortex at 30mm to the ac-pc line.

n1025 showed only subsignificant decreases at the level of anterior cingulate cortex and ipsilateral somatosensory cortex.

n1027 also showed predominant ipsilateral decreases in the hippocampus, lentiform nucleus and temporal (area 36), prefrontal (area 10) and occipital (areas 17 and 18) cortices, but also showed a contralateral decrease in anterior cingulate cortex.

In contrast subjects n1303 and n1311 both showed considerable contralateral decreases in rCBF in the hippocampus, subcallosal cingulate (area 25) and temporal (area 36), posterior cingulate (area 31), parietal (area 7), prefrontal (area 47), premotor (area 6), primary somatosensory, and inferior parietal (area 40) cortices. In addition ipsilateral decreases were observed in temporal cortex (area 37), parahippocampal gyrus (PHG), prefrontal cortex (areas 9 and 10) and primary somatosensory cortex.
Figure 4.4 Data from subject n536 experiencing stimuli to the back of the right hand. A. The SPM(t) values derived from the formal pixel-by-pixel comparison of the adjusted mean blood flows and variances for each of the two conditions, pain is contrasted with heat on the left and heat with pain on the right. B. The orthogonal projections of the statistical comparison at a threshold of p<0.001 (Z threshold 3.09). The colour scale below reflects the Z value of each pixel in the SPM(t) images only. Contralateral decreases in somatosensory cortex can be seen at 28mm to the ac-pc line. See table 4.3 and text for details.

Figure 4.5 Data from subject n538, A and B are as above. See table 4.4 and text for details.
Figure 4.6 Data from subject n1025, A and B are as before. There were no significant changes for this subject.

Figure 4.7 Data from subject n1027, A and B are as before. See table 4.4 and text for details.
Figure 4.8 Data from subject n1303, A and B are as before. See table 4.5 and text for details.

Figure 4.9 Data from subject n1311, A and B are as before. Somatosensory cortex shows a significant ipsilateral decrease at 24mm to the ac-pc line and a contralateral decrease at 40mm to the ac-pc line. See table 4.5 and text for further details.
Discussion

Table 4.6, over, summarises the areas of rCBF change in the female group from chapter 3 who received phasic pain stimuli and the areas of rCBF from the tonic group studied here. In general, this comparison shows that there is broad consistency between the areas of phasic and tonic pain activation. Increased rCBF is consistent in the anterior cingulate cortex, prefrontal cortex, insula and inferior parietal cortex. Decreases in rCBF are seen most consistently in posterior cingulate cortex and occipital cortex.

However PAG and medial frontal cortex show increased rCBF for the phasic group but not the tonic group. As there are no significant differences between the two groups for measures of anxiety or depression, it is unlikely that these differences are due to any differences in the subjects. In light of the heavy involvement of PAG in descending analgesia this finding suggests that an opioid driven mechanism may operate automatically in response to phasic pain. This may explain the differential impact of morphine analgesia on phasic and tonic pains, presumably the morphine has no effect on phasic pain as it cannot improve an already fully operating mechanism.

Two recent studies indicate that the medial frontal cortex is a major recipient of direct PAG input and can block the transmission of nociceptive responses evoked in the medial nuclei of the thalamus. These two findings suggest that the medial frontal cortex could be an extension of PAG regulated analgesia. However there is little evidence from the results here that the combined activation of PAG and medial frontal cortex leads to the experience of less pain. Other studies have implicated medial cortex in more general aspects of attention and emotional processing, and thus emphasize the relationship of medial cortex to anterior
Table 4.6 summarises the regions of rCBF increase and decrease for the female phasic group, reported in chapter 3, and the tonic group. Each tick indicates a significant change. PFC=Prefrontal cortex; OFC=Orbitofrontal cortex; Ptrl=Parietal; Tmprl=Temporal. Below are the group averages of the questionnaire data with the individuals marked with a {+} to indicate a greater score than both averages, a {-} to indicate a lesser score and a {0} to indicate no clear difference.
cingulate and prefrontal functions which is not surprising given its anatomical location.

A decreased rCBF to the somatosensory cortex was demonstrated at the p<0.01 level. This decrease in the somatosensory area can be accepted as significant within the context of a constrained search. However this decrease is clearly not as consistent across individuals or as profound as the decrease in occipital cortex. The occipital decrease is difficult to interpret as a pain related phenomenon and probably relates to a distribution of resources given the lack of necessity for any visual input. Thus, if the occipital decrease is taken as a reference, the somatosensory cortex would seem to have a direct role in some element of pain perception which has been suggested as localization. However it is expected that this mechanism should have an equal role in all subjects, the fact that two subjects showed no evidence of any change in the region of the somatosensory cortex is damaging to this hypothesis. Moreover, the fact that during phasic stimulation somatosensory cortex increases when pain input is maximal, as indicated in appendix I, suggests the somatosensory cortex to be specifically involved in pain processing per se.

A recent report by Drevets and colleagues suggests a possible solution to these conflicting results and interpretations. They have found that expectation of an incoming painful stimulus to the fingers resulted in a decreased rCBF to the ipsilateral face area of the somatosensory cortex with corresponding subsignificant changes on the contralateral side. In addition the magnitude of change correlated with anxiety levels which may vary systematically with stimulus parameters as well as varying from individual to individual. Thus the reported variability in somatosensory changes may be a product of suppression of sensory transmission from cutaneous receptive fields.
where significant stimuli are not expected and preservation of transmission in fields where such stimuli are expected. Such a variation in rCBF change is difficult for PET to detect and is more likely to be interpreted as a single area of increase or decrease depending on the magnitude and volume of the areas undergoing change. The fact that increased CBF to somatosensory cortex was previously recorded during the comparison of hot stimulation with warm stimulation (appendix I) also suggests that the increased complexity in somatosensory response is specifically related to the processing of pain, which may be related to the importance of localization as discussed elsewhere.57

In general, the results of this study suggest that the continued use of an acute phasic stimulus is acceptable in the study of chronic pain disorders using PET. In combination with the advantages of a phasic stimulus outlined in the introduction, particularly the precise nature and experimental control of a phasic stimulus, the results of this study suggest the continued use of a phasic stimulus is preferable. The next three chapters investigate the central action of phasic pain stimuli in three groups of pain patients: atypical facial pain; rheumatoid arthritis; and post extraction pain.
Chapter 5: Cortical and subcortical responses to pain in patients suffering atypical facial pain

Introduction

This chapter describes the extension of previous observations to the study of cerebral responses to pain in a group suffering from chronic atypical facial pain (AFP). This is a common form of facial pain which is usually described as a continual dull to severe ache with intermittent excruciating throbbing episodes localized to a non-muscular site. The pain may be bilateral with a wide extrafacial distribution and is not provoked by jaw movements and rarely relieved by analgesics. Bouts of pain may last for hours or days and the patient may have a history of intermittent pain over a period of many years. A common feature is that the pain may be provoked or potentiated by trauma or dental treatment. Apart from occasional marked reddening of the oral mucosa or slight swelling of the face, there are no clinical signs.

The absence of any clear clinical aetiology for AFP has led to its diagnosis as a psychosomatic disorder. Successful treatment of AFP with anti-depressant medication has led to the suggestion that AFP is a secondary disorder consequent on depression. Such a suggestion, however, has not been supported in recent drug trials. For example, in a double-blind controlled trial the tricyclic antidepressant drug dothiepin was found to give superior pain relief than placebo. However, pain relief was found to be independent of any antidepressant effect of the medication, suggesting that the drug had a muscle relaxant and central analgesic action appropriate to this form of pain disorder. As such, AFP can be seen as part of a wide spectrum of common pain disorders, the aetiology of which is largely unknown, but which have a loose association with stress, anxiety and
depression. Around 40% of the general population report frequent facial pain and headache which remains largely undiagnosed, and many patients referred for specialist consultation are found to be suffering from a pain with a strong affective component and a psychiatric basis. For example in one study, 63% of women presenting with pelvic disorder were felt to have no demonstrable physical disorder. Because it is difficult to identify these patients, they are usually subjected to excessive non-invasive and invasive investigation.

The association of emotional and mental suffering with the mouth may be interpreted in a number of ways, based on one's understanding of the anatomical, physiological and developmental aspects of oral function. Not only do the lips, tongue and oral mucosa have an exceptionally rich sensory innervation but also the muscles of emotional expression gain their principle insertions around the mouth. Furthermore, the cortical projection of this part of the peripheral nervous system is large compared to the trunk or legs. Thus from early embryonic development there is already a physical matrix that enables emotional factors to achieve great oral and facial significance.

Stressful events such as work, marital difficulties, bereavement, chronic illness in the family and financial problems have all been suggested as having a role in the formation of AFP. However it is not clear how stress can bring about a somatic illness nor is it clear how to understand the relationship between illness and psychological distress. Several studies have indicated that illness can be a product of, and be prolonged by, environmental stress, parental neglect and work pressure. Figure 5.1 considers these different conditions as risk factors which may trigger illness and presents a possible mechanism for the development of AFP. The
Work related pressure

Static motor tasks

Social Stress

Behavioural Facial Tension Dr. Visits

Cognitive Orientation to the face Feelings of Anxiety and Depression Belief in Ill Health

Biological Somatisation (A24) Somatisation (A24)

serotonin depletion

AFP

Disruption of descending analgesia

Parental Neglect

Figure 5.1. A causal model explaining the aetiology of atypical facial pain. Full arrows indicate direct causal links, dotted arrows partial causality and arcs risk factors potentiating the final mechanism. Stress in the social space is shown to impact on the behavioural and cognitive to produce atypical facial pain in the biological space either directly or as part of a generalized somatisation response. The model indicates that differential pressures placed on the sexes put women at a greater risk for AFP. This helps to explain the greater prevalence of this disorder in females. A24=area 24. See text for further details.

The model presented in figure 5.1 employs the methodology of 'causal modelling' and is an extension of the models presented in chapter I. The aim of the model is to explain how stress and serious life events might bring about somatisation, including atypical facial pain with all its associated symptoms and factors. Figure 5.1 develops the work of Leventhal (figure 1.3) to include experiences other than those
directly related to pain. In the model, stress is shown to produce facial tension (grimacing) which will produce higher levels of somatisation possibly related to pain schemas run by the anterior cingulate cortex (area 24). The elaboration of these schemas is here suggested to result in the development of AFP. In the model presented depression is independent of the mechanism producing AFP, although serotonin depletion may later accentuate AFP through detrimental changes in descending opiate analgesia.

The dependence of pain experience on psychological factors\textsuperscript{11,16,25} underlines the importance of environmental cues on pain processing. The latter may therefore be as susceptible to psychological factors as to changes in peripheral nociceptive input.\textsuperscript{228} For example, Lautenbacher et al\textsuperscript{229} have recently shown anxiety to play an important role in heat pain perception between the sexes. Over a three day period they observed that as women became less anxious about induced heat pain their pain tolerance approached that of the male group. Anxiety and impaired stress coping are also suggested to lower pain perception in depressive patients\textsuperscript{230} and dental patients.\textsuperscript{231} These findings justify the two way communication from cognition to biology in the model.

The work of Brown and Harris,\textsuperscript{232} Speculand et al\textsuperscript{233} and Feinmann et al\textsuperscript{104} have demonstrated the importance of life events as a cause of psychological distress. The latter authors emphasize that stress is a fundamental factor in the development of facial pain, including AFP. Thus social stress is in turn primary to cognition in the development of AFP and represents a point of departure between AFP and other pain disorders with a clear peripheral origin such as post extraction pain.

It is logical to suggest that the structures most likely to alter functioning in the CNS with AFP are those identified in previous PET
studies with pain which have a regulatory function and can be disrupted by stress and psychological disturbance. These studies have indicated the involvement of medial structures thought to be responsible for the elaboration of somatosensory signals into pain. It is expected that the AFP patient has fundamentally altered CNS systems involved in pain processing, in line with their distress and expectation of biological dysfunction. Of particular interest are the prefrontal and anterior cingulate cortices as these areas are considered responsible for controlling and directing attention and generating emotional responses, precisely the functions that are suggested by the model to be out of control in patients suffering AFP. Thus it is predicted that, in response to a pain stimulus, patients with AFP will show different responses as compared to age and sex matched volunteers in the regions of the anterior and prefrontal cortices.
Methods

Subjects

Six female atypical facial pain patients, age range 42-65 years (mean age 53) were matched to the six healthy age female controls reported in chapter 3. All twelve subjects were right handed and post menopausal.

The six patients suffered from left-sided atypical facial pain and had been prescribed antidepressant medication which was stopped three weeks prior to scanning. The duration of the pain ranged from 1-16 years (mean 7 years), and all patients had other associated symptoms such as headache, neckache, pelvic pain, irritable bowel and pruritus. Neurological examination and radiological (orthopantomogram and CT) findings were normal.

Permission and consent to carry out these studies was obtained as before.

Design and apparatus

The design and apparatus are the same as those used in the study of the female controls described in chapter 3 and appendix I. Each patient was lined up in the CTI 931 (2D) scanner parallel to the ac-pc line and emission scans completed using phasic heat and pain stimuli as described.

Procedure

Patients with atypical facial pain were recruited from the facial pain clinic at the Eastman Dental Hospital. All volunteers were given a thorough explanation of the procedure prior to their arrival at the Hammersmith Hospital.
The procedure for measuring psychological profile, obtaining painful and non-painful temperatures, setting up in the scanner and scanning technique was as for chapter 3.

**PET Data Analysis**

Preparation of the raw images for analysis was as for chapter 3.

Two planned statistical comparisons were performed: 1) To assess the central effects of induced pain within both groups; and 2) to assess any differences in neurophysiological correlations of pain and heat between the two groups.

1) Effects of induced pain within each group. The non-painful hot conditions (increasing heat, anticipation of pain) were compared with the painful hot conditions (increasing heat, anticipation of pain, pain). The resulting SPM(t) highlighted brain regions in which changes of synaptic activity was associated with pain.

2) Effects of induced pain between groups. This was assessed by contrasting the changes associated with pain between groups using the appropriate contrast to define the t-statistic. The test for a significant difference in the rCBF responses due to painful heat stimulation, in the two groups (normals and atypical facial pain patients) used the average error variance for the two groups for each pixel.

One tailed tests of significance were made looking for 1) increases in rCBF associated with induced thermal pain in each group separately, and 2) increases in the pain induced rCBF response in subjects with atypical facial pain over and above the increases seen in the volunteers.
Results

The results of the female controls are shown in table 3.1 and figures 3.1 and 3.2.

AFP within group result

Pain vs Heat

The left hand section of table 5.1 below shows the areas of significant change in rCBF for the comparison of pain with hot in atypical facial pain patients. The main areas of activation were contralateral in the lentiform nucleus, insula and thalamus, ipsilateral in the orbitofrontal cortex (area 47) and midline in anterior cingulate cortex (area 24). Figure 5.2 shows these areas in the form of SPM(t).

<table>
<thead>
<tr>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF Increases</td>
<td></td>
<td></td>
<td>rCBF Decreases</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>score</td>
<td>Region</td>
</tr>
<tr>
<td>Prefrontal Cx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Med. Frontal</td>
</tr>
<tr>
<td>Orb. Frontal</td>
<td>48</td>
<td>14</td>
<td>-8</td>
<td>4.542</td>
<td>Parietal Cx</td>
</tr>
<tr>
<td>(area 47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(BA 10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(BA 32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(BA 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(BA 7)</td>
</tr>
</tbody>
</table>

Table 5.1 Within group comparison of pain vs non-painful heat in the AFP patients.
Figure 5.2 Data averaged from the group of six AFP patients. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six patients. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a $P<0.001$ (Z threshold 3.09). The areas showing significant increases in blood flow are lentiform nucleus, insula, thalamus and anterior cingulate cortex.

Figure 5.3 A, as for figure 5.2., B and C with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are prefrontal, occipital, inferior parietal and frontal cortices.
Heat vs Pain

Significant decreases in rCBF are indicated in the right hand section of table 5.1 and are illustrated as SPM\{t\} in figure 5.3. Areas of decrease were seen in bilateral prestriate cortex, contralateral premotor (area 6), parietal (areas 7 and 40) and frontal cortices (area 8), and ipsilateral prefrontal cortex (area 10).

The comparison of rCBF increases in the AFP patients with increases in the female controls

A comparison of figure 5.2 with figure 3.1 indicates that there is greater rCBF increases in the thalamic region and lesser rCBF increases in the prefrontal region of the AFP patients compared with the female controls. In addition the anterior cingulate signal extends more inferiorly in the AFP patients than in the female controls. These observed differences were confirmed as significant at the P<0.01 level and are illustrated as SPM\{t\} in figures 5.4 and 5.5.
Figure 5.4 A, Anatomical features obtained by averaging all blood flow scans from the six females (A.f) and six AFP patients (A.afp). B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli assessed between the two groups. C, The SPM[t] values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions x group. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections, of the statistical comparison at a P<0.01 (Z threshold 2.33). Significant differences can be seen in the region of the prefrontal cortex.

Figure 5.5 A, Anatomical features obtained by averaging all blood flow scans from the six AFP patients (A.afp) and six females (A.f). B C and D as above illustrating the greater response in the AFP patients. Significant differences can be seen in the region of the thalamus and the anterior cingulate cortex.
**Questionnaire results**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>AFP patients (SD)</th>
<th>Female controls (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>16.0 (10.0)</td>
<td>4.8 (5.04)*</td>
</tr>
<tr>
<td>State Anxiety</td>
<td>23.0 (16.38)</td>
<td>13.7 (8.55)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>27.3 (15.98)</td>
<td>13.3 (5.39)*</td>
</tr>
<tr>
<td>PVAS - Ac.</td>
<td>62.8 (30.4)</td>
<td>68.3 (18.1)</td>
</tr>
<tr>
<td>McGill Sensory - Ac.</td>
<td>0.20 (0.12)</td>
<td>0.26 (0.15)</td>
</tr>
<tr>
<td>McGill Affective - Ac.</td>
<td>0.11 (0.17)</td>
<td>0.18 (0.21)</td>
</tr>
<tr>
<td>PVAS - C.</td>
<td>47.6 (12.8)</td>
<td>-</td>
</tr>
<tr>
<td>McGill Sensory - C.</td>
<td>0.28 (0.06)</td>
<td>-</td>
</tr>
<tr>
<td>McGill Affective - C.</td>
<td>0.14 (0.10)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.2 shows the results of the questionnaires given to each AFP patient and for the female controls reported in chapter 3. *Indicates between group significance at the p<0.05 level. BDI=Beck Depression Inventory; PVAS=Pain Verbal Analogue Scale; Ac=Acute induced pain; C=Chronic (AFP) pain.

Table 5.2 shows the results of the questionnaires given to all the AFP patients and female controls (reported in chapter 3). From the table it is clear that the AFP patients are more anxious and depressed than the control subjects. The higher depression score was confirmed as significant (t=2.44, p<0.05) as well as the higher trait anxiety (t=3.87, p<0.01). No other between group comparisons were significant.

Within the AFP group, both sensory ratings of the acute and chronic pain are higher than the respective affective ratings. These differences were confirmed as significant using Student's related t-test (t=2.70, p<0.05 and t=5.80, p<0.01 respectively). No other within group comparisons reached significance. Within group comparisons for the female controls are reported in chapter 3.
Discussion

This experiment has demonstrated differences in the central processing of a pain stimulus for an AFP group compared with normal volunteers. These differences were in the thalamus, prefrontal cortex and anterior cingulate cortex.

The difference in the thalamic region, being greater in the AFP patients, corresponds to the lack of a thalamic response in the female controls. The high variability of response in the thalamus means that it is not clear whether this difference does or does not represent abnormal processing.

In accordance with the general hypothesis outlined in the introduction, we were able to demonstrate differences between the two groups in the prefrontal and anterior cingulate regions. Specifically the atypical facial pain significantly attenuated the rCBF increase brought about by induced acute pain in the prefrontal cortex (area 10) whilst increasing rCBF in anterior cingulate cortex (area 24). It is not yet possible to say whether this pattern of response to acute pain is common to all forms of chronic pain or specific to atypical facial pain. A number of explanations for this pattern of rCBF are possible and later studies with other chronic pain disorders, such as arthritic pain, will enable us to discriminate between these possibilities.

Atypical facial pain is often associated with an emotional disturbance involving some serious life event, such as a bereavement, with inadequate support from relatives or spouse. The model outlined in figure 5.1 illustrates how this may result in the biological disorder of AFP, and this study begins to unravel the neurological substrates of the disorder. The anterior cingulate cortex is well placed to integrate variable stressors and to disrupt analgesic mechanisms having reciprocal connections with the medial thalamic
nuclei and projecting to prefrontal cortex, striatum and periaqueductal grey. Atypical facial pain, therefore, may be a 'hyperemotional' response to incoming sensory information. The observation that chronic pain loses its emotional component following frontal leucotomy and cingulotomy in combination with the findings of this study lends support to this hypothesis.

As mentioned earlier, Shallice has proposed that the process by which complex behavioural units or schemata are brought to conscious attention is the function of the 'supervisory attentional system'. This is part of the 'programming, regulation and verification of human activity' by the frontal lobes. Posner and Rothbart argue that this alert state is lateralized to the right lateral frontal lobe based on its close involvement with the regulation of the heart. The maintainence of vigilance is indexed by a marked slowing of the heart. The abnormal pattern of right prefrontal and anterior cingulate responses in these patients may therefore reflect an abnormal 'supervision' of attention and emotional schemata. This is consistent with the perception of physical symptoms proposed by Pennebaker. The common conviction of these patients that there is something structurally wrong with their face, combined with their high trait anxiety, is seen as providing a schema in which the likelihood of perceiving painful sensory input from the face is high. Attention may initially be focused on the face because of tensing or somatisation in response to stress, as indicated in the model, or because of dental treatment, or because of the more general emotive significance of the face. The next two chapters will assess these different possibilities.

