NEURAL MECHANISMS UNDERLYING PAIN PERCEPTION AND ITS ALTERATION BY CONSCIOUS STATE

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The mystery of pain

Pain has an element of blank;
It cannot recollect
When it began, or if there were
A day when it was not.

It has no future but itself,
Its infinite realms contain
Its past, enlightened to perceive
New periods of pain.

Emily Dickinson

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ABSTRACT (350 words)

Pain perception is highly dependant on the conscious state of the individual and the meaning of the pain. Patients who have pain associated with life-threatening diseases such as cancer may have a heightened state of arousal and focus on their pain, which serves to increase the pain experience. Conversely, professional athletes sustain devastating injuries and continue playing with little or no pain. The studies I have conducted for my Ph.D. have focused on how conscious state alters pain perception, as well as the neural circuitry underlying such modulation.

In separate studies, PET and fMRI were used to examine pain perception. The first study examined the cerebral structures necessary for the conscious experience of pain by administering increasing doses of propofol, a non-analgesic anesthetic. Results revealed that at sedative doses, subjects' pain perception was heightened, with associated increased activation in thalamus and cortico-limbic areas. When subjects lost consciousness and stopped responding to the painful stimulus, pain-evoked activation in thalamus and cortical regions (particularly anterior cingulate cortex (ACC)) was dramatically reduced, whereas cerebellar activation remained intact. The second study assessed the effect of hypnotic suggestions to alter the perceived *intensity* of the sensory-discriminative dimension of the pain experience. Findings revealed that an individual's interpretation of a painful event alters perception, and that the perceptual alteration is subserved by changes in activity in primary somatosensory pathways. The final study investigated the alterations in pain perception in a patient with chronic pain. Data showed that abnormal pain evoked by lightly brushing the skin (allodynia) activated the same cortical neural circuitry as normal pain, demonstrated that whether pain is provoked by normal activation of nociceptive pathways or by central disinhibition of pain pathways through loss of sensory input, there is a signature neural circuitry that corresponds to the conscious appreciation of pain.

Together, these studies demonstrate that there is a complex thalamo-cortical neural circuit that is activated during the conscious appreciation of pain, and that activation within this circuit can be modulated by conscious state, resulting in altered pain perception.

Résumé

La perception douloureuse dépend de l'état de conscience et de la signification de la douleur. Les patients présentant une douleur découlant d'une maladie comme le cancer peuvent montrer une conscience accrue et se centrer sur leur douleur, ce qui en augmente l'expérience. Inversement, les athlètes professionnels peuvent être victimes de blessures dévastatrices et poursuivre leur performance avec peu ou pas de douleur. Les études composant mon Ph.D. se sont centrées sur la modulation de la douleur par l'état de conscience et sur le circuit neural sous-jacent à une telle modulation.

Lors d'études indépendantes les méthodes du TEP et de l'IRMf furent utilisées pour examiner la perception douloureuse. La première étude a examiné les structures cérébrales nécessaires à la perception douloureuse consciente en administrant des doses croissantes de propofol, un agent anesthésique non analgésique. A des doses provoquant la sédation, la douleur était accrue et associée à une augmentation de l'activation du thalamus et des aires cortico-limbiques. A la perte de conscience, l'activité cérébrale associée à la douleur dans le thalamus et les régions corticales (particulièrement le cortex cingulé antérieur (CCA)) était dramatiquement réduite, alors que l'activité du cervelet demeurait intacte. La deuxième étude a évalué l'effet de suggestions hypnotiques pour altérer *l'intensité* perçue de la dimension sensori-discriminative de l'expérience douloureuse. L'interprétation qu'un individu fait d'un événement douloureux en altère la perception. Ces changements perceptuels sont associés à des changements d'activité du cortex somatosensoriel primaire. La dernière étude a examiné les changements perceptuels de la douleur chez une patiente souffrant de douleur chronique. Ces données démontrent qu'une douleur anormale évoquée par le toucher léger (allodynie) active le même circuit neural que la douleur normale. Ainsi, il existe une signature neurale correspondant à l'appréciation consciente de la douleur, peu importe si celle-ci est provoquée par

une activation normale des voies nociceptives ou par une désinhibition centrale des voies douloureuses secondaire à la perte d'input sensoriel.

Ces études démontrent la présence d'un circuit neural thalamo-cortical complexe activé durant l'appréciation consciente de la douleur. L'activation d'un tel circuit peut être modulée par l'état de conscience résultant en l'altération de la perception douloureuse.

Contribution of Authors

Chapter 2 contains a manuscript in preparation entitled "Mechanisms of propofol-induced pain modulation in humans: a positron emission tomography study". I conducted the study, data analysis and manuscript preparation. Drs. Backman, Fiset, Plourde provided patient anesthesia. Dr. Bushnell provided assistance in her capacity as research supervisor.

Chapter 3 contains a published manuscript entitled "Cortical representation of the sensory dimension of pain". I conducted the study, data analysis and manuscript preparation. Dr. Rainville assisted in data collection. Drs. Bushnell, Duncan and Rainville assisted with manuscript preparation.