It is apparent from the McGill scores that the chronic and acute pain were not triggering any exceptional emotional response in the atypical facial pain patients. In fact, the opposite was the case. The
AFP patients indicated a greater severity on the sensory scale of the MPQ for both their chronic pain and the induced acute pain, as did the female controls. This is not consistent with larger group studies of AFP which have indicated the dominance of emotional descriptors. One interpretation of this is the desire of the patients in this study to prove the reality of their atypical facial pain to the medical staff conducting the scanning procedure, by denying any emotional input to their disorder. Alternatively, if AFP patients are hypersensitive to incoming signals then the phasic, sensory nature of the acute stimulus may have been colouring and feeding into their experience of AFP. Hypersensitivity and rapid self integration are two key differences in response to physical stimuli suggested by figure 5.1 and the results of this study which are worthy of future investigation. These issues will be further discussed in chapter 8. The model presented in figure 5.1 can now be expanded to incorporate these additional findings and is shown in figure 5.6 overleaf.
Figure 5.6 develops the causal model from figure 5.1 to include the hypofrontal response and the possibility of changed responses to physical stimuli in AFP patients. The risk factors and the behavioural and social levels are as before and are not shown. A24 = area 24. See text for further details.
Chapter 6: Cerebral responses to pain in patients suffering from rheumatoid arthritis

Introduction

In the previous chapter, AFP patients were shown to produce a different rCBF response to pain than normal volunteers. This differential pattern of response was explained in terms of the abnormal psychological responses of patients with AFP, however the response could be explained more simply as a general consequence of any long term pain. To test the hypothesis that abnormal cingulate and prefrontal responses are particular to AFP and psychologically maintained pain, patients suffering pain from rheumatoid arthritis (RA) will now be investigated.

RA is a seriously debilitating disease that is reported to affect around 1% of the general population. The condition can effect people of all ages and sexes, but is most commonly seen between the ages of 20 and 50. As for AFP, women are affected more often than men; the overall ratio is 3:1 which compares to 4:1 for AFP.

Although, to date, there is no known cause or cure for RA, the disease does have clear biological markers which follow a reasonably predictable course. In early active rheumatoid disease there is soft tissue swelling associated with local antibody production and increased vascular permeability. A large number of substances, including cytokines, are then released some of which may cause damage to the synovium and cartilage. In late stage destructive RA, problems of deformity and loss of function predominate. Pain is a major complaint of patients suffering from rheumatic diseases, with incidence reported as two-thirds. However the degree of pain expressed by patients with equivalent clinical and radiographic disease features varies widely, some patients report intense pain in...
the absence of clear underlying pathology while others report no pain in the presence of late stage destruction.\textsuperscript{115}

There is no satisfactory explanation for this variability in pain response, the most common explanation is to identify some patients as good copers and others as bad.\textsuperscript{83} This fits the usual definition of coping as a psychological mechanism for managing external stress,\textsuperscript{245} however this explanation is tautological. If someone has the clinical signs of advanced arthritis in the absence of pain then he or she is deemed a good coper whereas if pain is reported in the presence of the same or fewer clinical signs then he or she is a bad coper. Thus, the absence or presence of pain is explained as a function of coping which is itself defined by the absence or presence of pain.

Thus far, we have identified that an AFP patients' central response to pain can be differentiated from the normal response and have interpreted this differential response as meaning the AFP patients are overinterpreting incoming sensory signals. By analogy with the arthritis patients, AFP patients may be characterised as 'bad copers'. To get away from the above tautology, however, the disorder must be seen as a consequence of some external influence.

AFP is presented in figure 5.6 as part of a generalised reorganization of the biological space to cope with external stress. This study investigates the central responses of six patients suffering chronic pain in association with rheumatoid arthritis (RA) to an acute pain stimulus. It is hypothesised that the RA patients will show a different pattern of activation in response to pain than the AFP patients reflecting the differing coping strategies and interpretations of pain that are associated with AFP and RA.
Methods

Subjects

Six female rheumatoid arthritis patients, age range 41-77 (mean age 62.3 sd 12.18) were matched to the six healthy female controls (chapter 3) and the six AFP patients (chapter 5). All 18 subjects were right handed and post menopausal.

Each of the RA patients had suffered inflammatory pain in either the knee, wrist, ankle or elbow for an average duration of 14 years (range 4-30 years). Treatment was predominantly with non-steroidal anti-inflammatory agents such as Fenbufen (marketed by Lederle as Lederfen®). All patients stopped their medication at least one week prior to the study.

Design and apparatus

The design and apparatus for delivering phasic pain and PET scanning was the same as that used in the study with the female controls described in chapter 3 and appendix I.

Procedure and data analysis

RA patients were recruited from the pain clinic at Hammersmith Hospital. The usual thermal stimulus was delivered to the non-inflamed skin of the back of the right hand. This site was cosegmental but distant from the inflamed joints. Final analysis was performed for normal controls vs RA and AFP vs RA in a similar manner to that described in chapter 5.
Results

The results for the controls are shown in table 3.1 and figures 3.1 and 3.2, the results for the AFP patients are shown in table 5.1 and figures 5.2 and 5.3.

RA within group results

No significant changes in rCBF were observed for either pain vs heat or heat vs pain comparisons. The non-significant changes are shown as SPM(t) in figures 6.1 and 6.2. Figure 6.1 shows that there are subsignificant increases in rCBF in contralateral insula, lentiform nucleus, thalamus, somatomotor cortex and anterior cingulate cortex, ipsilateral increases in prefrontal area 9 and bilateral increases in inferior parietal cortex (area 39/40). Subsignificant rCBF decreases can be seen in bilateral prefrontal areas 9, 10, 44, 45 and 46, contralateral hippocampus and ipsilateral posterior cingulate cortex.

Comparison of rCBF increases in the female controls and AFP patients with increases in the RA patients

A comparison of figure 3.1 with 6.1 indicates that there is greater rCBF in ipsilateral prefrontal areas 9, 10, 44, 45 and 46 and bilateral anterior cingulate cortex in the female controls compared with the RA patients. The prefrontal area 10 and anterior cingulate response were confirmed as significantly different at the p<0.01 level and are displayed as SPM(t) in figure 6.3.

A comparison of figure 5.2 with 6.1 indicates that there is greater rCBF increases in the bilateral thalamic region and anterior cingulate cortex and ipsilateral lentiform nucleus, insula and prefrontal area 10 of the AFP patients compared with the RA patients. These observations were confirmed as significant at the p<0.01 level and are displayed as SPM(t) in figure 6.4.
Figure 6.1 Data averaged from the group of six RA patients. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six patients. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. No areas show significant rCBF increases.

Figure 6.2 A, as for figure 6.1., B and C with reversed contrasts to give decreases. No areas show significant rCBF decreases.
Figure 6.3 A, Anatomical features obtained by averaging all blood flow scans from the six female controls (A.f) and six RA patients (A.ra). B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot assessed between the two groups. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for pain x group. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a p<0.01 (Z threshold 2.39). Significant differences can be seen in prefrontal and anterior cingulate cortex.

Figure 6.4 As above except the AFP patients replace the female controls. Significant differences can be seen in the region of the thalamus prefrontal and anterior cingulate cortex.
Questionnaire results

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>RA patients (SD)</th>
<th>Female controls (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>6.5 (2.07)</td>
<td>4.8 (5.04)</td>
</tr>
<tr>
<td>State Anxiety</td>
<td>9.0 (2.63)</td>
<td>13.7 (8.55)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>15.8 (6.32)</td>
<td>13.3 (5.39)</td>
</tr>
<tr>
<td>PVAS - Ac.</td>
<td>46.7 (21.4)</td>
<td>68.3 (18.1)</td>
</tr>
<tr>
<td>McGill Sensory - Ac.</td>
<td>0.18 (0.06)</td>
<td>0.26 (0.15)</td>
</tr>
<tr>
<td>McGill Affective - Ac.</td>
<td>0.07 (0.09)</td>
<td>0.18 (0.21)</td>
</tr>
<tr>
<td>PVAS - C.</td>
<td>29.6 (13.4)</td>
<td>-</td>
</tr>
<tr>
<td>McGill Sensory - C.</td>
<td>0.11 (0.08)</td>
<td>-</td>
</tr>
<tr>
<td>McGill Affective - C.</td>
<td>0.06 (0.06)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.1 shows the results of the questionnaires given to each RA patient and for the female controls reported in chapter 3. No between group analysis reached significance.

Table 6.1 shows the results of the questionnaires given to all the RA patients and female controls. There are no clear differences between the two groups except that the RA patients tended to rate the induced pain as less painful on all the measures used, however no differences reach significance.

Within the RA group both sensory ratings of the induced pain and their own chronic pain are higher than the respective affective ratings, this reflects the same pattern seen with AFP. However the differences here did not reach significance. A full analysis of all questionnaire data across all groups will be included in chapter 7.
Discussion

The fact that the RA patients studied here showed very little response to induced pain raises a number of interesting issues. Primarily this result indicates that the pattern of rCBF seen with AFP is more likely to be specific to that disorder rather than a generalized response to chronic pain. Specifically, the rCBF differences between normal volunteers and arthritis patients are likely to represent an important cortical adaptation in the presence of ongoing inflammatory pain which do not occur with AFP. It is not possible to determine the level at which these cortical responses are modified by ascending inputs. Insula receives projections from nociceptive specific components of the ventromedial nucleus (VMpo) of the thalamus. Connections between anterior insula and limbic cortex are widespread, although connections to anterior cingulate cortex are only partial. The anterior cingulate cortex almost exclusively receives nociceptive afferent input from the medial thalamic group of nuclei. As discussed previously, the cingulate cortex is also implicated in avoidance learning, attention and mood. Thus it is likely that the reduced responses to phasic pain may be related to enhanced coping and attentional strategies.

Both AFP and RA showed less rCBF increase in the prefrontal region compared with the control volunteers, particularly area 10. This region has also been found to have lower rCBF in depressed patients and has been suggested as a specific marker of depression. As the RA patients studied here were not significantly more depressed than the control subjects, the interpretation of hypofrontality as indicating depression may not be correct. It could, however, be a marker for a more generalised response to stress. Given the role of prefrontal cortex in attentional processing, this response could be characterised on the psychological level as
resignation. That is, a person facing a seemingly intractable situation gives up, this is commonly characterised as 'learned helplessness' and is generally accepted as an important element in depression if not constituting depression itself. However, learned helplessness may have a more benign form in acceptance. In contrast to the AFP patients, the RA patients had accepted their disorder, its lack of treatment, and were doing their best to get on with life despite of it. One of the patients from this group completed a life ambition of walking through the rain forests despite her severe debilitating arthritis.

This interpretation is consistent with the view that the anterior cingulate is responsible for the current processing of information. The lack of any response in the RA patients above a baseline response is in keeping with their motivation to limit the importance of pain information. This allows the models presented in figures 1.4, 1.5 and 5.1/5.6 to be restructured to account for the differing neuronal responses to pain. This is shown in figure 6.5 overleaf.

Rather than dividing patients into copers and non-copers this formulation places the emphasis on the differing strategies of dealing with pain and stress. All patients 'cope' but whether they cope well or badly depends on their understanding of their disease and their personal situation.
Figure 6.5 Resignation to disease is shown as characteristic of both RA and AFP. However, AFP patients respond by struggling with the medical establishment while RA patients accept the intractable nature of their disorder. As a consequence of resignation, both RA and AFP show hypofrontality, but differentiate with regard to anterior cingulate activity. The dotted lines and arrows indicate that the behavioural and social levels are not shown.
Chapter 7: Central responses to pain in subjects suffering post extraction pain and a summary of the results from chapters 3, 5, 6 and 7

Introduction

Central differences in response to an induced pain stimulus have been demonstrated between normal volunteers and AFP, and further differences have now been demonstrated between AFP and rheumatoid arthritis. This chapter looks at the central effects of an induced stimulus for subjects suffering a transient background pain from the extraction of a lower impacted wisdom tooth. Thus far the role of stress has been emphasised as a prime cause of the AFP patients perseveration on their pain. However, an alternative hypothesis is that the overt concern associated with AFP is due to the emotive significance of the facial area, thus reversing the causality from stress precipitating AFP to AFP precipitating stress. Learning theorists and developmental psychologists see the role of the mouth as providing a highly specialized and delicate field, which acquires a special capacity for the experience of pleasurable function or emotional pain at critical periods of exploration, feeding and establishing affectionate bonds. Tasting, eating, speaking and kissing give the oral region a special significance for everyone. Thus the increased anxiety and concern characteristic of AFP may be a generalised response to any sign of facial trauma. This hypothesis will be investigated with patients suffering pain following extraction of impacted, lower wisdom teeth.

In several ways, dental pain following extraction of a lower impacted wisdom tooth may be considered an ideal control for AFP. As for AFP, the intensity of post extraction pain has a high association with anxiety, is more prevalent in women than in men, and may be regulated by the 5HT system in...
descending monoaminergic pathways. However, there are obvious differences not least of which is the fact that dental pain is mostly controllable by analgesics and will disappear after a relatively short period of time. Comparisons of AFP and post extraction pain have shown that in general AFP patients have a greater perception of suffering a significant medical problem and show greater somatisation than do people suffering post extraction pain. Whether these are a consequence of long term facial pain or an inherent attribute of the AFP personality is not clear.

In this study six subjects suffering pain following routine left sided wisdom tooth extraction were compared in their central response to a painful and non-painful hot stimulus to the back of the right hand. These responses were then compared with those of pain free subjects and AFP patients. It is hypothesized that if the CNS response to pain in AFP is a reactive phenomenon consequent on simultaneous facial pain then no significant difference between the dental group and the AFP group should be observed.

In addition, this study includes a full analysis of depression, anxiety and McGill pain measures taken from the female controls, arthritis patients and AFP patients studied previously. Male subjects were used for this study because of ethical considerations prohibiting the use of young females. A discussion of the potential difficulties in comparing male/female PET responses is considered in appendix I. The between group PET analysis for this chapter is restricted to comparing dental pain with atypical facial pain.
Methods

Subjects

Data were received from six male patients with a mean age of 24 years (SD 2.4). All the subjects were suffering acute postoperative pain after having had their left sided wisdom teeth removed under local anaesthetic.

Design and apparatus

This study was carried out using phasic heat pain with the 931 PET camera. It replicates the design used in chapters 3, 5 and 6.

Procedure

All participating subjects were recruited from the Eastman Dental Hospital. The patients were recruited at the the time of dental review to consider their wisdom teeth. If extraction was considered necessary and the patients agreed to participate, a special appointment was made for their extraction. Where bilateral extractions were required two appointments were made. For the purposes of the scan, the left wisdom teeth were extracted in the morning at the Eastman Dental Hospital. Following the patient's recovery from the extraction procedure he was taken by taxi to the Hammersmith Hospital. From there the standard procedure was followed. Scanning began no less than four hours following extraction.

Non-steroidol anti-inflammatory agents and opioid based analgesic were available for the subjects immediately after the scanning procedure.
PET Data Analysis

Data analysis was as before, described in detail in chapters 3 and 5. Within group differences were assessed for pain vs heat and then this difference assessed across the dental pain and AFP group.
Results

The comparison of rCBF changes in response to pain and heat in the post extraction patients

Table 7.1 shows the areas of significant rCBF increase and decrease in response to pain in comparison to non-painful heat. These changes are displayed as SPM(t) in figures 7.1 and 7.2. Increased rCBF is observed in left Lentiform nucleus and the lateral edge of thalamus while rCBF decreases are seen in right sided hippocampus. In addition, subsignificant increases can be seen in ipsilateral insula and prefrontal cortex.

<table>
<thead>
<tr>
<th>rCBF Increases</th>
<th>rCBF Decreases</th>
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<tr>
<td><strong>Region</strong></td>
<td><strong>Co-ordinates x y z</strong></td>
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<td>Hippocampus</td>
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<td>Post extraction patients - left sided changes</td>
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<tr>
<td>Lentiform</td>
<td>-24</td>
</tr>
<tr>
<td>Lentiform/Thalamus</td>
<td>-26</td>
</tr>
</tbody>
</table>

Table 7.1 Within group comparison of pain and heat for the post extraction pain patients.
Figure 7.1 Data averaged from the group of six post extraction patients. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six patients. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The areas showing significant increases in blood flow are lentiform nucleus and thalamus.

Figure 7.2 As above except the t-contrasts have been reversed to give images of rCBF decrease. The only area showing a significant decrease in blood flow is the hippocampus.
The comparison of rCBF increases in the AFP patients and the post extraction patients

From figures 4.1 and 7.1 it can be seen that the AFP patients show greater rCBF increases in the region of the PAG, insula and anterior cingulate cortex. There is no apparent difference in the region of the prefrontal cortex. These observations were confirmed as significant differences between the two groups at p=0.01 and are displayed as SPM(t) in figure 7.3. In addition significant changes are seen in the inferior parietal cortex due to this area decreasing rCBF in the AFP group.

Figure 7.3 A, Anatomical features obtained by averaging all blood flow scans from the six AFP patients (A.afp) and six post extraction patients (A.ext). B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli assessed between the two groups. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions x group. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, the orthogonal projections of the statistical comparison at a P<0.01 (Z threshold 2.33). Significant differences can be seen in the PAG, bilateral insula, inferior parietal and anterior cingulate cortex.
Group comparisons of all questionnaire data

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<tr>
<th>Group</th>
<th>NPH°C (SD)</th>
<th>PH°C (SD)</th>
<th>Age (SD)</th>
<th>State-A. (SD)</th>
<th>Trait-A. (SD)</th>
<th>BDI (SD)</th>
</tr>
</thead>
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<tr>
<td>F. Ctrl</td>
<td>44.8 (1.90)</td>
<td>47.6 (0.73)</td>
<td>54.7 (9.3)</td>
<td>13.7 (8.67)</td>
<td>13.3 (5.39)</td>
<td>4.8 (5.04)</td>
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<td>52.3 (8.4)</td>
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<td>27.3 (15.98)</td>
<td>16.0 (10.00)</td>
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<td>15.8 (6.32)</td>
<td>6.5 (2.07)</td>
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<td>Pst Xtn</td>
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<td>46.2 (1.5)</td>
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<td>8.0 (5.70)</td>
<td>10.6 (8.00)</td>
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</table>

<table>
<thead>
<tr>
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<th>C-Sens (SD)</th>
<th>C-Aff (SD)</th>
<th>C-Pvas (SD)</th>
<th>Ac-Sens (SD)</th>
<th>Ac-Aff (SD)</th>
<th>Ac-Pvas(SD)</th>
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<td>46.7 (21.4)</td>
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<tr>
<td>Pst Xtn</td>
<td>0.34 (0.15)</td>
<td>0.17 (0.08)</td>
<td>62.6 (11.1)</td>
<td>0.22 (0.11)</td>
<td>0.12 (0.15)</td>
<td>60.8 (21.2)</td>
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</table>

Table 7.2 Means and standard deviations (SD) for information collected before and in between PET scanning. PH=the temperatures delivered as painful hot in degrees Celsius, NPH=the temperatures delivered as non-painful hot, State-A=State anxiety, Trait-A=Trait anxiety, BDI=Beck Depression Inventory, C-Sens=McGill Sensory score for the patients' own background pain, C-Aff=McGill Affect score for the patients' own background pain, C-Pvas=Visual analogue score for the patients' own background pain, Ac-Sens=McGill Sensory score for the induced acute pain, Ac-Aff=McGill Affect score for the induced acute pain, Ac-Pvas=Visual analogue score for the induced acute pain.

Table 7.2 shows the data acquired from the three pain groups studied (chapters 5, 6 and 7) and from the female controls (chapter 3). Comparisons with the control group and within group comparisons are included in the relevant chapters. For the post extraction patients studied here, it can be seen from table 7.2 that the extraction pain affective score is lower than the extraction sensory score (t=3.93, p<0.01), and that the induced thermal pain sensory score is lower than the extraction sensory score (t=3.5, p<0.05). In addition there was a trend towards a lower affective than sensory score for the induced thermal pain (t=2.48, p=0.056). There was no significant difference between the affective rating of the post extraction pain and the induced acute pain.

There were no significant differences between the post extraction group and the female controls for all of the questionnaire data collected. As expected, age was significantly higher in the control group (t=7.76, p<0.001).
Figures 7.4 through to 7.11 display graphically all the questionnaire data collected from the 4 groups studied. In summary, it can be seen that the AFP patients had the most disturbed psychological profile, being both more depressed and anxious than the other groups studied, and generally rated the induced pain as higher in intensity than the other two pain groups despite receiving the lowest temperatures. The post extraction group were the least psychologically disturbed but rated their facial pain very high.
Figure 7.4 The above graph shows the mean temperatures chosen as non-painful hot (NPH) and painful hot (PH) for each group. As would be expected, there is a significant main effect of temperature ($F_{1,40}=73.06, p<0.0001$) indicating that the subjects chose a significantly greater temperature for PH than NPH. The second main effect of group was also significant ($F_{3,40}=10.41, p<0.0001$) indicating that the groups can be differentiated according to the temperatures chosen for PH and NPH. The control group chose significantly higher temperatures than both the AFP and RA group ($t=3.2$ & $t=2.3$ respectively; $p<0.05$) No interaction effects were significant ($F_{3,40}=1.85, p=0.15$).