Chapter 4 contains a manuscript in preparation entitled "Peripheral and central mechanisms underlying allodynia in a nerve injured patient". I collected the psychophysical data, however the fMRI data collection and analysis were conducted with the assistance of Dr. Olausson. Dr. Bushnell assisted throughout the study in her capacity as research supervisor.

Preface

The present work consists of three stand-alone research manuscripts that share a common theme - how pain perception is represented in the human cerebral cortex and altered by conscious state. A general introduction and a general discussion are included at the beginning and the end of the thesis respectively. However, given the manuscript format of chapters 2 through 4, local introduction and discussion sections are also provided in each of those chapters. The purpose of the general introduction and general discussion is to provide the reader with a broader perspective than the often-limited focus of the journal articles. In particular, the general introduction includes a summary of the pain system and functional imaging techniques of the human brain. Similarly, the general discussion avoids redundancies with local chapter discussions and focuses instead on the broader implications of the present work.

Table of Contents

List of Tables

List of Figures

CHAPTER 1 - INTRODUCTION

1.1 Chapter Overview

There is a general agreement as to what we mean by the word "PAIN." Pain is defined by the International Association for the Study of Pain as an "unpleasant, sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage". As such, there should be common physiological, behavioural and autonomic events that accompany this experience. Acute pain is pain that begins suddenly within the intact nervous system and usually lasts for a short duration until healing. It is generally classified along somatic or visceral subdivisions. Somatic pain is well localized, sharp and clearly related to the offending stimulus and can be conveyed along Aδ and C fibres. Visceral pain is caused by distension and ischemia. It is often diffuse, dull, vague, and may be referred to another body site and is transmitted along Aδ and C fibres. But, how is acute pain represented in the brain?

The idea that a pain pathway exists from the site of injury in the periphery to a pain centre in the brain has been pervasive from the time of Descartes through the 20th century. Until a short time ago neurosurgeons were looking for the panacea of pain control, a pathway to cut, which would alleviate their patients' pain indefinitely. With the emergence of the gate-control theory of pain (Melzack & Wall, 1965), this idea began to fade and the notion that pain is a sensation highly amenable to modulation with multiple cerebral representations emerged.

Pain perception is highly dependent on the conscious state of the individual and the meaning of the pain. Beecher described soldiers who had grave injuries, yet felt little pain when the injuries meant they would leave the battle front. The same soldiers showed normal pain reactions to medication injections (Beecher, 1946). Patients who have pain associated with life-threatening diseases such as cancer may have a heightened state of arousal and focus on their pain, which serves to increase the pain experience. Similarly, when the perception of pain changes, acutely or chronically, does the cortical representation of pain change?

The pain experience is a pattern of biological and psychological phenomena so integrated as to constitute a functional unit with properties not derivable by summation of its parts. The emergence of the pain experience, I believe, is the result of a fusion of multiple modules, which comprise a pain network. Pain is an extremely complex experience comprising sensory, affective, autonomic, motor, attentional, descending inhibitory control and memory modules. Consequently, its representation within the brain requires an elaborate architectural hierarchy encompassing a diffuse network of bilateral structures

The studies I conducted have focused on the neural circuitry underlying the conscious appreciation of pain and how conscious state alters pain perception. Using detailed psychophysical examination and non-invasive brain imaging techniques (PET & fMRI), I undertook studies to determine the brain mechanisms responsible for the appreciation of pain as a function of the conscious state of the individual. Three fundamental questions were addressed. (1) What cortical regions are necessary and sufficient for the conscious experience of pain? (2) When the percept of pain changes, is activity in these cortical structures altered or does it remain the same? (3) How does chronic pain change the cortical representation of pain?

The pain experience and pain modulation must be understood within the context of its underlying physiology. I will therefore begin by addressing what is known about the pain system, including its peripheral and central components and endogenous pain modulatory circuits. This will be followed by a discussion of functional brain imaging techniques, namely PET and fMRI. These two techniques allow for a common framework to address the role of conscious state in the modulation of painful experience.

1.2 The Pain System

1.2.1 Peripheral afferent fibres

Primary afferent fibres serve as the transduction mechanism from physical energy into nervous impulse. Cutaneous peripheral afferent fibres can be categorized on the basis of diameter, structure and conduction velocity. Generally, Aβ fibres are large in diameter, myelinated and fast conducting, whereas Aδ fibres are intermediate in diameter, lightly myelinated and of intermediate velocity, and C fibres are thin in diameter, unmyelinated and slowly-conducting (Martin & Jessell, 1991).

All three types of cutaneous afferent fibres are capable of transmitting nociceptive information; however, under normal conditions it is only Aδ and C fibres that convey nociceptive information. The three major types of cutaneous primary afferent fibers, Aβ-, Aδ- and C fibres can be described along functional lines. Aβ fibres subserve touch, mild pressure, vibration as well as the sensation of joint position, Aδ fibres are known to transmit the sensation of cold and pain, whereas C fibres convey both warmth and pain (Martin et al., 1991).