Figure 7.5. The above graph shows the mean scores from the Beck Depression Inventory (BDI) for all subject groups. Standard deviations are indicated as error bars. A one way ANOVA indicated a significant main main effect of pain group ($F_{3,20}=3.73, p<0.05$). From the figure it can be seen that this effect is almost wholly accounted for by the high AFP score. The AFP patients scored significantly higher than the controls ($t=2.44, p<0.05$), the arthritis patients ($t=2.28, p<0.05$) and were just below significance in comparison with the post extraction patients ($t=2.16, p=0.056$).
Figure 7.6. The above graph shows the mean scores and standard deviations for the state anxiety questionnaire given to all subjects prior to their PET scan. There is no significant effect of group for this measure ($F_{3,20}=2.75$, $p=0.071$).

Figure 7.7. The above graph shows the mean scores and standard deviations for the trait anxiety questionnaire for all groups. As for depression, there is a main effect of pain group ($F_{3,20}=3.34$, $p<0.05$) which is almost wholly accounted for by the large AFP score. The AFP patients scored significantly higher than the controls ($t=3.87$, $p<0.01$), the arthritis patients ($t=3.16$, $p<0.05$) and the post extraction patients ($t=2.29$, $p<0.05$).
Figure 7.8. The above graph shows the mean scores and standard deviations of the visual analogue scale for each of the patient groups suffering chronic pain (the post extraction pain is included as a 'chronic' pain). There is a main effect of pain group ($F_{2,15}=10.52$, $p<0.001$) with both the AFP and the post extraction patients rating their chronic pain significantly higher than the ratings of arthritis pain ($t=4.64$, $P<0.001$ and $t=2.38$, $p<0.05$ respectfully). There is a trend towards higher pain rating of AFP compared with post extraction pain ($t=2.17$, $p=0.055$).

Figure 7.9. The above graph shows the mean scores and standard deviations of the visual analogue scale for each of the groups acute (induced) pain. There was no main effect of group for this measure ($F_{3,20}<1$).
Figure 7.10. The above graph shows the mean MPQ sensory rating for the acute and chronic pains (the female controls obviously have no chronic pain score). There is a significant main effect of group ($F_{2,30}=5.401$, $p<0.01$) indicating that the groups can be differentiated according to the sensory rating of pain. There is, however, no main effect of pain type ($F_{1,30}=1.60$, $p=0.14$) and the interaction effect only approaches significance ($F_{2,30}=2.89$, $p=0.07$).

Figure 7.11. The above graph shows the mean MPQ affect ratings for the acute and chronic pains. There is no main effect of group ($F_{2,30}=1.73$, $p=0.19$) or pain type ($F<1$).
Discussion

<table>
<thead>
<tr>
<th>Region</th>
<th>Female group</th>
<th>AFP</th>
<th>Arthritis</th>
<th>Post extraction</th>
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<td></td>
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</tr>
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Table 7.3 Summary of the PET data collected from each of the groups. Each tick indicates a significant change (increase or decrease) in blood flow at the p<0.001 level for each of the groups studied. A + indicates a significantly larger score than the control score, a 0 indicates no significant difference.

This study has demonstrated central differences between the response of AFP patients to a pain stimulus and the response of post extraction patients. From table 7.3 above it can be seen that the AFP patients showed significant increases in rCBF in the region of the PAG, insula and anterior cingulate cortex which were not significantly increased in the post extraction patients. The fact that the post extraction patients showed similar decreased metabolism in the prefrontal cortex as the other pain groups suggests this is a normal response to phasic pain in the presence of another continual pain.
This may represent a loss of vigilance\textsuperscript{69} or reduced control of the supervisory attentional system during continuous pain\textsuperscript{182}. This may also account for the recently reported poor performance of chronic pain patients suffering high levels of pain on an attentionally demanding task\textsuperscript{257}.

The higher rCBF in the AFP anterior cingulate is more difficult to interpret. In keeping with the earlier discussion, the high anterior signal suggests that this region is the central marker of AFP, a product of the peculiar nature of AFP whereby AFP becomes the 'sink' for all the patients worries and stress. However, it is also possible that the post extraction patients have such intense baseline pain that the cingulate increase in response to the induced pain is minimised. This second conclusion is all the more likely given the larger affective and sensory response to their post extraction pain over and above the induced pain. This is consistent with reports of tonic pain stimuli inhibiting the experience of phasic pain\textsuperscript{208} and may indicate that this psychological phenomenon is mediated by processing in the anterior cingulate cortex. If this is so then the heightened AFP response in the anterior cingulate represents an over responsive pain mechanism, as suggested previously, that suppresses their concurrent experience of facial pain. This is the opposite experience of the post extraction group where the facial pain excludes the induced pain to the hand. This possibility receives support from the fact that the AFP patients rated their AFP as much less bothersome during this experiment than is normally recorded from group studies\textsuperscript{240} and which was evident from the recorded data in the patients' clinical notes. Direct assessments of AFP in the presence of phasic pain have not been completed.

In addition, the interpretation of cingulate as being 'overloaded' by the dental pain implies that pain processing in the cingulate is
lateralised to the left, as discussed earlier. Thus the cingulate may have a specific role in the attentional/motivational processing of painful stimuli which is suppressed during pain modulation.

Decreases in rCBF were far more widespread in the AFP group than the post extraction patients. The decreases in parietal area 40 and posterior cingulate cortex suggest further reorganization of attentional and orientating mechanisms,69 while the decreases in frontal area 32 could relate to alterations in the sensitivity to simple stimulus features of the environment,218,258 which may include pain. Thus, in all, this data emphasises the importance of attentional mechanisms in the regulation of important emotional stimuli as suggested elsewhere.28 In other words, new incoming sensations are dominated by the medial pain system to the exclusion of other sensations, and weighted towards pain experience.

The suggestion that mental disorder is best understood through the consideration of mental functions, such as mood, cognition and perception259 implies that the higher depression and anxiety in the AFP subjects may be a consequence of their failing control over their pain mechanisms rather than part of the causal mechanism itself. This could explain why the arthritis patients despite having severe pain do not show any signs of depression or anxiety, their control mechanisms are presumably still fully operational. The low anxiety and depression in the post extraction patients is not surprising, these subjects were self selecting volunteers and it is unlikely that anxious individuals would have volunteered for such a difficult and arduous experimental procedure. The issue of depressed mood alone and its impact on central pain mechanisms will be considered in future research which is underway by the author. The role of attention in pain is to be examined in the final two studies.
Chapter 8: The impact of morphine on atypical facial pain and post extraction pain: A controlled study

Introduction

Opioid analgesics are often used to relieve moderate to severe pain. In particular, nociceptive pains are generally thought to be responsive to opioids\(^{260}\) though, paradoxically, they have been reported as ineffective in the treatment of dental pain.\(^{124,125,261}\) Opioids are, in contrast, rarely prescribed for idiopathic disorders such as AFP and neuralgias such as trigeminal neuralgia and are claimed to be of little use for these types of disorders.\(^{33,262}\) Recently, however it has become clear that opioids can have an effect on far more pain disorders, particularly the neuralgias, if the dose is adequate and adverse side effects are controlled for.\(^{263}\) It is also widely recognised that the mechanism of analgesia may not be intensity reduction but rather a reduction in affective processes.\(^{33,264}\)

These issues are important in consideration of Seymour's studies of dental pain which mostly employed dihydrocodeine, a weak opioid with bothersome side effects such as constipation, and only recorded limited pain measures.\(^{261}\) As Seymour's work remains the mainstay of opioid research into the control of dental pain, whether or not the bothersome quality of dental pain is susceptible to a higher dose of opiate with more limited side effects remains unresolved.

The differential suppression of the affective processes of pain while leaving sensory processing active has caused some confusion in the interpretation of 'mood changes'.\(^ {265}\) Jadad et al reported that patients who received self paced doses of morphine sulphate never experienced pain relief in the absence of a change in mood and conclude, perversely, that pain relief is therefore not dependent on mood change.\(^ {265}\) However, it is not surprising that patients become
less anxious as their pain eases, but this does not answer the question of what is behind the easing of their pain; a reduction in the sensory or affective mechanisms or both? Jadad et al confuse mood change with an inherent aspect of pain, this thesis has stressed the importance of understanding how these mechanisms interplay, seeing them as inherent to the pain experience.

Studies with $^{11}$C-diprenorphine have shown that opioid binding mainly concentrates in the medial pain system, that is the anterior cingulate cortex, prefrontal cortex, medial thalamus and striatum. A pilot study with morphine and PET monitoring of blood flow has shown that relief from cancer pain correlates with increased blood flow to the prefrontal, anterior cingulate, and insula cortices and caudate and putamen. These changes are more specific than expected from the distribution of opioid receptors and are interpreted as the physiological focus of neuronal networks involved in morphine analgesia, though this is not without controversy. These studies thus emphasise the integrative nature of the opioid system with the pain system in general.

The understanding of prefrontal and anterior cingulate cortex as central regulators of attention suggests that morphine may be limiting the affective or bothersome component of pain via distraction. That is, the patients are no longer bothered by pain because they are in a highly distractable state and able to ignore it. Asking a patient to rate their pain has the effect of drawing it briefly back into conscious focus and thus producing an intensity rating but not an affective response as it does not have time to occur. This interpretation is consistent with reports that morphine disrupts normal cognitive functioning.

In this chapter, the efficacy of morphine analgesia for dental pain was reevaluated, using separate sensory and affective measures,
and contrasted with its efficacy for AFP. Assessments of patients
cognitive ability before and after morphine was made using a
previously validated attentional task based loosely on the Stroop
task. This was carried out as a double blind study. It was
hypothesized that neither the sensory nor the affective component of
AFP would be affected by morphine because the pain is driven by an
internal monitoring system set towards the experience of pain. While
in contrast, it was expected that the dental pain would show a
decreased affective component.

In addition two subjects were recruited for a PET study using
morphine to relieve post extraction pain and an induced pain
stimulus to the hand. Initially it was expected that this would form a
separate study which would complement the clinical and
psychological insight into the effects of morphine with a neurological
understanding. However there were considerable problems in
recruitment and the PET study was abandoned after two subjects.
Data from these two subjects is presented here in preliminary form.
Methods

Subjects

Data were obtained from 31 patients (23 female and 8 male) with a mean age of 35 years (SD 11 years). 11 subjects were AFP patients (mean age 45, range 27 to 59 years) and 20 were post extraction patients (mean age 29, range 20 to 50).

The 11 AFP patients had all suffered chronic idiopathic pain for a duration of at least one year to a maximum of ten years (see table 8.1). None suffered from any kind of mental illness though all were depressed and anxious and many (75%) were taking or had recently taken antidepressant medication. All medication was stopped two weeks prior to the experiment.

The post extraction group consisted of 20 patients suffering from acute postoperative pain (see table 8.2). Of these, one received a proplast insert to augment the lower mandibular border, one had a premolar surgically removed, one had wisdom teeth and a cyst removed and the remainder had wisdom teeth only removed. Twelve were treated under local anaesthetic and eight under a general anaesthetic. Details on the patients age, sex and other relevant information can be found in tables 8.1 and 8.2.

Patients were all fully informed about the purpose of the study and all gave informed consent. The protocol was approved by the ethical committee of the Eastman Dental Hospital where the study took place.

Two further male subjects requiring wisdom teeth extraction, separate from the above clinical study, were recruited for a PET scan at the Hammersmith Hospital (ages, 28 and 39).
Table 8.1 Data for the patients suffering Atypical Facial Pain (n=11, 3M, 8F).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Pain Duration</th>
<th>Pain Description</th>
<th>Last Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>F</td>
<td>40</td>
<td>5 years</td>
<td>Throbbing pain Rt side face radiating to Rt ear, eye &amp; shoulder</td>
<td>30 mg nortriptyline</td>
</tr>
<tr>
<td>UD</td>
<td>F</td>
<td>54</td>
<td>3 years</td>
<td>Dull throbbing left side face, eye, neck &amp; shoulder</td>
<td>30 mg nortriptyline, 1.5 mg fluphenazine</td>
</tr>
<tr>
<td>GK</td>
<td>M</td>
<td>44</td>
<td>5 years</td>
<td>Dull throbbing right floor of mouth</td>
<td>20 mg fluoxetine</td>
</tr>
<tr>
<td>GT</td>
<td>M</td>
<td>47</td>
<td>7 years</td>
<td>Headache, earache, joint pain on Lt side</td>
<td>30 mg nortriptyline</td>
</tr>
<tr>
<td>SM</td>
<td>F</td>
<td>47</td>
<td>1 year</td>
<td>mid-frontal region penetrating Rt eye</td>
<td>none</td>
</tr>
<tr>
<td>TT</td>
<td>M</td>
<td>49</td>
<td>1 year</td>
<td>Throbbing, shooting, Rt side face</td>
<td>none</td>
</tr>
<tr>
<td>JE</td>
<td>F</td>
<td>59</td>
<td>4 years</td>
<td>Dull, occasionally sharp mostly Lt ear</td>
<td>75 mg dothiepin</td>
</tr>
<tr>
<td>PAB</td>
<td>F</td>
<td>48</td>
<td>10 years</td>
<td>Constant pain lower Rt teeth</td>
<td>10 mg cypromine, 1 mg trifluoperazine</td>
</tr>
<tr>
<td>AM</td>
<td>F</td>
<td>27</td>
<td>1 year</td>
<td>Pain Lt ear &amp; under eyes</td>
<td>20 mg nortriptyline</td>
</tr>
<tr>
<td>AG</td>
<td>F</td>
<td>37</td>
<td>4 years</td>
<td>Dull ache Lt cheek radiating to joint and lower face</td>
<td>10 mg codiene, 5 mg diazepam</td>
</tr>
<tr>
<td>ES</td>
<td>F</td>
<td>45</td>
<td>2 years</td>
<td>Pain Lt side face</td>
<td>30 mg nortriptyline</td>
</tr>
</tbody>
</table>

**Design**

This study employed a mixed design, with subjects grouped into either those receiving morphine or placebo. Thus two independent variables were under investigation, drug: morphine versus placebo, and group: AFP versus post extraction pain. Within these groups, pain dimensions were rated according to sensory and affective components and these were timed as pre-drug, at each bolus injection of morphine (every ten minutes: time 1 to time 5 - see figure 8.1), and post drug. The dependent variables for the pain
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Procedure Undertaken</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>F</td>
<td>50</td>
<td>Proplast implant lower border mandible (G.A.)</td>
</tr>
<tr>
<td>FM</td>
<td>F</td>
<td>20</td>
<td>Surgical XLA 38</td>
</tr>
<tr>
<td>PW</td>
<td>M</td>
<td>35</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>SL</td>
<td>F</td>
<td>35</td>
<td>Surgical XGA Lower wisdom tooth</td>
</tr>
<tr>
<td>DB</td>
<td>F</td>
<td>24</td>
<td>Surgical XGA 38,48</td>
</tr>
<tr>
<td>AS</td>
<td>F</td>
<td>24</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>MF</td>
<td>F</td>
<td>28</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>JW</td>
<td>F</td>
<td>48</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>TK</td>
<td>F</td>
<td>28</td>
<td>Surgical XLA 38, forceps XLA 18, 28</td>
</tr>
<tr>
<td>AG</td>
<td>M</td>
<td>27</td>
<td>Surgical XGA 19, 18, 28, 38</td>
</tr>
<tr>
<td>FM</td>
<td>F</td>
<td>34</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>SD</td>
<td>F</td>
<td>21</td>
<td>Surgical XLA 48, forceps XLA 18</td>
</tr>
<tr>
<td>GC</td>
<td>M</td>
<td>22</td>
<td>Surgical XLA 38</td>
</tr>
<tr>
<td>DAS</td>
<td>F</td>
<td>21</td>
<td>Surgical XGA 38, 48, elevation 18, 28</td>
</tr>
<tr>
<td>NS</td>
<td>M</td>
<td>32</td>
<td>Surgical XLA 15 root</td>
</tr>
<tr>
<td>AM</td>
<td>F</td>
<td>27</td>
<td>Surgical XGA 37, 38, 48, elevation 28</td>
</tr>
<tr>
<td>PF</td>
<td>F</td>
<td>25</td>
<td>Surgical XLA 48, elevation 18</td>
</tr>
<tr>
<td>JG</td>
<td>F</td>
<td>22</td>
<td>Surgical XLA 48</td>
</tr>
<tr>
<td>MN</td>
<td>F</td>
<td>24</td>
<td>Surgical XGA 48, elevation 38</td>
</tr>
<tr>
<td>MP</td>
<td>M</td>
<td>34</td>
<td>Surgical XGA 38, 48, elevation 28, 48, cyst enucleation</td>
</tr>
</tbody>
</table>

Table 8.2 Data for the post extraction patients. XLA=extraction under local anaesthetic, XGA=extraction under general anaesthetic. Teeth numbered according to ADA system.

Dimensions were ratings taken for sensory and affective components every 10 minutes (after the initial rating), and after drug administration using verbal analogue scales (VAS - appendix III). A further dependent variable, the modified Stroop task, was used to assess attentional processing before and after drug administration. It was hypothesized that those receiving morphine would become less attentive and hence perform this task slower than those receiving placebo.

The two subjects recruited for the PET study were compared in their response to an intermittent ramp of painful heat and no
stimulus both in the absence and presence of morphine. Thus a number of within subject comparisons were created; painful heat vs no stimulus in the presence and absence of morphine; morphine vs no morphine in the presence and absence of induced pain. A non-stimulus baseline was chosen so as to be able to examine the impact of morphine on post extraction pain in the absence of any other input. McGill and VAS responses were recorded as before.

**Apparatus**

AFP and post extraction pain ratings were obtained using a series of verbal VAS's (appendix III). These self-rating scales were scored from 0, no pain, to 100, the most intense pain imaginable (sensory) or from 0, not bothered by their pain at all, to 100, the most unpleasant or bothersome pain imaginable (affective). The VAS's were supplemented with a 'pain story' adapted from that used by Kupers et al. used to increase the patients' understanding of the sensory and affective aspects of pain by using common everyday illustrations (see appendix VII). The patients grasp of this concept was assessed with a VAS confidence rating from 0, no understanding at all, to 100, complete comprehension (appendix III).

A modified version of the Stroop task was presented to each subject via a Macintosh portable computer and Psychlab™ software. 59 sets of two cards were presented in succession containing randomly allocated numbers of characters incongruent with individual character values (appendix VIII shows examples of the test stimuli used).

Patients were cannulated using either a 21 Y-Can or a small butterfly cannula for drug administration. The patient was monitored throughout using a pulse oximeter. The opioid antagonist naloxone
hydrochloride (400 micrograms/ml) and anti-emetic metoclopramide hydrochloride (10 mg) were continuously available.

Anxiety and depression were assessed using the Spielberger Evaluation Questionnaire (appendix IV) and the Beck Depression Inventory (BDI-appendix V).

PET scans were recorded using the 953B camera described previously. The morphine dose was delivered by an infusion pump Perfusor VI set at a rate of 60ml/hr to deliver 20ml of solution in 20 minutes.

Procedure - morphine trial

All participating subjects were recruited from the Eastman dental Hospital. As previously, the post extraction patients were recruited at the time of their dental review and a special appointment made for their extraction. The AFP patients were contacted by telephone and an appointment organised following a two week washout period during which medication was not taken. All patients were informed on recruitment that the trial consisted of administration of either morphine or placebo in a double blind fashion, and that they would be asked to complete psychological questionnaires before and after administration. After reading the information sheet and asking any questions the subjects were asked to sign a consent form if they were willing to participate.

Initially the post extraction group were recruited from the general anaesthetics surgical ward. Although mostly cases of surgical wisdom tooth removal were used, other cases, a difficult lower premolar root extraction, a wisdom tooth and cyst enucleation and a proplast insertion to the lower mandibular border were also used as those were judged to generate comparable amounts of post-operative pain. The anaesthetist was asked to withhold the routine peri-
operative opioid analgesic fentanyl and, following an erroneously administered analgesic to a recruited subject, the patient's drug chart was marked. Once the operative procedure was complete, the patient was allowed to recover and rated for sensory pain by the use of the VAS. When this rating was consistently 40 or more the drug trial began.

A number of problems with this procedure were noted:-

1) The time for pain to be experienced post-operatively was extremely variable with some patients not feeling any pain more than 3 hours post-operatively. This length of time took the study beyond the hours of surgery and thus it was no longer possible for a qualified anaesthetist to be available and continuation of the trial would have violated the ethical restrictions. In an attempt to decrease the post-operative time before pain, the procedural policy of infusing lignocaine with adrenaline prior to surgery was discontinued. This greatly increased post operative pain, swelling and bleeding in two patients and was thus considered no longer within the ethical guidelines surrounding the study.

2) The patients scheduled for a general anaesthetic were difficult to recruit. This was considered to be because of apprehension of the procedure due to increased anxiety already associated with an overnight stay.

Consequently, patients who agreed to wisdom tooth removal under local anaesthetic were recruited. Where bilateral extractions were required, one side was completed and an appointment scheduled for the other. For the purposes of the trial, the extraction procedure was completed in the morning after which the patient was conveyed to a rest room. When a consistent rating of pain greater than 40 on the VAS was recorded the trial began.
All patients were given a bed in the hospital surgical ward. Once the patients were comfortable they were cannulated by the resident anaesthetist. A pulse oximeter was attached to the index finger of each patient to monitor respiratory and cardiovascular functions. All patients were asked to rate their nausea, drowsiness and depression status using a series of VAS's (appendix III). Escape analgesia (morphine), an opioid antagonist (naloxone) and an anti-emetic (metaclopramide) were made available at this point.

Following completion of the state anxiety inventory the subjects were given the following instructions regarding the modified Stroop task.

'You are about to be presented with a series of playing cards on the screen. You will notice that the cards have numbers arranged in them rather than diamonds, clubs, etc. The cards will always appear in pairs. Your task is to ignore the actual character values and find the card with the most characters in it. Then you should hit the key which corresponds to that greater number.'

Following a practice trial using the first three card pairs and the resolution of any queries, further instructions were given.

'For the actual experiment there will be 59 card pairs including the 3 you have just seen. It is expected that it should take you around 4 minutes to complete. There are no tricks involved, there will always be one card with more numbers than the other and there will never be less than 1 number in either card and never more than 9. Work at your own pace trying to go as fast as you can without making mistakes. Don't worry if you do make a mistake, it doesn't beep or flash or stop it just keeps going and it is important that you keep going as well. Finally, don't worry if you find it difficult or frustrating, you are supposed to!'
The experimenter watched the subject through the first 8 screens to ensure that the subject was working properly through the task, and then moved out of view until the subject had finished.

Upon completion the subjects were informed about the sensory and affective parameters of pain experience. They were told that pain intensity refers to how strong or intense the pain is while affect refers to how unpleasant or bothering the pain is. The subjects were given the pain story and asked to read through it at their own pace and to ask any questions. After this the subjects were asked to rate their confidence for distinguishing affect from intensity, only if the subject was at least 70% confident did the trial proceed otherwise further explanation was given. Current affective and sensory ratings were taken prior to the baseline injection (time 0 see fig. 8.1) of saline.

The ward nurse was given the randomization envelope and instructed to enter the patients name into their relevant patient section (section 1 AFP; section 2 post extraction pain) in the next available space. If so stated in the randomization the nurse was to administer corresponding to 0.15 mg/kg body
ml with saline in a syringe. If the placebo, 20 ml of saline was to be drawn up the experimenters, the clinician involved and to the contents of the syringe. The contents administered gradually. Every ten minutes the injection of 4 ml via the intravenous ses were administered. Following each bolus intensity VAS scores were recorded. This chemically in figure 8.1 overleaf.
of the bolus injections, the attentional task same instructions. Ratings were taken for
nausea, drowsiness and depression using the VAS scales previously described. The cannula was then removed and the patient given tea or coffee if so desired. Before being finally discharged the purpose of the experiment was explained and each subject was requested to complete the state anxiety questionnaire, the trait anxiety questionnaire and the BDI. Patients were then thanked and a taxi organised if they had not already arranged for a friend or relative to collect them. The whole procedure took 2-3 hours.

Procedure - PET study

Wisdom tooth extraction was carried out under local anaesthetic as for the main clinical trial. Following extraction, the two patients used in this study were taken to the Hammersmith Hospital by taxi and the usual procedure for alignment and preparation was followed. The only omission was that subjects did not have to establish a non-painful temperature to the back of the right hand as this was not to be used for this experiment.

The subjects were informed that they were to receive six scans, three of painful hot and three with no stimulus, prior to receiving a twenty minute infusion of either morphine or placebo. The infusion and randomization was prepared in advance by the on site senior registrar in oncology and was measured at 0.15 mg/kg in 20 ml of

<table>
<thead>
<tr>
<th>Baseline</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0min</td>
<td>10 min</td>
<td>20 min</td>
<td>30 min</td>
<td>40 min</td>
<td>50 min</td>
</tr>
</tbody>
</table>

Group 1
Saline Morphine Morphine Morphine Morphine Morphine

Group 2
Saline Saline Saline Saline Saline Saline

Figure 8.1: Schematic representation of drug or placebo administration.
saline. The experimenters, the clinician involved, radiographers and subject were all blind to the contents of the syringe.

Initially, it was expected that the PET study would mirror the clinical study and twelve subjects were planned as a double blind study with placebo. However there was a higher than expected drop out rate, two subjects refused to continue at the mid point of the experiment, and there was far greater difficulty in recruiting patients for this study. In view of these difficulties, the extreme pain experienced by subjects and the extra length of this study compared with the previous dental study, it was decided that the project went beyond the spirit of the ethical guidelines and was abandoned after two subjects. The randomization revealed that both these subjects had received morphine.

**PET data analysis**

The fact that only two subjects completed the experiment limited the analysis that could be carried out. Individual analysis was carried out for pain vs no stimulus across morphine, i.e. three no stimulus and three pain prior to morphine infusion and three no stimulus and three pain following infusion. As the presence or absence of morphine and dental pain is common to both the pain and no stimulus this analysis should reveal only the central effects of induced pain to the right hand. Individual analysis was also carried out for morphine vs no morphine across pain conditions. Again, as the presence or absence of induced pain and dental pain is common to both the morphine and no morphine conditions this analysis should reveal only the central effects of morphine. The two subjects were then combined to examine the effects of morphine on dental pain only and the effects of morphine on induced pain only.
Results

Pain affect and sensory ratings

Figures 8.2 and 8.3, overleaf, show the group results from each recording of the patients sensory or affective AFP rating respectively. Time 1 indicates pre-drug administration, time 2 is the rating following baseline administration of saline, times 3-5 are at each 10 minute bolus injection of either saline or morphine and time 6 is the post drug or saline measure. There is no significant effect of morphine over placebo for the final measure of either sensory or affective pain.

Figures 8.4 and 8.5 show the group results from each recording of the patients sensory or affective post extraction pain rating respectively. Times are as for the AFP ratings. There is a significant effect of morphine as opposed to placebo for both the measure of sensory and affective pain components.

Reaction times

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre RT (SD)</th>
<th>Post RT (SD)</th>
<th>t-value</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Xtn morph.</td>
<td>306.5 (95.9)</td>
<td>287.1 (93.0)</td>
<td>2.51</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post Xtn placebo</td>
<td>301.6 (60.5)</td>
<td>263.6 (43.8)</td>
<td>4.68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AFP morphine</td>
<td>303.2 (70.5)</td>
<td>295.0 (43.3)</td>
<td>0.23</td>
<td>0.83</td>
</tr>
<tr>
<td>AFP placebo</td>
<td>324.4 (112.2)</td>
<td>276.8 (82.7)</td>
<td>4.65</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 8.3. Mean reaction times for completion of the modified Stroop task.

From table 8.3 it can be seen that all groups improved their speed of performance on the Stroop task from their pre experimental attempt to their post experimental attempt as would be expected from practice. This improvement is significant for all groups except the atypical facial pain patients who received morphine. It is also notable that the improvement in speed is attenuated in post extraction pain with morphine. However no between group analysis reached significance.
Figure 8.2 Pain sensory ratings in atypical facial pain patients after morphine and placebo administration. In comparison with placebo morphine did not significantly reduce the final rating.

Figure 8.3. Pain affect ratings in atypical facial pain patients after morphine and placebo administration. In comparison with placebo morphine did not reduce the final rating.
Figure 8.4. Pain sensory ratings in post extraction pain patients after morphine and placebo administration. In comparison with placebo morphine significantly reduced the final rating (P<0.01).

Figure 8.5. Pain affect ratings in post extraction pain patients after morphine and placebo administration. In comparison with placebo morphine significantly reduced the final rating (P<0.05).
Questionnaire scores - from the clinical trial

Figures 8.6-8.9 summarise the results of the questionnaire data.

Figure 8.6. Beck depression scores for both patient groups. The psychological rating from the Beck (page 1) is not significantly different between the two patient groups. However the somatic rating (page 2) is significantly higher (p<0.05) in the atypical facial pain group.

Figure 8.7. Trait anxiety scores for both patient groups. Trait anxiety was significantly higher in the atypical facial pain group (p<0.05).
Figure 8.8. State anxiety scores for both patient groups before (ST1) and after (ST2) morphine. Although state anxiety is decreased for both patient groups following administration of morphine, this decrease is only significant (p<0.05) for the post extraction patients.

Figure 8.9. State anxiety scores for both patient groups before (ST1) and after (ST2) placebo. No significant differences are apparent following administration of placebo.

In summary, only the post extraction group benefitted from morphine in comparison with placebo and this benefit was for both the affective and sensory components of their pain. This effect of
morphine could not be explained by the impact of morphine upon attention which did not statistically differ between the two pain groups. However, it is intriguing to note that only the atypical facial pain patients failed to improve significantly on the attentional task whilst receiving morphine.

Both groups gave comparable ratings for their psychological depression but the atypical facial pain patients scored significantly higher on measures of somatisation and trait anxiety. State anxiety showed a consistent decrease in response to morphine although this was, again, only significant in the post extraction group. State anxiety was not altered by the administration of placebo. This anxiety data is complicated by the fact that the atypical facial pain patients who were to receive morphine began the study by chance with a higher state anxiety than the placebo group. In contrast, the post extraction groups began the trial with similar ratings of anxiety and the morphine group became significantly less anxious.
## PET results

### rCBF Increases

<table>
<thead>
<tr>
<th>Region</th>
<th>n843 morph.</th>
<th>n843 pain</th>
<th>Paired morph.</th>
<th>Paired pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAG</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHG</td>
<td></td>
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<tr>
<td>Thalamus</td>
<td>√</td>
<td></td>
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<tr>
<td>Caudate</td>
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<td></td>
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<tr>
<td>Lentiform N.</td>
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</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A. Cingulate</td>
<td>√</td>
<td>√</td>
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<td></td>
</tr>
<tr>
<td>Post. Cingulate</td>
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</tr>
<tr>
<td>PFC area 9</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
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<td>PFC area 44</td>
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<td></td>
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</tr>
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<td>FC area 32</td>
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<td>FC area 8</td>
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<td>S1,2,3</td>
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### rCBF Decreases

<table>
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<tr>
<th>Region</th>
<th>n843 morph.</th>
<th>n843 pain</th>
<th>Paired morph.</th>
<th>Paired pain</th>
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<td>Insula</td>
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<tr>
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<td></td>
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<tr>
<td>Post. Cingulate</td>
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</table>

**Table 8.4** Summary of the PET results. Each tick indicates a significant response (P<0.001) in the indicated area. Paired morph. = morphine vs no morphine (or vice versa) assessed in the absence of induced pain using both subjects together. Paired pain = pain vs no stimulus (or vice versa) in the absence of morphine assessed using both subjects together.
As PET data were obtained from only two subjects the results are summarised in table 8.4. The full PET data is included as an appendix at the back of the thesis (appendix IX).

**Questionnaire results - for the PET subjects**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Pre morphine</th>
<th>Post morphine</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n683</td>
<td>n843</td>
</tr>
<tr>
<td>State Anxiety</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>BDI</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PVAS induced</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>McGill Aff induced</td>
<td>0.73</td>
<td>0.21</td>
</tr>
<tr>
<td>McGill Sens induced</td>
<td>0.74</td>
<td>0.33</td>
</tr>
<tr>
<td>PVAS Wisdom Teeth</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>McGill Aff Wisdom</td>
<td>0.48</td>
<td>0.29</td>
</tr>
<tr>
<td>McGill Sens Wisdom</td>
<td>0.68</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Table 8.5 shows the results of the questionnaires given to each subject in the PET experiment.

Table 8.5 indicates that subject n683 was clearly not responding to the morphine with analgesia, in fact his pain ratings increased following the administration of morphine. In contrast subject n843 reduced all pain ratings in response to morphine.
Discussion

The results have failed to verify the hypothesis that morphine differentially effects the affective component of pain while leaving the sensory component intact. The post extraction patients showed clear decreases in both their affective and sensory ratings of pain while this effect was not significantly greater than the placebo effect for the AFP patients. As such, the results are at variance with the findings of Seymour\textsuperscript{124} who reported no pain relief for dental patients receiving opioids, Gracely et al\textsuperscript{26} who reported differential suppression of sensory processing during tooth pulp stimulation in the presence of fentanyl and Kupers et al\textsuperscript{33} who reported differential suppression of affective processing in the presence of morphine. However, our results are in broad agreement with Kupers et al\textsuperscript{33} and Arner and Meyerson's\textsuperscript{262} findings that morphine is ineffective in the treatment of idiopathic pain.

Seymour's study of dental pain found increased pain after administration of Dihydrocodeine.\textsuperscript{261} However, Seymour failed to differentiate affective from sensory processing and so may have heightened the possibility of getting a positive response when enquiring as to pain levels. The finding is still puzzling, though, as we have shown here that both aspects of post extraction pain are diminished in the presence of morphine. It is possible that Seymour's hyperalgesia was due to the drugs unwanted side effects such as nausea, drowsiness and grogginess. This is probable as the dose used in Seymour's study was comparatively higher than that used in this study and furthermore, Dihydrocodeine has been shown to metabolise to Dihydromorphine at high concentrations.\textsuperscript{274} Dihydromorphine is suspected to act as an antagonist, therefore making pain worse. It is important when considering which opioid to
employ in the treatment of pain that pain reduction is not at the expense of intolerable and unmanageable side effects.\textsuperscript{263}

It has been suggested that a reduction in the sensory but not the affective component of acute pain by opioids when compared to placebo is associated with a situational context.\textsuperscript{265} Thus, when Gracey et al\textsuperscript{26} administered Fentanyl the placebo effects that reduce unpleasantness may have been partially offset by the dysphoric side effects of anxiety, fear and nausea known to accompany the administration of narcotics to human subjects free of pain.\textsuperscript{275} Furthermore, Graceley’s subjects were all waiting to have oral surgery which is liable to have increased their feelings of stress and anxiety, especially as the experiment involved electrical tooth pulp stimulation. This may explain why Price et al\textsuperscript{264} successfully reduced pain ratings to a thermal pain stimulus applied to otherwise pain free subjects with low doses of morphine. This difference in results is perceived to be due to ‘radically different psychological contexts’, the subjects of the Gracely study were tested while experiencing side effects and just prior to oral surgery, the subjects of the Price study lay on beds in stress free conditions throughout. This in part explains our success in reducing post extraction pain with morphine. Our patients were relaxed and comfortable and the stressful procedure related to their visit (i.e. the extraction) had been completed by the time the drug trial commenced. Moreover as the patients were self selecting it is unlikely that any overtly anxious patients would have volunteered and the administration of morphine in small bolus doses minimised the incidence of adverse side effects.

The finding that the AFP patients showed no improvement over the trial with morphine in comparison with placebo appears to confirm the finding of Kupers et al\textsuperscript{33} who showed morphine to be ineffective for idiopathic pain. However unlike Kupers, it is clear
from figs 8.2 and 8.3 that the placebo was reducing the AFP patients' experience of affective and sensory pain and that this placebo reduction accounts for our lack of significant findings with respect to morphine. Interestingly, the AFP patients showed a marked sensory decrease at the 30 minute point (figure 8.2) in response to the morphine. The total dose administered at this point would have been very small (approx 4mg) and is unlikely to have had any physiological effect on their pain (as indicated by the lack of response in the dental patients at this point). However, the patients are liable to have felt a slight giddiness or nausea, and may have concluded that they were receiving a real pharmacological substance resulting in a heightened placebo response. This is consistent with the general finding of a high placebo responsiveness in this patient population. This finding is also consistent with the hypothesis that AFP is driven by an attentional mechanism which can be displaced once the patient believes he or she is being treated.

It is also notable that the AFP patients were more disrupted in their attentional performance in the presence of morphine than were the post extraction patients. Although this did not result in a significant difference between the groups it is consistent with the hypothesis that the AFP attentional supply is already limited by their overt orientation to incoming stimuli with the expectation of pain or unpleasantness.

As expected, the trait anxiety scores for the post extraction group were significantly lower than the AFP group, this is in keeping with this patient group's general psychological distress. However, from the patients BDI score although it is clear that the AFP patients were particularly concerned with their physical well being, they gave surprisingly low scores of psychological depression. One could summarise this as meaning the AFP patients were at pains to
demonstrate they have a ‘real’ illness and were consciously refusing to admit to any psychological weakness. This was noted as a possibility in chapter 5. Alternatively, it is possible that these patients are overtly anxious without concomitant depression, though this is discordant with our previous findings and other research. 

As the patients for this study included more new referrals, with a shorter history of pain than those from chapter 5, this finding can be explained if depression is seen to develop later in the illness, as a response to a continuously helpless situation. In keeping with the previous discussion of chapter 5, anxiety is more concordant with the understanding of AFP as a response to life stress expressed as facial pain. The tenacity of anxiety in the AFP group is indicated by the fact that while the post extraction group showed a significant reduction in state anxiety following administration of morphine the AFP group did not.

The failure to confirm our initial hypothesis that morphine acts via attention must be balanced against the unexpected finding that when morphine alleviates pain it attacks all aspects of pain. In other words, it is not surprising that we have not confirmed our proposed mechanism for the action of morphine as we have shown morphine to act in a way that was unexpected. The general view that morphine renders pain ‘less bothersome’ is clearly not the generalised action of morphine and needs serious review. However, we provide some evidence that the specific action of morphine in AFP may operate via an attentional mechanism. More patients are required to confirm this and many other variables need further analysis. In particular the patients’ psychological make up needs to be related more closely to the pain ratings to account for the variation in post-operative pain resultant on pre-operative anxiety, and the pain ratings themselves need to be related more closely to the attentional task.
Low levels of pain are unlikely to impinge on a limited resource of attentional capacity and therefore patients with low levels of pain are liable to dilute any effect of morphine releasing this attentional capacity.

The PET results are summarised in table 8.4. Unfortunately, the fact that data were only received from two subjects means that the interpretation of this data must be cautious. Nevertheless, the data does provide some fascinating insights into the central action of morphine. In comparison with earlier studies\textsuperscript{268} there is broad agreement as to the involvement of anterior cingulate and prefrontal cortex as well as insula, caudate and temporal cortex. These effects may not, however, be specific to pain relief as both subjects showed increased rCBF in these areas but only subject n843 gained pain relief.

n843 showed increased rCBF response to morphine in PAG, cerebellum, posterior cingulate and prefrontal areas 9, 10, 45 and 46. The role of the PAG in pain relief is well known and documented earlier, the role of cerebellum and posterior cingulate is much less documented and more difficult to explain. Coupled with the more extensive disruption of prefrontal areas it could represent a generalised disruption of motor coordination and cognition which is not consistent across individuals.\textsuperscript{277} In contrast, subject n683 showed much less prefrontal rCBF increases in response to both morphine and pain which suggests the possibility that he was displaying aspects of internalization characteristic of AFP. His remarkably high affective response to both his own facial pain and the induced pain stimulus adds support to this hypothesis. Thus the 'full response' to morphine may be blocked by the psychological profile of the patient as described for AFP. The lack of any PAG response in this subject suggests that the classic descending analgesic system was either not
operating or was already operating at maximum prior to the infusion of morphine.

The lack of any significant increase in rCBF in the somatosensory cortex for the two individual subjects in response to induced pain was puzzling. As there was no non-painful baseline in this study, a somatosensory increase was expected. However, as discussed in appendix I and chapter 4, the somatosensory cortex is liable to show a decreased rCBF as a consequence of pain anticipation which will weight against any final overall increase, in addition to this effect, the morphine has here been shown to increase rCBF to somatosensory cortex in one subject across pain conditions and in the two subjects combined in response to their dental pain. This was an unexpected effect of morphine and would have had the effect of suppressing the observed somatosensory response in the two subjects separately as individual analysis was performed across morphine conditions. When the subjects were paired and the effect of induced pain compared with no stimulus examined in the absence of morphine a somatosensory response was observed.

This finding suggests a more generalized response to morphine than first anticipated. Important inputs to the PAG have been reported from the frontal and insula cortex, the amygdala and the thalamus as well as the anterior cingulate cortex. Increased rCBF to the PAG were observed earlier in response to a hot stimulus as compared to a warm stimulus (appendix I). This suggests the activation of a pre-emptive analgesic mechanism which begins to operate as stimulus information arises. Given the lack of any PAG response to tonic pain, it seems particularly likely that this operates only in the presence of a stimulus which rises rapidly in intensity. This may suppress the immediate effects of injury and allow escape action to be taken.
Chapter 9: An investigation of central processing with the Stroop task and pain. A within subjects design

Introduction

The understanding of AFP presented here (chapter 5) has emphasised the importance of attentional processing in the experience of chronic pain. Fundamentally it has been argued, here and elsewhere,\textsuperscript{239,280} that if a person’s attention is focused on a potentially painful experience, pain will tend to be perceived more intensely than normal. The converse of this is the well documented phenomenon of distracting attention away from pain\textsuperscript{281,282} which can diminish or abolish the painful experience. In chapter 7 it was suggested that the central correlate of this phenomenon may be the left anterior cingulate cortex.

Many studies attribute the analgesic effect of distraction to the existence of a general purpose attentional system of limited capacity.\textsuperscript{283,284,285,286} According to this viewpoint information being processed in this general system constitutes the contents of the subject’s current conscious awareness. The limited capacity of the system means that a subject’s conscious awareness of pain is reduced to the extent that he or she directs attention to other internal or external events. The effect, however, is limited. Distraction of attention is only effective in abolishing pain if the pain is steady or rises slowly in intensity.\textsuperscript{150} Pain that rises suddenly and sharply is not controllable by distraction, but even pain that rises steadily in intensity can not be controlled indefinitely by distraction. The beneficial effect of experimental distraction, such as viewing slides, begins to fall away after approximately two minutes of stimulation,\textsuperscript{287,288,289} and is no better than control intervention at later ratings.\textsuperscript{290} This suggests that the pain leaks into conscious
attention and rapidly takes over even when actively trying to suppress the sensation.

The intrusive nature of pain is similar to the disruptive effects of divided attention tasks. Many find it difficult to do two things at once, often because of inherent mechanical limitations, such as trying to whistle and sing at the same time, but also because of competition for the limited resource of attention. This is most clearly illustrated during execution of the Stroop task in which subjects are required to name a colour in which words are printed; colour naming is slowed down when the letters to be named spell a colour that is different from that of the letters, for example the word ‘red’ written in green letters. The automatic process of reading takes attentional resource to the detriment of the consciously driven task of naming the colour of the word. The question to be addressed here is whether the functional anatomy underlying attention shows overlap with that of pain.

Many of the subjects and groups reported in this thesis have shown prefrontal increases in rCBF in response to pain. Patients with frontal lobe lesions show poor performance on the Stroop task, classically they perseverate on the word name, unable to ignore it, and continually name the word. Bench et al report increased rCBF in right orbitofrontal cortex, and right prefrontal cortex (area 46/10) in response to conflict blocks of the Stroop task. In addition, Corbetta et al have reported increased rCBF in right dorsolateral prefrontal cortex (area 10) during a divided visual attention task and Petersen et al have reported left prefrontal cortex (area 10/47) for both visual and semantic association tasks. Pardo et al, however, did not report prefrontal activation during their study of Stroop.

Posner has argued that the prefrontal cortex (area unspecified) regulates the attentive state whilst waiting for an
incoming signal. Shallice and Grafman have both argued that the prefrontal cortex initiates switches in behaviour when a novel or changed situation arises, what Shallice has dubbed 'supervisory attention'. All three authors describe the function of prefrontal cortex as mediating the organization of information that is about to come on line, i.e. be consciously acted upon. The area that is broadly considered responsible for the final conscious activity is the anterior cingulate cortex.

Tables 9.1 and 9.2 overleaf illustrate the range of tasks that anterior cingulate is involved in and the range of variation in the position of cingulate activity. Bench et al have suggested that the function of cingulate cortex differs along its length and do not suggest a central site for focal attention as implied by Posner. Certainly, in general, pain activation falls posterior to those activation protocols shown in table 9.1. However, despite the fact that both Pardo and Bench used the same protocol, Pardo's cingulate activation is approximately 20 mm posterior to Bench's. In addition, Pardo's cingulate activation is 20 mm anterior to the female volunteers studied here using pain (chapter 3). Also, within the pain studies there is considerable variation in the position of cingulate activity, ranging from 48 mm anterior to 24 mm posterior, a difference of 72 mm in functional activation. Given the spatial resolution of PET, the variability in anatomical morphology and the variation in reported activation sites it is not possible to say that these studies represent the functional heterogeneity of anterior cingulate cortex.

Using an extended scan protocol which allowed the use of sixteen scans to be performed in a single individual, this study investigates the functional anatomy of pain processing and the Stroop task, separately, within each of six individuals. Coregistration with MRI was included to record the degree of morphological variation
Table 9.1. Coordinates of anterior cingulate activations in various PET studies excluding pain.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Activation protocol</th>
<th>Coordinates (mm)</th>
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<tbody>
<tr>
<td>Pardo et al.</td>
<td>Stroop task</td>
<td>X: 10 Y: 19 Z: 30</td>
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<td></td>
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<td>X: 7 Y: 17 Z: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X: 17 Y: 25 Z: 28</td>
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<tr>
<td>Bench et al.</td>
<td>Stroop task</td>
<td>X: 18 Y: 40 Z: 4</td>
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<td></td>
<td></td>
<td>X: 20 Y: 42 Z: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X: 22 Y: 42 Z: 12</td>
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<tr>
<td>Frith et al</td>
<td>Verbal fluency</td>
<td>X: 4 Y: 23 Z: 36</td>
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<tr>
<td></td>
<td>Motor generation</td>
<td>X: -3 Y: 16 Z: 34</td>
</tr>
<tr>
<td>Petersen et al.</td>
<td>Auditory sensory task</td>
<td>X: -12 Y: 34 Z: 18</td>
</tr>
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<td></td>
<td>Visual association task</td>
<td>X: 2 Y: 24 Z: 28</td>
</tr>
<tr>
<td>Corbetta et al.</td>
<td>Divided attention</td>
<td>X: -7 Y: 13 Z: 24</td>
</tr>
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<td></td>
<td></td>
<td>X: -11 Y: 35 Z: 24</td>
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Table 9.2. Coordinates of anterior cingulate activations in various PET studies of pain processing.

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Coordinates (mm)</th>
</tr>
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<tbody>
<tr>
<td>Talbot et al.</td>
<td>Multiple position phasic pain (male volunteers)</td>
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<td></td>
<td></td>
<td>X: -5 Y: -17 Z: 39</td>
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<tr>
<td>Jones et al.</td>
<td>Single position phasic pain (male volunteers)</td>
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<td>Derbyshire et al.</td>
<td>Single position phasic pain (female volunteers)</td>
<td>X: -10 Y: 0 Z: 40</td>
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<tr>
<td></td>
<td>Single position phasic pain (single volunteers)</td>
<td>X: -2 Y: -24 Z: 44</td>
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<td></td>
<td></td>
<td>X: 2 Y: 16 Z: 24</td>
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<tr>
<td></td>
<td></td>
<td>X: -2 Y: -12 Z: 32</td>
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<td>X: 4 Y: 8 Z: 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X: -4 Y: 48 Z: 8</td>
</tr>
<tr>
<td></td>
<td>Single position phasic pain (AFP)</td>
<td>X: 0 Y: -16 Z: 36</td>
</tr>
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</table>

within these samples of anterior cingulate cortex and to more precisely locate the functional overlap of pain and attentional processes. One consideration within the current discussion is the fact that all the Stroop studies have reported right sided cingulate
may be a specific pain attentional/motivational area. From table 9.2 there is a predominant left sided cingulate response to pain, however the majority of subjects were stimulated on the right hand and two subjects did show a right sided (ipsilateral) response. It is not clear at this stage to what extent the cingulate may be lateralised, thus for this study the left hand was used for pain stimulation in order to maximise the possibility of overlap and to further investigate the laterality of cingulate responses to pain.
Methods

Subjects

Six right handed male volunteers (mean age 27, s.d. 5 years) were used for the following study. All subjects gave informed written consent. As for the other studies, this study was approved by the local ethics committee and by ARSAC-UK.

Design

Each scanning session consisted of 16 2min 45secs PET scans. Each scan was separated by 7 minutes to allow decay of radioactivity to <5% of the peak value in the preceding scan. Two heat (one painful heat, one non-painful heat) stimulations and two Stroop tasks were each performed four times during the session. The order of the tasks was randomised to control for systematic changes over time due to factors such as arousal and habituation. The two stimulations produced the first within subject variable, painful heat versus non-painful heat, and the two tasks produced the second within subject variable, incongruent colour words (Stroop) versus congruent colour words (Stroop control). In each Stroop condition the subjects were asked to name the ink colour and ignore the word. The coloured words measured 15-32 mm by 12 mm and were displayed for 1.5 sec with an interstimulus interval of 1 sec. The order of the colours presented was varied randomly within and between each task. This design entailed a direct within subjects comparison of the central effects of attention with those of pain.

Pain quality was measured by the McGill pain questionnaire and intensity via the pain VAS. Anxiety and depression were assessed prior to the scanning session with the Spielberger anxiety scale and the Beck depression inventory.
**Apparatus**

The heat stimuli were all delivered to the back of the left hand using the Marstock thermal threshold stimulator described earlier.

The software to generate and present the stimuli was written by Professor C. Frith (MRC Cyclotron Unit, Hammersmith Hospital, England) in BASIC on a BBC Microcomputer (Acorn computers Ltd., Cambridge, England). The coloured words (Blue, Green, Red or Yellow) were presented on a 12 in. RGB monitor (KAGA Electronics Co. Ltd., Tokyo, Japan) placed approximately 40 cm from each subject. A white cross 5 mm by 3 mm presented 5 mm below the coloured stimulus served as a fixation point. Prior to the scan, examples of the Stroop task were shown using a SPARC 2 workstation (SUN microsystems Europe Inc., Surrey, UK).

PET scans were performed using the ECAT 953B (Knoxville, USA) tomograph, whose physical characteristics have been described earlier. MRI scans were obtained using a 1 Tesla Picker HPQ Vista system described earlier.

**Procedure**

Subjects were prepared for the application of painful and non-painful heat as described previously. In addition subjects were shown an example of the Stroop conflict task (red printed in green, yellow printed in blue and blue printed in red) and it was explained that everyone finds this task challenging and demanding. Each subject was instructed that during the scanning session they would receive four conflict sessions and four congruent sessions and that for each they should concentrate on the colour of the ink, ignoring the word name, and naming the ink colour internally. Mistakes should be corrected quickly.
Each subject underwent 16 sequential scans over the course of a single 3 hour session. Positioning and rCBF measurements were carried out as described previously. Each thermal stimulus and each task was commenced 5 seconds prior to the start of the scan. After each measurement verbal confirmation was obtained that subjects had experienced the stimulus or task appropriately.

MRI scans were acquired for each subject within two weeks of their PET study.

*PET data analysis*

Group analysis and individual coregistrations were carried out as described earlier. Comparisons were made between Stroop and Stroop control tasks and between painful heat and non-painful heat stimulations.
### Results

<table>
<thead>
<tr>
<th>Region</th>
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<td>(BA 24)</td>
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Table 9.3 coordinates of the pixels where the most significant increases in blood flow were identified in each comparison for both stimulation and Stroop comparisons. Coordinates refer to the stereotaxic atlas of Talairach and Tournoux. The Z score is a measure of the degree of significance of the difference and is the number of standard deviations from the mean t-value in the (t) statistical map illustrated in figures 9.1 - 9.4.
Group results

The increases in rCBF seen in the pain activation in comparison to heat and in the Stroop activation in comparison to control are shown in the left hand section of table 9.3 above and illustrated in figures 9.1 and 9.3. The areas activated in common were right insula cortex and anterior cingulate cortex, though this was right sided for pain and predominantly left sided for Stroop. Selective activations were seen for pain stimulation in left insula, bilateral thalamus, bilateral lentiform nucleus, right premotor cortex (Brodman’s area 6, extending to area 4) and right prefrontal cortex (area 9). Selective Stroop activations were seen in left inferior frontal area 45, Wernicke’s area (Brodman’s area 21), premotor area 6 and right inferior parietal area 39. Prefrontal increases were left sided in response to Stroop and right sided in response to pain.

The decreases in rCBF seen in the pain activation in comparison to heat and in the Stroop activation in comparison to control are shown in the right hand section of table 9.3 and illustrated in figures 9.2 and 9.4. The areas of rCBF decrease in common were medial frontal cortex and posterior cingulate cortex. However the medial frontal decreases were more superior for the pain comparison than the Stroop comparison and the cingulate decreases were on opposite sides (left sided pain and right sided Stroop). Selective decreases were seen for the pain comparison in midtemporal area 21, premotor area 6, inferior parietal areas 39 and 40 and anterior cingulate. Selective Stroop decreases were seen in left prestriate area 19 and in right prefrontal cortex areas 9 and 10 and midline area 10.
Figure 9.1 Data averaged from the group of six males. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six males. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The colour scale below reflects the Z value of each pixel in the SPM(t) images only. The areas showing significant increases in blood flow are lentiform nucleus, insula, thalamus, prefrontal area 9, lateral premotor cortex and anterior cingulate cortex.

Figure 9.2 A, as for figure 9.1, B and C with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are premotor, inferior parietal, frontal, temporal, posterior cingulate and anterior cingulate cortices.
Figure 9.3 Data averaged from the same group of six males. A, As for figure 9.1 B, the arithmetical difference between adjusted mean blood flows for Stroop and Stroop control. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The colour scale below reflects the Z value of each pixel in the SPM(t) images only. The areas showing significant increases in blood flow are insula, inferior parietal, prefrontal, temporal, premotor and anterior cingulate cortex.

Figure 9.4 A, as for figure 9.3., B and C with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are prefrontal, posterior cingulate, frontal, anterior cingulate and occipital cortices.
Individual results

The results from the group analysis suggest the possibility that there is functional overlap between pain and Stroop in the anterior cingulate cortex as hypothesized. In order to further investigate this, the results are here extended to single subjects. The variation in position and activation of anterior cingulate cortex will be analysed for each subject.

Table 9.4 displays the maximum Z-score for rCBF increases in anterior cingulate cortex for each subject. In general the single studies bear out the results of the group analysis; there is a tendency towards right sided (contralateral) rCBF increases in cingulate cortex in response to pain and left sided rCBF cingulate increases in response to Stroop; averaging across the coordinates in table 9.4, the x position averages at +3 mm in response to pain, -2 mm for Stroop.

<table>
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Table 9.4 coordinates of the pixels where the most significant increases in blood flow were identified in each comparison for the area of the anterior cingulate cortex. Coordinates refer to the stereotaxic atlas of Talairach and Tournoux. The Z score is a measure of the degree of significance of the difference and is the number of standard deviations from the mean t-value in the (t) statistical map.
the y position +8 mm pain, +7 mm Stroop and the x position +34 mm pain, +34 mm Stroop. However, to a degree, these averages disguise the extent to which the individuals differ in the position of their cingulate activation. For pain, there is a range of 42 mm in the x direction, 62 mm in the y direction and 36 mm in the z direction. For Stroop there is a range of 44 mm in x, 38 mm in y and 20 mm in z. Between the two conditions there is no exact overlap in peak rCBF, the centre of the Stroop cingulate activation always differs from the corresponding subjects pain cingulate activation. However figures 9.5-9.7 show that there is considerable spread and all subjects show at least limited overlap in the region of the cingulate from pain to Stroop. In particular subject n1233 demonstrates considerable overlap between the two cingulate activities while subject n1248 shows virtually no overlap at all. Figure 9.5 illustrates the SPM(t) maps for these two subjects and Table 9.5 lists all the activation sites for these two subjects. Although tables 9.4 and 9.5 indicate little overlap between these two subjects at the maxima of rCBF increase, from figure 9.5 it can be seen that there is considerable overlap in rCBF change between these two subjects.

For the pain comparison, both subjects show increased rCBF in the thalamus (below threshold in n1248), prefrontal cortex (below threshold in n1233), caudate (below threshold in n1248), lentiform nucleus (though significant on opposite sides), insula cortex and ipsilateral anterior cingulate cortex. There are also common subsignificant rCBF increases in contralateral somatosensory cortex.

For the Stroop comparison, both subjects show frontal increases in rCBF, which are more medial and anterior in n1248, and both subjects show anterior cingulate increases, lateralised to the left in n1233.
### Table 9.5 coordinates of the pixels where the most significant increases in blood flow were identified in each comparison for subjects n1233 and n1248 (excluding anterior cingulate cortex shown in table 9.4). Coordinates refer to the stereotaxic atlas of Talairach and Tournoux. The Z score is a measure of the degree of significance of the difference and is the number of standard deviations from the mean t-value in the (t) statistical map illustrated in figure 9.5.

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<th>Region</th>
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<th>y</th>
<th>z</th>
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<td><strong>Pain - left sided rCBF Increases</strong></td>
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210
Figure 9.5 Subjects n1233 and n1248 SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for the conditions indicated (i.e. pain and heat or Stroop and Stroop ctrl). The colour scale is arbitrary, threshold (p<0.05) is indicated by the bottom left hand pixel.

Figure 9.6 As above for subjects n1175 and n1183.
Figure 9.7 As above for subjects n1194 and n1246.

Coregistration

Figures 9.8 and 9.9 show the increases in rCBF for pain and Stroop in subjects n1233 and n1248, respectively, at the level of maximum overlap in rCBF increase within the anterior cingulate cortex. Figure 9.8 indicates that there are two different foci of cingulate activation for this subject in response to pain. The more anterior of the two foci corresponds most closely to the Stroop activation, though this is slightly more inferior for the Stroop condition. Both these sites are close to the area designated 'middle area 24b' by Vogt, and correspond to the central cingulate activation commonly reported with painful stimuli. Figure 9.9 indicates that the pain response for subject n1248 is also close to middle area 24b though it is rather more lateral than expected,
Figure 9.8 Increased rCBF at the level of the cingulate for pain vs heat and Stroop vs Stroop ctrl for subject n1233. The blood flow has been co-registered with the subjects own MRI scan and is shown in three projections, sagittal, coronal and horizontal. The yellow cross indicates the point of maximum rCBF overlap in the cingulate region.

Figure 9.9 As above for subject n1248.
while the Stroop response is more posterior and closer to 'caudal area 24b'. However, this subject has a greater rCBF increase in response to pain in the subcallosal cingulate (area 25) which can be seen in figure 9.10.

The projection of each subject's left medial surface is illustrated in figures 9.10 and 9.11 with the coregistered pain and Stroop rCBF increases respectively. As can be seen, the position of cingulate rCBF increases in response to pain varies from posterior (Brodman's areas 31 and 23 or Vogt's areas 23a and 23b, seen in subjects n1175 and n1246) through anterior (Brodman's area 24 or Vogt's areas 24a', b' and c', seen in subjects n1194 and n1233) to very anterior (Brodman's area 24 or Vogt's areas 24a, seen in subjects n1233 and n1248). In addition, subject n1233 shows an rCBF increase in Vogt's area 23c, n1233 and n1248 show rCBF increase in Brodman's area 25 and n1183 shows no change (though rCBF increases are apparent deep in the right hemisphere, see table 9.4).

Figure 9.11 shows the corresponding cingulate rCBF increases in response to the Stroop task. Again the position varies from posterior (subject n1183) through anterior (All subjects except n1183) to very anterior (subject n1246). In general the Stroop sites are more superior to the pain sites (in the 'c' band of Vogt), n1194 being the main exception.

This process was repeated for the surface of the brain in order to study the varying rCBF of somatosensory cortex as described in chapter 3 and appendix I. Surface projections of rCBF increases in response to pain are illustrated in figure 9.12 while decreases are shown in 9.13. Subjects n1194 and n1233 show increased rCBF in response to pain in somatosensory cortex contralateral to the stimulus, n1194 also shows an ipsilateral decrease. Subject n1183 shows a contralateral decrease.
Figure 9.10 Projections of each subject's left medial hemisphere in sagittal orientation with the rCBF increases in response to pain indicated in red.

Figure 9.11 Projections of each subject's left medial hemisphere in sagittal orientation with the rCBF increases in response to the Stroop task indicated in red.
Figure 9.12 Surface projections of the cerebral cortex for each subject presented horizontally (anterior towards the top of the page). rCBF increases in response to pain are indicated in red.

Figure 9.13 Surface projections of the cerebral cortex for each subject presented horizontally (anterior towards the top of the page). rCBF decreases in response to pain are indicated in red.
Comparing SPM with coregistration

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<td>n1175</td>
<td>n1194</td>
</tr>
<tr>
<td>PAG</td>
<td>s</td>
<td>√</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>s</td>
<td>√</td>
</tr>
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</tr>
<tr>
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</tr>
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<tr>
<td>Primary Motor Cx</td>
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<td>√</td>
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<td>Occipital area 18</td>
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<td>s</td>
</tr>
<tr>
<td>Occipital area 17</td>
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</table>

Table 9.6 Each tick indicates a significant increase in rCBF in response to pain at the p<0.001 level for the SPM or co-registration procedure. An 's' indicates rCBF increase was observed at a sub-significant level. A strike through indicates that the SPM observation was not confirmed by the co-registration. An underline indicates that the area was not first observed with SPM.
Table 9.6 shows the areas of significant and subsignificant rCBF increase in response to pain as indicated by the SPM images and the areas of significant increase as indicated by the co-registration images. Just under 70% of those areas observed as either significant or subsignificant in the SPM were observed as significant in the coregistration. Just under 25% of the areas described as increasing rCBF from the coregistration were not previously described as part of the SPM images. This is, in part, to be expected given the higher resolution and anatomical specificity of MRI and the consequent lesser use of smoothing when preparing PET images for coregistration as compared with stereotactic fitting to the atlas. However, the fact that nearly 30% of all the areas described as increasing rCBF in response to pain were not replicated in the two techniques is of concern and whether these numbers represent refinements or anomalies will be discussed.

Questionnaire results

<table>
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<tr>
<th>Subject</th>
<th>NPH(^0)C</th>
<th>PH(^0)C</th>
<th>Age</th>
<th>State-A. Trait-A.</th>
<th>BDI</th>
<th>Ac-Sens</th>
<th>Ac-Aff</th>
<th>Ac-Pvas</th>
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<td>45.5</td>
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<td>6</td>
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<td>-</td>
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<td>12</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>n1233</td>
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<td>44.5</td>
<td>26</td>
<td>16</td>
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<td>1</td>
<td>0.25</td>
<td>0.27</td>
</tr>
<tr>
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<td>36.0</td>
<td>41.0</td>
<td>22</td>
<td>9</td>
<td>19</td>
<td>2</td>
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<tr>
<td>n1248</td>
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<td>42.5</td>
<td>31</td>
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<td>26.7</td>
<td>7.8</td>
<td>9.8</td>
<td>3.8</td>
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<td>0.11</td>
</tr>
<tr>
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<td>(2.1)</td>
<td>(1.6)</td>
<td>(5.3)</td>
<td>(5.6)</td>
<td>(6.9)</td>
<td>(4.7)</td>
<td>(0.03)</td>
<td>(0.12)</td>
</tr>
</tbody>
</table>

Table 9.7 Information collected before and in between PET scanning. PH=painful hot, NPH=non-painful hot, State-A=State anxiety, Trait-A=Trait anxiety, BDI=Beck Depression Inventory, Ac-Sens=McGill Sensory score for the induced acute pain, Ac-Aff=McGill Affect score for the induced acute pain, Ac-Pvas=Visual analogue score for the induced acute pain.

Table 9.7 shows the results of the questionnaire data collected before and during the PET scan. McGill data for two subjects was not
collected because of subject difficulties in understanding which led to interference with the PET procedure. These results are comparable with those indicated in chapters 4 and 5. Although it is notable that subject n1194 is borderline depressed.
Discussion - group

The main hypothesis of functional overlap in an unspecified area of anterior cingulate cortex is supported by the group results where the central cingulate activation from the Stroop comparison to the Pain comparison only differs by 10 mm in the y direction and 4 mm in the x direction. This Stroop activation site is considerably more posterior than that seen in Pardo et al's and Bench et al's studies and also considerably more superior than that of Bench et al. Thus the first conclusion of this study is to emphasise the danger of assuming heterogeneous function on the basis of variable activation sites. The variation probably being more a product of morphology and as yet unspecified properties of plasticity with respect to location of function. This will be discussed in more detail when considering the individual results.

This activation of midline cingulate cortex during noxious stimulation of the skin confirms the findings of previous reports. The present study also showed an additional site of area 24 (perigenual cingulate) inferior and anterior to the more common midline activation. This area has been seen previously in individual cases but has only been reported as part of a group when comparing heat with warm for the males in appendix I, suggesting an involvement in intensity coding or anticipation. However, a study of an epileptic patient by Bancaud and Talairach suggests that electrical stimulation of perigenual cortex can evoke fear, thus it is possible that this region of cingulate cortex is involved in the affective responses to noxious stimuli while the more superior response is involved in the attentional orientation as indicated by the overlap with Stroop processing. In addition, there were two sites of decreased rCBF in cingulate transition cortex (area 24 becoming area 23). These latter sites may be of particular interest in the PET paradigm where
an individual must inhibit reflexive withdrawal responses to a noxious stimulus of predictable intensity and where visual guidance of the noxious reflex is not relevant to the procedure. Posterior cingulate cortex (area 23) has important connections with areas involved in visuomotor functions, and has been implicated in visual guidance of avoidance behaviours.\textsuperscript{298}

Increased rCBF to the insula, thalamus, lentiform nucleus and prefrontal cortex in response to pain confirms previous reports.

The results from the Stroop part of the study show only limited consistency with previous reports. All reports have indicated the importance of the anterior cingulate cortex, though the precise coordinates of its functional anatomy are disputed. Thus, the interpretation of anterior cingulate cortex as being responsible for the attentionally mediated selection of colour naming versus colour reading is supported by this study. In common with Bench et al,\textsuperscript{68} we report rCBF increases in inferior parietal cortex (area 39) and prefrontal cortex (area 45) and in common with Pardo et al\textsuperscript{67} we report temporal (area 21) and premotor cortex (area 4/6). At odds with both published studies we report insula activation, this area may however be the same as that reported by Pardo et al as 'buried postcentral'. These additional areas indicate that the Stroop task requires an extensive and distributed network of processing centres for stimulus encoding and verbal output. Specifically, the prefrontal and parietal cortex are known to sustain attention,\textsuperscript{299} while the motor cortex is presumably preparing the mouth, larynx, chest, etc for speech\textsuperscript{168} (suppressed in this experiment) and Wernicke's area is tackling the linguistic contradiction of word colour and word name. This contradiction will only be present in the incongruent condition, all other aspects of verbalisation, such as low level stimulus detection, should be consistent for both the congruent and
incongruent words. It is not clear what role the insula may play in this context.

The inconsistencies between the three studies may be explained in part by the differing methodologies. Pardo et al used a display period of 1.3 s, an off period of 0.35 s and a scan procedure lasting 95 s. Thus, during each scan, Pardo presented 58 words which were displayed for a total time of 75 s. Bench et al used a display period of 1 s, an off period of 1 s and a scan procedure lasting 120 s. Thus, during each scan, Bench presented 60 words displayed for a total time of 60 s. In a second experiment, Bench et al replicated the procedure of Pardo et al. During this study a display period of 1.5 s, an off period of 1 s and a scan procedure of 165 s were used. Thus we presented 66 words for a total period of 99 s. In addition, Bench used a series of baseline conditions including crosses, congruent words and neutral words, during two experiments consisting of 6 scans each. (Most of Bench’s significant results came from the comparison of Stroop with crosses.) Pardo et al used only congruent and incongruent conditions, as we did, and only carried out two scans for each subject, one congruent scan followed by an incongruent. Our study involved 16 scans with the Stroop conditions spread randomly throughout. These differences in design are likely to lead to variability in the relative degree of word processing, preparation for or suppression of verbalisation and response selection.

Bench et al report the occurrence of important time effects that had a profound impact on their final results. They observed that rCBF to the prefrontal cortex showed attenuation over time while rCBF to the anterior cingulate cortex showed time related increases. Both these effects reduced the final significance of the results from the cognitive subtraction. These time effects may have been eliminated from our procedure because of the relatively long duration of the
scan and the breaks in between the Stroop tasks, facilitated by the occurrence of an entirely different experience (i.e. pain or heat). Alternatively, as this study employed scanner 953(B), we are liable to have picked up more subtle changes than both Pardo or Bench. Despite these differences, the consistent finding of increased rCBF to the cingulate cortex confirms the importance of this area in selective attention.

Discussion - individual results

Table 9.8 overleaf indicates the areas of rCBF increase in response to pain or Stroop (excluding anterior cingulate cortex responses which are recorded in table 9.4) as indicated on the SPM analysis (figures 9.7-9.9). Overall the table emphasises that beyond the cingulate cortex there is very little functional overlap from the pain condition to the Stroop task, which is not particularly surprising. This finding supports the hypothesis that the neural correlate of distraction resides in the anterior cingulate cortex. However, it is clear that within the cingulate itself there is much room for variability. One reason for this variability may be that attention per se is not that well localised within the anterior cingulate and that attention to response selection - willed or reflex, word processing, motor response may be variably activated and hence produce the variability in location.

Nevertheless, the midline, rostrocaudal section of area 24 (i.e. the superior SPM site) is the most consistently activated area of the cingulate cortex in response to both pain and Stroop, and it is this section which shows the most overlap from the Stroop task to the pain stimulation. Thus this mid-rostrocaudal part of cingulate cortex is the most likely candidate as a generalised attentional processing unit which will have a profound influence in many varied tasks.
including avoidance learning and memory. Three subjects also showed increased rCBF to the very anterior tip of area 24 towards and including area 25 of the cingulate cortex in response to pain. This region has previously been shown to be involved in affective functions. This finding thus suggests that there may be two discrete

<table>
<thead>
<tr>
<th>Region</th>
<th>Group n1175</th>
<th>Group n1183</th>
<th>Group n1194</th>
<th>Group n1223</th>
<th>Group n1246</th>
<th>Group n1248</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF Increases Pain</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>rCBF Increases Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.8 Summary of the PET data for the group and individuals. Each tick indicates a significant increase in rCBF in response to pain or Stroop at the p<0.001 level.

including avoidance learning and memory. Three subjects also showed increased rCBF to the very anterior tip of area 24 towards and including area 25 of the cingulate cortex in response to pain. This region has previously been shown to be involved in affective functions. This finding thus suggests that there may be two discrete
areas of anterior cingulate involved in attention and affect. Finally, there is a confusing array of increases and decreases in the posterior cingulate transition cortex (area 24 becoming area 23). These changes may relate to active avoidance, collateral connections with parietal area 7 suggest a possible network for visuomotor control.

Interestingly, such a network is liable to be suppressed in the current situation which may account for the decreased rCBF observed.

The differences in response in the somatosensory cortex can now be partly explained in terms of the differing self selected temperatures for non-painful hot and painful hot. Subjects n1194 and n1233 both showed increased rCBF in the contralateral somatosensory area. The 'pain window' (difference between painful hot and non-painful hot) was $2.5^\circ C$ for n1194 and $3.5^\circ C$ for n1233, i.e. both subjects fell into the lower pain window which was shown in appendix I to produce rCBF increase. In contrast n1183 showed decreased rCBF in the somatosensory cortex associated with a larger pain window, $4^\circ C$ in this case. However, by such logic we would expect to see an rCBF decrease for n1246 (due to the large pain window of $5^\circ C$) but no significant change was observed. In chapter 4 it was indicated that changes in rCBF may also be related to pain anticipation and associated anxiety, as n1246 reported high trait anxiety but low pain intensity, the lack of change in somatosensory cortex for this subject may represent an interaction effect whereby the patients high trait anxiety led to the selection of a lower pain temperature and thus less anticipation of pain and less associated rCBF decrease.
Discussion - laterality

The group result of increased anterior cingulate CBF in the contralateral, right hemisphere in response to pain confirms what would be expected by classical theory. However, this finding does not support the suggestion of a specialised pain attentional/motivational area in the left cingulate cortex. Of the eight cingulate sites recorded in the comparison of pain with heat (table 9.4) only three were left sided. In addition, the previously reported laterality of the right cingulate during the processing of Stroop has also not been confirmed. Of the ten cingulate sites recorded for the Stroop comparison only five were on the right side. This adds weight to the conclusion that there is no specific pain or attentional 'centre' constant across a population but that there is instead a limited functional variability from individual to individual.

Discussion - comparing stereotaxis with co-registration

Table 9.6 illustrates that 25% of reported rCBF increase are not replicated across both stereotactic fitting to the atlas of Talairach and Tournoux and fitting to the subjects own brain. Given the high fidelity of the subjects own MRI and his anatomy we should expect that the co-registered images represent refinements of the more general picture given by fitting to the atlas. Even so, it is of concern that such a high proportion of the reports of significantly increasing rCBF in the SPM were not confirmed as present in the MRI. Some of this discrepancy can be accounted for by the fact that it is difficult to accurately pinpoint areas in the brain stem on the SPM. However, this still leaves 12% of areas not accounted for in the coregistered images. Equally it is of concern that 24% of the areas reported as significantly increasing rCBF in the MRI were not previously recorded in the SPM even at a subsignificant level. Of all the areas reported,
both significantly and subsignificantly increasing rCBF, 26% (56 regions) are not replicated in the two methods of analysis. Part of this discrepancy will be due to difficulties of interpretation. Where an rCBF site sits between two adjacent areas of cortex a subjective interpretation on the part of the researcher is necessary to decide which area is the 'true' one. Subtle changes in the analysis process may tip the rCBF response into the 'untrue' site. For example, the posterior cingulate activation reported in the coregistration of subject n1183 is likely to have been interpreted as anterior cingulate in the SPM.

In the absence of any 'gold standard' for comparison it is probably better to err on the side of caution and only interpret those areas which are consistently implicated by group studies and give a robust signal in the individual.

**General conclusion**

There is a clear overlap between the attentional processes involved in Stroop and the processes involved in pain in the region of the anterior cingulate cortex in the group study. This confirms the proposed hypothesis and is concordant with the general view that the anterior cingulate is responsible for much on-line processing. This group finding was not confirmed by every subject which suggests a possible additional attentional system. The fact that cingulotomy does not produce the devastating changes that would be expected to occur in response to losing such an important function as on line processing demonstrates that the CNS retains the plasticity to overcome such loss. This plasticity is possibly a consequence of the cingulate only being a part of a distributed network for attention elements of which occur as a part of normal functioning reflected in the varying individual results. However caution is warranted in the
interpretation of the individual results both because discrepancies have been shown between the coregistered results and the SPM results and because this experiment pushed the PET technology to the outer limits of its capabilities. Using 16 runs in a subject necessitated a lowering of radiation dosage per run, and the use of four conditions meant less runs per condition. It is therefore not surprising that the individual results were not as robust as might be ideally expected.
Chapter 10: Conclusions and future studies

What is the neuropsychology of pain?

At the beginning of this thesis it was stated that 'many interacting areas of the brain are involved in the processing of pain... there is no 'pain centre" [p. 30]. It is clear that the concept of a specific pain centre is at variance with the individual results, reported throughout, and the group results summarised here in table 10.1. Such an outcome is not particularly surprising. While it is

<table>
<thead>
<tr>
<th>Region</th>
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<th>rCBF Decreases</th>
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</tbody>
</table>

Table 10.1 Summary of the areas of significant rCBF increase and decrease in response to pain for each of the groups studied. Each tick indicates change significant at the p=0.001 level.
probable that different areas of the brain, beyond the primary sensory areas, are organised into specialised functions, conscious experience is dependent upon the simultaneous functioning of many parts of the brain.\textsuperscript{300,301,302,303,304} Pain signals project to widespread parts of the brain, and it is increasingly evident that virtually all of the brain plays a role in pain. Even seemingly unrelated brain activities such as seeing, hearing and thinking are important in defining the final experience. Seeing the source of injury, hearing the sounds that accompany it, and thinking about the consequences of injury all contribute to the final experience. Moreover, the nervous system is able to form new connections and thereby provide new pathways for sensory input. This plasticity is evident in physiological studies which show that after destruction of fibres to a central neural structure, the branches of the neurons from adjacent areas now dominate the activity of the structure\textsuperscript{305} and in studies of rats which have shown that thalamic nuclei previously unresponsive to pain respond vigorously to nociceptive stimuli following arthritis.\textsuperscript{84}

Nevertheless, there is an apparent core of structures which show consistency across the normal individuals and groups studied. These structures are lentiform nucleus, insula, anterior cingulate cortex and prefrontal cortex (areas 9, 10 or 46). These four areas showed increased rCBF in all normal groups and in approximately 60% of the normal individual subjects studied. Additional neuronal circuits may be activated because of variations in methodology, personality, individual psychology, or social context.

**Variation at the neurological level**

Classical views of nociceptive information processing emphasize the role of the lateral thalamic nuclei and primary and secondary somatosensory cortices in somatotopic localization and intensity
coding of noxious stimuli. In the introduction this view was
callenged because these structures, corresponding to the projections
of the lateral pain system, have no role in affect and learning
processes that mediate long-term avoidance of noxious stimuli. In
contrast, nociceptive neurons in the anterior cingulate cortex have
large receptive fields with little or no somatotopic organization, but
are rapidly adapting and can thus carry out the regulation of
motivational/affective functions. In broad terms this thesis has born
out the importance of the anterior cingulate cortex and thus stressed
the importance of the medial pain system in the processing of acute
pain stimuli. However, it has become increasingly clear that the
somatosensory projection system has a clear role in some aspect of
pain processing, most probably localization although a role in
anticipatory anxiety (appendix I and chapter 4) and even descending
analgesia (chapter 8) cannot be entirely ruled out. This may
eventually transcend our previous dismissal of the lateral system in
pain processing.

It is developing an understanding of the contribution of medial
and limbic structures to pain processing that represents the most
exciting challenge, however. Many areas beyond the anterior
cingulate cortex, most notably prefrontal cortex, insula and PAG, have
been implicated as consistent parts of any pain network. If
processing in the medial pain system is to be understood, a new
conceptual framework is required to resolve the contributions of
limbic structures to attention and affect (i.e., the suffering response
to a noxious stimulus), motor control, and avoidance learning and
memory. There can be little doubt that the failure of classical 'pain'
theories to account for chronic pain syndromes is due to their
attention to structures which have little relevance to affect. These
areas will now be examined in turn.
I. Attention and affect

Neurosurgical lesions are effective in relieving pain when they involve the white matter underlying area 24, however, the midline portion of area 24, often recorded during PET, may not be involved specifically with affective responses to pain. The anterior cingulate cortex is a functionally heterogeneous area, as discussed in chapter 9. This paradox is resolved through an understanding that the loss of affect is indirect, it is related to a loss of attentional resource which makes it easier for the patient to ignore their pain. This explains the emphasis on attentional mechanisms when discussing chronic AFP and RA pain, and may also explain the low affective responses on the McGill pain questionnaire (see table 10.2). This midline portion of area 24 receives bilateral projections from prefrontal area 46 which is, in turn, heavily interconnected with prefrontal area 9. In the discussion of chronic pain processes, area 24 was considered in conjunction with the prefrontal cortex, which also had a significantly elevated CBF in the majority of the pain free volunteers, as contributing directly to attentional control. It has been proposed by Shallice and supported by Frith and colleagues that the prefrontal cortex regulates the intrinsic generation of language or motor schemata. It is possible that the interactions of area 24 and prefrontal cortex are engaged by the subject to mediate the inhibition of pain or motor schemata. This inhibition or 'disengagement' again suggests the reduction of affect following a frontal lesion to be an indirect effect through loss of attentional control and subsequent 'affective flattening' of schematic output.

A direct affective input, which is not consequent on attentional mechanisms, may come via the more anterior section of cingulate cortex and the subcallosal cingulate region (area 25), seen in some of the individual subjects and in the final group study (chapter 9). It is
possible that this region is incorporated in the greater cingulate response seen during the processing of pain in AFP patients (chapter 5). It is also possible that other networks may be involved in the affective processing of pain. Elevated rCBF in the anterior insula in response to pain indicates the insula as a potential candidate. A number of studies have reported on the connections between the insula and cingulate cortex, which suggest pronounced connections with posterior insula and limited connections with the anterior insula and the anterior portion of area 24. It is possible, therefore, that the anterior insula and anterior area 24 are engaged simultaneously in a parallel distributed network involved in affective responses to noxious stimuli.

II. Motor control

An important behavioural aspect of the present PET paradigm is the need to restrain movement in spite of a noxious but bearable somatic stimulus. Motor activity associated with active avoidance and nocifensive responses may be guided by the lentiform nucleus, which fires in expectation of movement. The large projection of anterior cingulate cortex and prefrontal cortex to the neostriatal area suggests that this circuit may also be important for somatomotor function. In addition, nocifensive movements may be guided by sensorimotor associations in area 7b of inferior parietal cortex. Projections of area 7b to area 23 on the cingulate gyral surface and in the cingulate sulcus have been reported. Since posterior cingulate cortex has already been implicated in visuospatial functions including postsaccadic information processing, it is quite likely that posterior cingulate and parietal cortices are involved in visually guided nociceptive responses. In the present experiments, however, the subject was always in a dimly lit room and was required not to make
visually guided movements. The predominant reductions in rCBF in
the posterior cingulate cortex is thus consistent with the hypothesis
that components of processing not engaged during the nociceptive
experience, such as visual processes, are not activated. The confusing
pattern of increase and decrease in the parietal cortex can be partly
resolved if inferior parietal areas 39 and 40 are understood to be
involved in the orientation of attention, which is engaged during the
nociceptive stimulus used here, while area 7 is involved in the
orientation of motor tasks which are not engaged. Areas 39 and 40
show a more consistent increase across subjects and groups while
area 7 shows a more consistent decrease. Furthermore, these three
areas are difficult to disentangle on the SPM{t} images, where
coregistration with MRI is used the situation improves and tends to
confirm the general picture (see for example figures 3.6, 3.10 and
3.12 and table 9.6).

III. Avoidance learning and memory

One of the most uniform effects of cingulate lesions in animal
behaviour is the disruption of active avoidance learning.\textsuperscript{71,72,73} It has
been shown that neurons in rabbit anterior cingulate cortex acquire a
discriminative neuronal response to two different frequency auditory
stimuli before the animals perform the avoidance task at a
behavioural level. This was discussed in chapter 5 as being the
possible neuronal correlate for rapid integration of pain relevant
information and the development of pain schemata.\textsuperscript{25,27,28}
Connections between area 24, the insula and amygdala-hippocampal-
prefrontal circuits are proposed to constitute a network within which
long and short term fear avoidance is regulated. The evidence for this
network is difficult to obtain using PET, both the hippocampus and
amygdala are small structures with many complicated clusters of
nuclei which may produce variable patterns of rCBF increase and
decrease. Such patterns are not likely to be detected in these small
structures using PET. Nevertheless, the predominance of right
prefrontal cortex over the left prefrontal cortex seen in response to
pain does suggest memory retrieval, possibly indicating the
activation of pain related or visuospatial schemata.

A series of neuronal circuits may thus be engaged during
noxious stimulation in a series of parallel distributed networks: 1)
Sensory discrimination in primary and secondary somatosensory
cortices; activation of this region is responsible for reference of a
noxious event to a particular part of the body surface; 2) attentional
and affective responses to pain stimuli involving prefrontal cortex
and midline area 24 with a possible orienting input from inferior
parietal cortex. The anterior section of area 24 and anterior insula
may specifically process pain/suffering responses to noxious stimuli;
3) acquisition of nocifensive responses involving the cingulate motor
areas in area 24, prefrontal cortex with visual guidance from parietal
areas 7 and posterior cingulate cortex; 4) avoidance, and recall of
pain schemata involving amygdaloid-area 24 connections, prefrontal
cortex and hippocampal loops. These various circuits are illustrated
in figures 10.1-10.5.

The degree of overlap between the results reported here and
the results of PET studies using entirely different tasks is
remarkable. Although the matrix of areas activated is unique to pain,
such overlap raises the possibility that many of the activation sites
identified with pain stimuli actually correspond to ancillary
responses such as motor inhibition and spatial orientation. It remains
largely unresolved whether the anatomical overlap of functional
areas indicates that there are similar operations being performed
which are common to the various procedures or whether the areas
contain mixtures of cell groups or layers that exhibit different functions. With such a view it may be suggested that the thalamus is the real 'pain centre' as has recently been discussed\textsuperscript{245} and is suggested by the predominantly thalamic response of the dental patients (chapter 7). However, nociceptive specific neurons have now been identified in cingulate cortex\textsuperscript{74} and the widespread nature of opioid analgesia suggests investigations into other areas of the brain may reveal similar results. Each circuit may form part of a 'multiple draft'\textsuperscript{304} in the process of forming a final experience rather than any one circuit representing the defining moment.

In general, the patients show varying degrees of disturbance in the circuits illustrated in figures 10.1-10.5, the AFP patients have a heightened cingulate response but no prefrontal, the post extraction patients have only a thalamic and lentiform response and the arthritis patients have no statistically significant responses at all.

Circuit 1

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{circuit1.png}
\caption{Localization of noxious stimuli. Th=thalamus; S\textsubscript{1}=Primary Somatosensory cortex; S\textsubscript{2}=Secondary Somatosensory cortex. Arrows represent excitatory connections.}
\end{figure}
**Figure 10.2** Orientation and attention to noxious stimuli. Th=Thalamus; A23=Brodman's Area 23; A24=Area 24; A25=Area 25; PFC=Prefrontal cortex; A40=Area 40 (Inferior parietal cortex). Arrows represent excitatory connections, shaded circles represent inhibitory connections.

**Figure 10.3** The affective response to a noxious stimulus involving the anterior portion of area 24 and insula. Arrows represent excitatory connections; dotted arrows represent weaker connections.
Figure 10.4. Nocifensive response involving cingulate motor areas (A24), prefrontal cortex (PFC) and lentiform nucleus (LN) in the intrinsic generation and preparation of motor commands as well as parietal cortex (A7) and posterior cingulate (A23) for visual guidance (inhibited). Arrows represent excitatory connections, shaded circles represent inhibitory connections.
Figure 10.5 Avoidance and learning. Amy=Amygdala; Hipp=Hippocampus. Arrows represent excitatory connections.

The McGill pain questionnaire

Table 10.2 summarises the data from the McGill pain questionnaire, recorded for six subjects in each group. Each tick indicates that one subject from that group chose that word to describe either the induced pain (indicated in brackets with an 'T' for each patient group) or their own pain where applicable. Taking only those words which received three or more ticks it can be seen that the female group described the phasic pain as a penetrating, burning heat, the phasic group (four subjects from the Stroop experiment, chapter 9, and the two subjects who received left sided stimulation, chapter 3) gave a more elaborate description; describing the pain as
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Table 10.2 Summary of the McGill data received from each subject. Each tick indicates that the word was chosen by a subject to describe either the induced pain (indicated by a bracketed 'I' for each of the patient groups) or their own background pain.
a searing heat which was stabbing, shooting and sharp. In contrast the tonic pain was described as a nagging, stinging and pricking heat. Thus out of the normal groups considered here, only the tonic group indicated any emotional response to the pain. This finding of greater affective response to a continual tonic stimulation is consistent with other reports.

The AFP group described the induced pain in similar terms to the male phasic group, the main difference being that the AFP patients additionally described the pain as tender. This was indicated as surprising in chapter 6 because it was expected that the AFP response to induced pain would be more emotional due to the differential incorporation of pain into their over-active affective channel.\textsuperscript{25} However, if the channel directing their experience of pain is in actuality circuit 2a (figure 10.2) then no increase in affect should be expected. The arthritis group described the pain equally in sensory terms (a throbbing, shooting, pricking, sharp, burning pain), by comparison the post extraction response to the induced pain was slightly subdued, it was only described as a sharp, stinging burning heat.

This is in distinct contrast to the description of their dental pain. The dental pain was described as a pressing, tender ache which was annoying and troublesome and can be compared to the AFP patients description of their facial pain as a pulsing, aching, tender, tight heat which was miserable and nagging. Thus both facial pains produced emotional responses, though the AFP response was less than expected,\textsuperscript{240} suggesting the involvement of circuit 2b. It is possible that circuits 2a and 2b interact to produce differential suppression of different pains. In chapter 7 it was concluded that the AFP pain was inhibited by the experience of phasic pain, whereas the opposite was the case for post extraction pain (i.e. the extraction pain
inhibited the phasic pain. From chapter 9 it appears that this inhibition process takes place via the anterior cingulate cortex, incorporating circuit 2a (figure 10.2). Could the suppression of tonic pain involve decreased rCBF to the cingulate while suppression of phasic pain requires increased rCBF to the cingulate (figure 10.6)? This suggests that the shutting down of a tonic pain is a passive process (circuit 2b goes quiet), whereas the shutting down of a phasic pain is more active (circuit 2b goes quiet under the dominance of 2a).

![Diagram](image)

Figure 10.6 indicates that phasic pain inhibiting (closed circle) tonic pain leads to an inhibition of cingulate rCBF whereas inhibition of phasic pain leads to increased (arrow) rCBF to the cingulate.

Such an interpretation is consistent with the differing psychological profile of the AFP patients as compared to the normals, arthritis patients and post extraction patients. The AFP patients are continuously monitoring and elaborating pain as opposed to letting it slip into the background. The interpretation of the arthritic response is that this shut down process has become an automatic part of the patients control mechanism and is thus spilling over into the experience of phasic stimuli, hence the lack of either circuit at a significant level. Chapter 6 suggested that this process was related to prefrontal activity, through either acceptance or resignation to illness, but not directly influenced by it. Chapter 8 examined whether this attentional process may be modulated by morphine and suggested some evidence that prefrontal response to pain is necessary for morphine to influence pain perception. It is possible that the increased rCBF to anterior cingulate cortex induced by morphine infusion only reduces pain under certain circumstances.
Morphine was not of benefit to the AFP patients possibly because their 'mind-set' is towards illness.

**Variation in the neurotransmitter systems**

Different neurotransmitter systems are thought to reflect different behavioural and cognitive networks. Thus the dopamine pathway is considered responsible for movement disorders, schizophrenia, suspicion, novelty seeking and introversion; the norepinephrine pathway is considered responsible for depression and shyness and the serotonin (5-HT) system is considered also to be responsible for depression as well as aggression, reward dependence and impulsiveness. The opiate system is broadly seen as the pain inhibiting system with concomitant production of euphoria. The complex responses to pain indicate that all these generalizations are simplifications. There are no neurons or neurotransmitters which are indisputably linked to a single, specific psychological experience, and the neurotransmitter systems are clearly inter-related.

The 5-HT system is important in pain responses, primarily the descending opiate system fails in the absence of serotonin. 5-HT systems are also considered important in learning the relevance of aversive stimuli, animals depleted of 5-HT overrespond during extinction. That is, they cannot disengage a learned response. This suggests a possible mechanism of coping with chronic aversion via a kind of disengagement mediated by the median raphe nucleus and projections to the hippocampus. Possibly AFP patients do not have the 'critical mass' of 5-HT necessary to break away from their pain. This would explain both their over-attentive orientation to pain and their lack of response to morphine. One direct implication is that anti-depressives should not be as effective in the control of arthritis pain as for AFP because arthritis pain is driven by a dissimilar
mechanism. The evidence for this is mixed and was discussed in chapter 1. If, during arthritis, the 5-HT system is fully operational, in conjunction with the opiate system which has been shown to increase activity during arthritis,\(^{318}\) then this will inhibit incoming pain signals and may explain the small rCBF response to pain seen with this group.

Chapter 8 provided limited evidence that descending analgesia is dependent on an operational PAG mechanism, however this result is tentative based on only two subjects.

In summary it is suggested that pain is suppressed or maintained by a complex interplay of many differing areas of the brain in conjunction with relevant neurotransmitters. Specifically it is proposed that AFP is associated with 5-HT depletion which enhances the elaboration of pain networks and at the same time inhibits descending analgesia, whilst arthritis is associated with elevated levels of opiates which possibly works in conjunction with 5-HT systems to limit the relevance and elaboration of their pain (through circuits 2a and 4 in particular). Dental pain has shown the beginnings of this 'arthritis response' in that the dental patients showed a distinct decrease in areas of significant activity in response to pain which may be a product of increased opioid release. It is important to note, however, that the study with morphine indicates this response may not be applicable for all subjects. Indeed the large variation of central responses to pain in normal volunteers brings the final question; what makes one person an AFP patient and another a recovered dental patient?

**The contextual or societal variation**

An answer to the above question in terms of the individuals biochemistry has an unfortunate element of circularity: a subject is described as suffering pain, but the description is turned on its head
when the persons' pain is accounted for in terms of their 'predisposition to pain', this reduces to saying pain patients are pain patients. Elaboration with reference to neurobiology and neurochemistry does not improve the argument but merely pushes it further from source. One partial resolution is to say that biochemical levels and neural architecture is set a birth in such a way as to guarantee the later experience of certain disorders or behaviours.\textsuperscript{319} However, such an approach is narrow in its focus. Part of this thesis has argued that the neurology and biochemistry can be virtually the same while the experience is radically different due to the interpretations and expectations of the subject. While variability in CNS responses may give an indication of the underlying mechanisms involved in certain disorders, the view that personality is tied to inherited traits denies the plasticity of the CNS and exaggerates the extent to which neural organisation predetermines behaviour.\textsuperscript{320}

The search for a 'pain centre' is symptomatic of this view and has produced many neurosurgical and neuro-stimulation techniques for pain control. All such techniques have proved at best variable in their usefulness and have often led to a worsening of the patients pain. Furthermore, the theory that there is a computational process in the brain which creates pain independently and passes the information to a centre for consciousness (such as the anterior cingulate cortex) tends towards a dualistic interpretation of consciousness:

'while materialism of one sort or another is now a received opinion approaching unanimity, even the most sophisticated materialists today often forget that once Descartes's ghostly res cogitans is discarded, there is no longer a role for a centralized gateway, or indeed for any functional center to the brain. The pineal gland is not only not the fax machine to the Soul, it is also not the Oval Office of the brain. The brain is Headquarters, the place where the ultimate observer is, but there is no reason to believe that the brain itself has any deeper headquarters, any inner sanctum, arrival at which is the...
necessary or sufficient condition for conscious experience. In short, there is no observer in the brain.' Dennet [p. 106].

There is no one-to-one relationship between neurology and psychological experience in the way suggested by a pain centre. In the thirty years since the publication of the gate control theory of pain many more examples of the complex interlocking of biology, personality and social stress have come to the fore. For example, hypersecretion of cortisol following certain stresses may cause impaired hippocampal 5-HT receptor functioning which may underlie the vulnerability to depression associated with chronic psychosocial distress, whereas hypersecretion of cortisol following surgery may underlie the facilitation of rest and recovery. The individuals involved are likely to be in difficult situations but the depressive's interpretation is liable to be radically different from the surgical patient's. Depending on the situation the outcome of the same biochemical response can be very different. In chapter 5 it was indicated that stress can lead to the development of AFP which can now be suggested to be a specific consequence of the constant priming of circuit 2a (figure 10.2) and elaboration of circuit 4 (figure 10.5). This is not a predetermined outcome, however. Stress can lead to the development of many things (such as aggression, for example) only in certain historical circumstances will it lead to an illness such as AFP. Today using the 'sick role' is seen as the only escape by ever increasing numbers of people. Studying the neurochemistry of such patients will undoubtedly reveal important insights and understanding regarding the workings of the CNS, but on its own it will not provide the full causal framework.
Conclusions and future studies

The main achievement of this thesis has been to illustrate that there are a core of structures which are involved in central pain processing. These structures relate to the medial pain system and are altered to varying degrees in patients with differing pain disorders. This variation is related to a number of neural circuits associated with and directly involved in the processing of pain which may be variously modulated by neurotransmitter concentrations of which the most important are probably opioids and serotonin (5-HT). Not all the circuits may be activated by pain in every subject and seem not to operate in the same manner in every patient. For example, some patients have a clear response to morphine while others do not. In addition it is clear that there is much variation in central responses to pain, part of this variation can be accounted for in the differential use of subsidiary pain mechanisms such as localization. While further sources of variation at the levels of cognition, behaviour and society are discussed. The implication is that patients may be manipulated in their use of pain control mechanisms according to their personal situation, psychological outlook and biochemical set up. There are broadly three questions which future research should address:

1) What effect does variation in applied temperature have on rCBF?
2) Can the central mechanisms outlined in this thesis predict patient outcome in response to pharmacological intervention?
3) Can the central mechanisms be manipulated by changes in the patients outlook, behaviour and social position?

To answer the first question it will be necessary to apply a heat stimulus in stepwise fashion over a series of scans such that the first scan is not at all painful and the final scan is very painful. This
approach has been pioneered with respect to memory and
correlational analysis has highlighted those central structures which
are involved in the rising complexity. Complementary to this
approach could be an experiment in which the subject closes off the
stimulus at just hot, just pain and just tolerable for separate scans.
This will provide images of rCBF change at the borders of
psychological experience and illustrate, for example, whether the
somatosensory cortex really does switch its functioning in response
to pain and/or in response to anticipatory anxiety.

To answer the second question rheumatoid arthritis patients
could be given anti-depressant medication, this would directly
answer the question of whether this form of treatment is less useful
than for AFP as suggested here. However, this approach assumes
arthritis to be a homogeneous pain which it probably is not and so
such a trial should be carried out in conjunction with psychological
profiling with a particular emphasis on pain coping mechanisms.

To answer the third question it will be necessary to extend
cognitive transformation programs to the treatment of AFP, which
has been recently begun, and to study those so treated with the PET
procedure used previously in chapter 5. Spontaneous remissions and
changes in circumstances could also be utilised to further study the
relationship between life events and the onset of AFP or painful flare
ups in RA.

The variability and plasticity of CNS structures dealing with
pain gives hope that the experience of pain may be less limited by
natural constraints than previously believed. Only our own ability
and ingenuity will demonstrate the truth, or otherwise, of this
statement.
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APPENDICES
Appendix I: Sources of variation in response to pain and some problems of methodology

Introduction

Just over half of the studies in this thesis have used male subjects, this is because radiation has special risks with respect to pregnancy. Thus, where females have been employed, they have all been of post-childbearing age. In chapter 3 individual results from five young male volunteers were compared with a group of six older female volunteers. Chapters 5, 6 and 7 involved comparisons of patients which included a mix of males and females. This introduces two important questions, the question of sex differences and age differences in response to pain.

There are many reports in the experimental literature with regard to sex difference in pain response, many of which focus on pain tolerance, but a persistent pattern has not emerged. Older studies tended to find greater pain tolerance for men in response to a variety of pain stimuli, including electric shock, cold pressor and thermal stimulation. Recent studies, however, are more equivocal and often report no differences. Lautenbacher and Strian and Lautenbacher and Rollman have sought alternative explanations and recently suggested that body size or anxiety play an important role in pain perception between the sexes. There are additional differences in skin thickness and subcutaneous fat between the sexes which may contribute to an observed sex difference in pain response. An alternative argument is that the form of pain induction is responsible for the differences. Lautenbacher and Rollman found large sex differences in the perception of electrocutaneous stimulation, replicating the earlier findings of Rollman and Harris. Feine et al, using a smaller heat probe than Lautenbacher, have also
shown large gender effects. It is suggested that differences in spatial summation between the sexes give rise to these gender effects. In addition, animal studies which have found sex differences support explanations of gender effects given in terms of biology. The possibility of a systematic CNS difference in response to pain between males and females would undermine some of the comparisons carried out in this thesis and is therefore worth investigating.

A large number of studies have investigated the influence of age on pain response and the results are equivocal. No change in perceived pain or symptoms with age has been reported for dental pain, decreased pain with age has been reported for chronic back pain and induced pain to the foot, and increased pain with age has been reported for joint disorders due to a combination of more joints being affected as well as increasing pain in those previously problematic. Recent studies with rats support the hypothesis that pain becomes easier to cope with in later life, or at least no more difficult. Other studies suggest a sex by age interaction such that women find pain easier to cope with later in life due to the easing pressures of home and family. This latter finding is important as it suggests that the differential experience of pain across gender may be mediated by psychological and social factors. If sex differences in somatosensory perception can be explained by variables that influence the results in both sexes in a similar way, such as life stress, then no special biological sex variables need be hypothesized.

A further issue is the interpretation of decreases. Throughout this thesis the comparison of heat vs pain has been interpreted as indicating rCBF decreases. However, in the absence of a second baseline, it is not possible to say for sure that such changes are not due to heat specific changes (i.e. increases in response to heat as
opposed to decreases in response to pain). An initial study of acute pain processing in male volunteers by Jones and colleagues did incorporate a second baseline condition, a warm stimulus (as opposed to painful hot and non-painful hot), which was not reported. A second baseline helps in the interpretation of the final results, specifically it can give additional information regarding whether a structure is encoding stimulus intensity or stimulus quality. A steady increase in rCBF from heat to pain would suggest intensity coding, whereas a more sudden intervention of an area suggests a more specific role in registering the changing quality of the stimulus. Furthermore, a second baseline allows an examination of the changes occurring with respect to the control condition. Changes that are interpreted as increases in rCBF in response to the experimental stimulus may be a result of decreases in rCBF in response to the control stimulus. The opposite is also true, changes that are interpreted as decreases in rCBF in response to the experimental stimulus may be a result of control specific increases. Without a second baseline, or any absolute measure of blood flow, there is no means of discriminating these possibilities. This is important as the interpretation of decreases has become of particular relevance in the somatosensory area. However, a second baseline often gives little other information and has recently been suggested to give no information at all, and also reduces the number of available scans for the main experiment, thus reducing the final signal to noise ratio and reliability of the results.

This study investigated the contribution of gender to central pain response via the use of PET with a group of six females and a group of six males. The two groups were not aged matched, the males being younger, thus allowing discussion of age differences. As the male group incorporated a second baseline, the relative merits and
failings of this approach were analysed and discussed.
Methods

Subjects

The six female volunteers used for chapter 3 (mean age 54.6 s.d. 9.3) and the six males used for Jones' study (mean age 35.5 s.d. 9.4) were used for the following studies.\(^\text{19}\)

Design

All subjects were compared in their response to an intermittent ramp of both painful and non-painful heat. All subjects were scanned six times in one single session. The female subjects received three painful hot scans and three non-painful hot scans. A third stimuli was included for the males which was described as warm. Thus the male subjects received two painful-hot, two non-painful hot and two warm scans. No measure of pain response outside the PET camera (such as the McGill pain questionnaire) was included for the male volunteers.

Apparatus

All heat stimuli were produced by a Marstock thermal threshold stimulator described in chapter 3. Scans for all subjects were obtained using the CTI model 931-08/12 Knoxville, U.S.A. PET camera which is described in detail in chapters 2 and 3.

Procedure

Unlike the female subjects, the males did not receive any questionnaires prior to scanning nor during the scan procedure. As well as determining temperatures which were described as painful hot and non-painful hot to the back of the right hand, the male subjects also determined a warm temperature.
All subjects were positioned in the scanner as before and the C$^{15}$O$_2$ scanning protocol employed.

**PET Data Analysis**

Before making any comparisons the procedures of image realignment, stereotaxis and ANCOVA were completed with Gaussian smoothing of 20mm (FWHM) in X, Y, and Z dimensions. The differences between one condition and another were then assessed independently for the two groups, via the appropriate contrasts, using the t-statistic. This analysis yielded two possible comparisons for the females (pain vs heat and heat vs pain) and six possible comparisons for the males (pain vs heat, pain vs warm, heat vs warm and the reverse).

Differences between the two groups were assessed using the two non-painful hot and the two painful hot scans from the males matched at random with two non-painful hot and the two painful hot scans from each of the females. t-contrasts were then applied to assess the difference in rCBF increases due to pain between the males and females. This contrast was applied in the same way as that described in chapter 5 for females vs AFP.
Results

The comparison of rCBF changes in response to pain and heat in the female controls

These results are presented in chapter 3. See table 3.1 and figures 3.1 and 3.2.

The comparison of rCBF changes in response to pain, heat and warm in the male controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
<th>Region</th>
<th>Co-ordinates</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentiform N. 24</td>
<td>-2 8</td>
<td>3.210</td>
<td>Occipital Cx 54</td>
<td>-80 4</td>
<td>3.249</td>
</tr>
<tr>
<td>Caudate/insula</td>
<td>24 20 12</td>
<td>3.512</td>
<td>(BA 19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal Cx (BA 44/45)</td>
<td>18 34 16</td>
<td>3.179</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf. Parietal (BA 39)</td>
<td>-58 28</td>
<td>3.109</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A1.1 within group comparison of pain vs non-painful heat in the male controls.

Pain vs Heat

Table A1.1 shows the areas of significant rCBF increase and decrease in response to pain in comparison to non-painful heat. These changes are displayed as SPM(t) in figures A1.1 and A1.2. Increased rCBF is observed in contralateral PHG, thalamus, lentiform nucleus and anterior cingulate cortex. Ipsilateral increases can be
Figure A1.1 Data averaged from a group of six males. At the top are transverse images of the brain after stereotaxic normalization, with the distances from the AC-PC plane indicated. A, Anatomical features obtained by averaging all blood flow scans from the six males. B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a $P<0.001$ ($Z$ threshold 3.09). The areas showing significant increases in blood flow are lentiform nucleus, caudate, insula, prefrontal areas 44 and 45, parietal area 40 and anterior cingulate cortex.

Figure A1.2 A, as for figure A1.1., B and C with reversed contrasts to give decreases. The areas showing significant decreases in blood flow are frontal cortex, occipital cortex and inferior parietal cortex.
seen in lentiform nucleus, caudate, insula, prefrontal cortex (areas 44 and 45) and inferior parietal cortex (area 39). In addition there are subsignificant increases in bilateral prefrontal cortex (areas 9 and 10).

**Heat vs Pain**

Throughout this thesis 'heat vs pain' has been interpreted as indicating decreases in rCBF in response to pain. The possibility that this comparison represents heat specific changes (i.e. increases in rCBF in response to heat but not pain) has been discounted. Because of the inclusion of a second baseline with this male group this interpretation can be more thoroughly investigated.

From table A1.1 rCBF can be interpreted as decreasing in contralateral frontal cortex (areas 10 and 32) and inferior parietal cortex (area 40) and bilateral occipital cortex (areas 18 & 19). In addition from figure A1.2 it can be seen that there is a subsignificant decrease in the region of the contralateral somatosensory cortex. These decreases can be considered further in the light of the final comparison.

**Non-painful hot vs warm.**

Table A1.2 (overleaf) shows that contralateral heat specific increases occur in PAG, thalamus, the inferior portion of anterior cingulate cortex, the prefrontal cortical strip running from area 44 to area 10 and inferior parietal cortex. These increases are presented as SPM(t) in figure A1.3.

The increase in anterior cingulate cortex does not show any overlap with the increase seen for pain vs heat (fig. A1.1) and the increases in prefrontal cortex are on the opposite (left) side, suggesting these changes to be heat specific. The thalamic rCBF...
Table A1.2 within group comparison of non-painful hot vs warm for the male controls.

<table>
<thead>
<tr>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male controls</td>
<td>-8</td>
<td>-22</td>
<td>-16</td>
<td>3.952</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-16</td>
<td>-22</td>
<td>4</td>
<td>3.481</td>
</tr>
<tr>
<td>Anterior cingulate (BA 24)</td>
<td>-10</td>
<td>26</td>
<td>4</td>
<td>3.422</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>-44</td>
<td>34</td>
<td>12</td>
<td>3.512</td>
</tr>
<tr>
<td>(BA 44, 45, 46 &amp; 10)</td>
<td>-50</td>
<td>-46</td>
<td>40</td>
<td>3.229</td>
</tr>
<tr>
<td>Inf. parietal cortex (BA 40)</td>
<td></td>
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</tbody>
</table>

increase is in the same position as the thalamic increase in pain vs heat, suggesting that CBF increases to the thalamus are related to intensity or possibly anticipation of pain.

Overlap with the heat vs pain comparison can be seen in the inferior parietal area suggesting a pain specific decrease.

Figure A1.3 A, as for figure A1.1., B, the arithmetical difference between adjusted mean blood flows for non-painful hot and warm stimuli. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a P<0.001 (Z threshold 3.09). The areas showing significant increases in blood flow are PAG, thalamus, anterior cingulate, prefrontal cortex and inferior parietal cortex.
The comparison of rCBF increases in the females with increases in the males in response to painful heat compared with non-painful heat.

From figures 3.1 and A1.1 several differences between the female response to pain and the male response appear to be apparent. The similarities and differences are summarised in table A1.3.

Differences are most apparent in the region of the brain stem, stretching from the PAG to the thalamus and caudate. However, none of these differences were shown to be significant when applying between group contrasts at a p<0.001. Only at the lowest available threshold (P<0.05) did any significant differences appear. These differences are illustrated in figure A1.4 which show the difference between the two groups as an SPM(t).

<table>
<thead>
<tr>
<th>Region</th>
<th>rCBF Increases</th>
<th>rCBF Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>PHG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentiform Nucleus</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ant. Cingulate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post. Cingulate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal area 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal area 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal area 44</td>
<td></td>
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<tr>
<td>Prefrontal area 45</td>
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</tr>
<tr>
<td>(Prefrontal cortex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal area 32</td>
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<td></td>
</tr>
<tr>
<td>Inf. Parietal area 39</td>
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<tr>
<td>Inf. parietal area 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital cortex</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A1.3 Each tick indicates a significant change (increase or decrease) in rCBF at the P<0.001 level for the male and female within group comparisons presented separately.
Figure A1.4 A, Anatomical features obtained by averaging all blood flow scans from the six females (A.f) and six males (A.m). B, the arithmetical difference between adjusted mean blood flows for painful hot and non-painful hot stimuli assessed between the two groups. C, The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for each of the two conditions x group. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D, The orthogonal projections of the statistical comparison at a P<0.05 (Z threshold 1.69). Significant differences can be seen in the region of PAG, temporal cortex, prefrontal cortex and inferior parietal cortex.

The illustration confirms the impression of table A1.3 showing increased rCBF in the females over and above the males in the PAG, frontal area 32 and bilateral prefrontal cortex (areas 9 and 10). However, there is also increased rCBF in the females in Wernicke’s area (temporal area 22) and subsignificant increases in the thalamus which are more difficult to explain.

The low level of significance required to demonstrate difference between the two groups means that differences are bound to arise merely on the basis of chance alone. This has been demonstrated statistically\(^\text{?1}\) and is illustrated here in figure A1.5 which shows the comparison of two groups of six subjects chosen at
random from the six males and six females meaning that any differences must be a product of chance effects. Following exactly the same procedure for analysis this comparison yielded significantly different responses in frontal, temporal and posterior cingulate cortices.

![Figure A1.5](image)

**Figure A1.5** A, the arithmetical difference between adjusted mean blood flows for painful hot vs non-painful hot assessed between two random groups. B. The SPM(t) values derived from the formal pixel by pixel comparison of the adjusted mean blood flows and variances for the condition x group interaction. The colour scale is arbitrary, threshold significance is indicated by the lower left pixel for each plane. D. The orthogonal projections of the statistical comparison at a P<0.05 (Z threshold 1.69). 'Significant' differences can be seen in frontal, temporal and posterior cingulate cortex.

*Further investigation of somatosensory activation*

From the results of chapter three and the studies reviewed here it is clear that there is some variation with somatosensory cortex rCBF. Two of the subjects reported earlier showed increased rCBF in the somatosensory cortex while a third subject showed subsignificant decreases. The male subjects reported here also show rCBF decreases in the somatosensory cortex.
Increased rCBF in somatosensory cortex has been interpreted as a consequence of variation in sensory discrimination or individual response possibly related to anxiety. However the male group showed subsignificant increases in somatosensory cortex in response to heat and decreases with painful stimulation. This suggests a specific switching down of somatosensory rCBF in response to pain.

Thus one explanation of the variable somatosensory response across the groups might be the difference in the intensity of the stimulus received. The average difference in temperature between the painful-hot and non-painful hot for the males was $6.54^\circ C$ (SD $1.98^\circ C$) while for the females it was $2.82^\circ C$ ($1.27^\circ C$). This difference is significant ($t=3.88 \ p<0.01$). This result suggests that as the heat difference becomes larger, somatosensory rCBF decreases. This hypothesis was investigated further by splitting the twelve male and female subjects into three groups of four based on the size of their heat difference as illustrated in figure A1.6.

![Figure A1.6](image-url)

*Figure A1.6* Each stimulus ramp began at $25^\circ C$ and increased to a maximum temperature which varied according to the scan type (painful or non-painful heat) and individual perception. The above illustration shows the variation in the peak painful-hot and non-painful hot for the three derived groups of four.
The largest heat difference yielded a separation of 7.9\(^{0}\)C, the smallest 2.2\(^{0}\)C with an intermediate difference of 4.3\(^{0}\)C. It is notable that this variation is almost entirely due to the variation in establishing a non-painful hot temperature rather than differences in pain perception across the subjects. These differences in heat application are highly significant (F\(_{2,9}\) = 48.44, p<0.0001).

Each of the three groups of four was investigated for changes only in the somatosensory cortex using the appropriate contrast for the t-statistic for the six conditions. As the search for the somatosensory cortex was constrained by a knowledge of its location, Z scores significant at the P<0.05 level could be accepted as confirming the hypothesis of change in this region.\(^{21}\)

The results of the analyses are illustrated as SPM\(\{t\}\) in figures A1.7 and A1.8. Figure A1.7 shows the increases in rCBF in the region of the somatosensory cortex for the four derived groups. As can be seen rCBF shows a significant increase in the somatosensory cortex only with the smallest heat difference. Figure A1.8 shows the reverse relationship. Decreases in rCBF are apparent with both the larger heat differences.
Figure A1.7 A, C and E indicate the position of somatosensory cortex (circled) on the averaged blood flow images for all runs in all the four subjects. B, D and F show the significant increases in blood flow in response to pain which are circled in the region of the somatosensory cortex. Only the smallest heat difference shows a significant response.

Figure A1.8 A, C and E as above. B, D and F show the decreases in blood flow in response to pain for the region of somatosensory cortex. Both the larger heat differences display increased rCBF in the region of interest.
Discussion

Differences in response between males and females in response to pain have been investigated using PET and yielded differences in the region of the PAG, temporal cortex and frontal cortex. However, caution towards these results is warranted by the comparison of two random groups taken from the total sample of twelve subjects. This comparison yielded significant differences between the two groups in major areas of the brain and indicate the danger of over-interpreting the difference between males and females. In the absence of any hypothesis driven search, unless this sex difference can be validated in a second study its relevance is highly questionable and the PET data is therefore not discussed further.

The large differences in non-painful heat stimuli chosen by the two groups indicate that the female group had a higher pain threshold. This finding is at odds with the published research with a probe approaching the size of the Marstock thermode (2.5 cm²).\(^7,19\)

As indicated in the introduction, age can have a favourable interaction with sex for the experience of pain in women. Where younger women experience greater episodes of migraine, elder women experience less.\(^22\) It may be that the effect of female hormones accounts for this change, though the mechanism of hormonal effect in pain disorders is not understood. Fluid and salt retention, platelet aggregation or change in serotonin or prostaglandin levels could also be responsible.\(^23,24,25\) However, these variables are also known to vary diurnally and diurnal variation has been shown not to affect thermal sensitivity measures.\(^26\) Important lifestyle differences between men and women, which become less important with age, have also been indicated as responsible for differences in biology.\(^27\) These issues are reviewed in chapter 5 in the consideration of AFP. In sum the central differences
demonstrated between men and women in response to pain are small and can be largely explained as a consequence of methodological differences between the male and female study. It is possible that differences between men and women are larger at a younger age when hormonal variations and lifestyle differences are greatest. Hence the older age of the females in comparison with the males in this thesis is fortuitous. In light of these findings the use of older females as a comparison with younger males, used in particular in chapter 7, is considered acceptable with a certain amount of caution.

The comparison of heat with warmth for the male group gave some important insights into the interpretation of rCBF changes in response to pain. The increase in PAG in response to heat suggests that the descending analgesic system begins to operate prior to the actual experience of pain. This is consistent with much experimental evidence which demonstrates that many people involved in serious injury fail to experience any pain at the time of injury nor for several hours afterwards\(^2\) such 'anticipatory analgesia' may explain more anecdotal reports of acts of bravery in the face of hostile conditions and injury. As the male volunteers did not give any ratings of their pain experience it is not possible to compare subjective experience with neural activity in this study. The fact that the thalamus showed significant increases in rCBF in response to heat confirms this structure as being centrally involved in passing all sensory information to the cortex and highlights its possible role in encoding the intensity of a stimulus. However the lack of overlap in the anterior cingulate cortex for these comparisons suggests that this structure could be involved in both intensity coding, as has been suggested elsewhere,\(^2\) and affective processes. The functional heterogeneity of anterior cingulate cortex is discussed in chapters 1 and 9. The increases in prefrontal areas may relate to the intrinsic
organisation of responses to sensorimotor events as has been
suggested by Frith et al.\textsuperscript{23} The fact that this response is contralateral
and the pain prefrontal response is usually ipsilateral suggests that
this activity represents a heat specific increase which may have little
to do with pain processing. It must, however, remain constant as it is
not seen as decrease in response to pain. The observed increase in
inferior parietal cortex can be judged as a heat specific response as it
is subsequently seen as a decrease in response to pain. This may
relate to Posner's orientating response in preparation for an expected
stimulus.\textsuperscript{30}

Apkarian's work with tonic stimulation has led to the intriguing
possibility that nociceptive input to the somatosensory cortex inhibits
neurons which primarily process innocuous inputs.\textsuperscript{31} However, the
results of the subgroup analysis reveal the opposite possibility. The
pain stimuli used here and by others consists of a sharp pain
experience preceded and followed by no input or innocuous (heat)
input. By contrast, Apkarian's pain stimulus was a tonic heat
stimulus. Apkarian's result implies, therefore, that the somatosensory
activation seen in other reports may reflect net activation of non-
nociceptive neurons. This conclusion is not supported by the
separation of the group of twelve into three subgroups of four.
Subgroup 1 had a high heat threshold but barely increased the
stimulus for the experience of pain. Thus this small heat difference
may reflect a larger nociceptive input, the non-painful temperature
bordering close to pain with the painful temperature clearly
breaching pain threshold. The opposite is true of subgroups 2 and 3
with larger heat differences due to a lower heat threshold. Here the
subjects may have experienced a non-pain input as part of the
cognitive subtraction. Thus when the difference between non-painful
hot and painful hot contained less innocuous input the net activation
gave a somatosensory increase, suggesting somatosensory responses to be pain specific.

This suggestion, however, also runs into difficulties as it cannot explain why somatosensory increased its CBF in the comparison of hot with warm stimulation. A recent report suggests that both increases and decreases may be occurring within the somatosensory cortex depending on the region to be stimulated and the level of anticipatory anxiety associated with the experiment. Thus it remains unclear whether the main function of the somatosensory cortex is to register the quality of non-painful stimuli, a function which interferes with the perception of pain and is therefore inhibited in the presence of a painful stimuli, as suggested by Apkarian; or whether the main function of the somatosensory cortex is to register the quality of pain per se, as suggested by Talbot et al. This issue is pursued further in the investigation of tonic pain in chapter 4. What is clear is that the presence of pain is likely to result in a change in rCBF to the somatosensory cortex but the mere presence of pain is not sufficient to predict the direction of the rCBF changes.
References to Appendix I


2. Westcott, T.B., Huesz, L. Boswell, D. & Herold, P. (1977) 'Several variables of importance in the use of cold pressor as a noxious stimulus in behavioural research.' Perceptual and motor skills, 44, 401-402.


### Appendix II. The McGill pain questionnaire

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Appendix III. The visual analogue scales (VAS's) used throughout

1. No Pain to Excruciating Pain
   
2. Not at all Bothersome to Extremely Bothersome
   
3. No Intensity to Maximum Intensity
   
4. Not Drowsy to Maximum Drowsy
   
5. No Nausea to Maximum Nausea
   
6. Not Depressed to Maximum Depressed
   
7. No Confidence to Maximum Confidence
Appendix IV. Spielberger self evaluation questionnaire:
State anxiety

| Name ____________________________ | Date __________ |

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

1. I feel calm ................................................................. 1 2 3 4
2. I feel secure .................................................................. 1 2 3 4
3. I am tense ...................................................................... 1 2 3 4
4. I am regretful ............................................................ 1 2 3 4
5. I feel at ease .................................................................. 1 2 3 4
6. I feel upset ..................................................................... 1 2 3 4
7. I am presently worrying over possible misfortunes ........ 1 2 3 4
8. I feel rested .................................................................... 1 2 3 4
9. I feel anxious .............................................................. 1 2 3 4
10. I feel comfortable ..................................................... 1 2 3 4
11. I feel self confident ................................................... 1 2 3 4
12. I feel nervous ............................................................ 1 2 3 4
13. I am jittery .................................................................... 1 2 3 4
14. I feel "high strung" ...................................................... 1 2 3 4
15. I am relaxed ............................................................... 1 2 3 4
16. I feel content ............................................................. 1 2 3 4
17. I am worried .............................................................. 1 2 3 4
18. I feel over-excited and "rattled" ................................. 1 2 3 4
19. I feel joyful ............................................................... 1 2 3 4
20. I feel pleasant ............................................................ 1 2 3 4
Appendix IV. Spielberger self evaluation questionnaire:

Trait anxiety

Name __________________________________________ Date ____________________

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

21. I feel pleasant .......................................................... ©  ©  ©  ©
22. I tire quickly .......................................................... ©  ©  ©  ©
23. I feel like crying ..................................................... ©  ©  ©  ©
24. I wish I could be as happy as others seem to be .......... ©  ©  ©  ©
25. I am losing out on things because I can't make my mind up soon enough .................................................. ©  ©  ©  ©
26. I feel rested .............................................................. ©  ©  ©  ©
27. I am "calm, cool, and collected" ............................... ©  ©  ©  ©
28. I feel that difficulties are piling up so that I cannot overcome them ©  ©  ©  ©
29. I worry too much over something that doesn't matter ©  ©  ©  ©
30. I am happy ............................................................. ©  ©  ©  ©
31. I am inclined to take things hard ............................ ©  ©  ©  ©
32. I lack self confidence ............................................. ©  ©  ©  ©
33. I feel secure ............................................................ ©  ©  ©  ©
34. I try to avoid facing a crisis or a difficulty ................ ©  ©  ©  ©
35. I feel blue .............................................................. ©  ©  ©  ©
36. I am content ........................................................... ©  ©  ©  ©
37. Some unimportant thought runs through my mind and bothers me ©  ©  ©  ©
38. I take disappointments so keenly that I can't put them out of my mind .................................................. ©  ©  ©  ©
39. I am a steady person .............................................. ©  ©  ©  ©
40. I get in a state of tension or turmoil as I think over my recent concerns and interests ................................ ©  ©  ©  ©
Appendix V. The Beck depression inventory (BDI)

Name: ______________________
Marital Status: ___________ Age: ______
Education : ___________ Sex: ______
Occupation: ______________________

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2 or 3) next to the one statement in each group which best describes the way you have been feeling during the past week, including today. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1 0 I do not feel sad
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4 0 I don't get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything any more.
   3 I am dissatisfied or bored with everything.

5 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel guilty most of the time.
   3 I feel guilty all of the time.

6 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

8 0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9 0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10 0 I don't cry any more than usual.
    1 I cry more now than I used to.
    2 I cry all the time now.
    3 I used to be able to cry, but now I can't cry even though I want to.

11 0 I am no more irritated now than I ever am.
    1 I get annoyed or irritated more easily than I used to.
    2 I feel irritated all the time now.
    3 I don't get irritated at all by the things that used to irritate me.

12 0 I have not lost interest in other people.
    1 I am less interested in other people than I used to be.
    2 I have lost most of my interest in other people.
    3 I have lost all of my interest in other people.

13 0 I make decisions about as well as I ever could.
    1 I put off making decisions more than I used to.
    2 I have greater difficulty in making decisions than ever before.
    3 I can't make decisions at all anymore.

______ Subtotal Page 1 Continued on Back
140 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

150 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

160 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

170 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

180 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

190 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes ______ No ______

200 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

210 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

______ Subtotal Page 2
______ Subtotal Page 1

_________________________
______ Total Score
### Appendix VI. Common abbreviations used

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<td>Acute</td>
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<td>Affective</td>
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<td>Atypical Facial Pain</td>
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<td>Anterior Cingulate</td>
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<td>Beck Depression Inventory</td>
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<td>C</td>
<td>Chronic</td>
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<td>Cerebral Blood Flow</td>
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<td>Cortex</td>
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<td>Pain Visual Analogue Scale</td>
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<td>rCBF</td>
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Appendix VII. The pain story

Please read the following short stories, they should help you understand the distinction between intensity and bothersome:

Mary arrived in Spain for her holiday and immediately went to the beach. The sun was shining brightly and she had to wear her sunglasses to block it out. It was so hot under the sun that Mary was forced into the sea to cool off several times. Mary really enjoyed being in the sun, it made a change from the rain in London.

The next day Mary returned to the beach, there was some cloud overhead which blocked some of the sun's power, but it was still hot. Mary left the beach early because the heat was making her feel sticky and uncomfortable, she spent the rest of the day in the cool shade of a bar.

Mary wasn't bothered by the intensity of the sun on her first day but by the second day, even though the sun was less intense, she wanted to escape from it.

Tommy likes rock music, especially when it is loud, but Tommy's mum cannot stand rock music, even if it is playing softly. Tommy can play his music quietly only if mum is not trying to concentrate. Tommy's mum prefers classical music and when she is in the car she plays it loud to drown out the traffic, classical music irritates Tommy, especially if he is being collected from school!

Tommy enjoys rock music but it bothers his mother, even when the volume is down and the sound less intense. If she is trying to work
then it really annoys her. On the other hand loud classical music makes Tommy cringe but his mother really enjoys it.

Jim suffers pain in his lower back, even though the pain is slight it irritates him all the time and sometimes stops him from doing his job as a milkman and from lifting weights in the gym. Michelle has a lot more pain than Jim, but she manages to do most of the things she has always done and largely the pain doesn't concern her.

Jim is bothered by his pain, even though it is not very intense, because it means he can't do some of the things he used to enjoy. Michelle has a more intense pain than Jim but it does not particularly bother her and she is able to carry on her life as before.

The three stories indicate how intensity can be separated from the bothersome or annoying quality of a sensation. How confident are you now that you can make the distinction between the intense and bothersome qualities of your pain?
Appendix VIII. The playing cards for the modified Stroop task

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Appendix IX. Raw data for the two PET subjects from chapter 8

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Table A9.1 n683 blood flow changes in response to morphine across pain and rest conditions.

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Table A9.2 n683 blood flow changes in response to pain across morphine conditions.
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Table A9.3 n843 blood flow changes in response to morphine across pain and rest conditions.