1.2.1.1 Nociceptors

Nociceptors are nerves used for receiving and transmitting painful stimuli. They have been identified within the majority of structures that contribute to pain sensation including the skin (Ochoa & Torebjörk, 1989), muscle (Lewis, 1942), joints (Coggeshall, Hong, Langford, Schaible, & Schmidt, 1983) and viscera (Cervero, 1985). Application of direct mechanical (Burgess & Perl, 1967), thermal (Yarnitsky, Simone, Dotson, Cline, & Ochoa, 1992) or chemical stimuli (Baron et al., 1999) can activate either type of nociceptive primary afferent fibres, Aδ or C. The conscious appreciation of pain involves two components. The thinly myelinated Aδ fibres are responsible for the initial, fast component of the pain experience, perceptually felt as a pricking type of pain (Campbell & Lamotte, 1983; Lewis & Pochin, 1937). The unmyelinated C fibres are responsible for the second, slow component of the pain sensation, experienced as a dull and aching

feeling (Lewis et al., 1937; Price, Hu, Dubner, & Gracely, 1977). Selective blockade of these afferent fibres dissociate the components of the pain experience. Therefore, inhibition of C fibres result in sharp, isolated, punctate pain (Konietzny, Perl, Trevino, Light, & Hensel, 1981) whereas blockade of the Aδ fibres results in burning and dull pain exclusively (Ochoa et al., 1989). Similarly, when a train of 4-8 constant waveform heat pulses is applied to the forearm of human subjects, the pricking first pain mediated by Aδ fibres is suppressed while the aching sensation of the second pain conveyed by C fibres is enhanced (Price et al., 1977). These studies demonstrate that the first and second components of the pain experience can be dissociated.

1.2.2 Dorsal Horn

Dorsal root ganglia contain the cell bodies of the primary afferent fibres. These fibres enter the dorsal horn of the spinal cord by way of the dorsal root. The dorsal horn is divided into laminae based on neuronal function and cytoarchitecture as described by Rexed (1952). These laminae contain the organized termination of primary afferent fibres. Cutaneous unmyelinated nociceptive afferent fibres primarily project to the substania gelatinosa or lamina II with a small number of projections to lamina I and lamina V (Light, Trevino, & Perl, 1979; Woolf & King, 1987). Aδ fibres form abundant connections with lamina I and to a lesser extent laminae II and V (Woolf & Fitzgerald, 1986; Light et al., 1979; Woolf et al., 1987). Aβ fibres synapse with second order neurons in laminae III-IV and to a lesser degree in laminae V (Schneider, 1992; Brown & Fyffe, 1981).

The afferent fibres then synapse on dorsal horn sensory projection neurons, either nociceptive-specific (NS) neurons or wide-dynamic-range (WDR) neurons. NS neurons, as their name implies, convey nociceptive-specific information which they receive from Aδ and C fibres and reside almost exclusively in laminae I-II and to a lesser extent in laminae IV-V (Kumazawa & Perl, 1978; Kumazawa, Perl, Burgess, & Whitehorn, 1974; Willis, Trevino, Coulter, & Maunz, 1974). In

contrast, WDR neurons communicate gentle touch, firm pressure, pinch, and pain by increasing their level of neuronal discharge (Price, Hayes, Ruda, & Dubner, 1978). WDR are located in high concentrations in lamina V and to a lesser extent in laminae I, II, IV, VI and receive afferent input from Aβ, Aδ and C fibres (Price & Mayer, 1975).

1.2.3 Ascending Nociceptive Pathways

Numerous ascending projections send nociceptive information either monosynaptically or polysynaptically to supraspinal targets via pathways in the anterolateral or dorsal quadrants of the spinal cord. Pathways in the anterolateral quadrant include the spinothalamic, spinomesencephalic and spinoreticular tract, whereas pathways in the dorsal quadrant include the spinocervicothalamic tract and the dorsal column postsynaptic pathway.

1.2.3.1 Spinothalamic tract

The spinothalamic tract (STT) is the primary pathway for pain transmission, but it also subserves thermal and tactile transmission (Chung, Kenshalo, Jr., Gerhart, & Willis, 1979; Craig & Kniffki, 1982). Cells of the STT originate in the laminae I, IV and V, decussate in the white commissure and ascend via the anterolateral quadrant (Apkarian & Hodge, 1989a; Willis, Kenshalo, Jr., & Leonard, 1979). As the STT approaches the thalamus, it divides into three parts: lateral, medial, and posterior. The lateral projection originates in laminae I and V and projects to the VPL (ventralposterolateral nucleus), the VPI (ventral posterior inferior nucleus) and the PO_m (medial part of the posterior complex). The medial projection emanates from the dorsal and ventral horn and extends to the CL (central lateral nucleus; Apkarian & Hodge, 1989b; Boivie, 1979). The posterior projection originates in lamina I and terminates in the VM_{po} (Dostrovsky & Craig, 1996a).

1.2.3.2 Spinoreticular tract

Also located in the anterolateral quadrant of the spinal cord is the spinoreticular tract (SRT). Neurons within this tract project from the deep layers of the dorsal horn and layers VII and VIII of the ventral horn (Kevetter, Haber, Yezierski, Chung, & Willis, 1982). They project to the caudal medulla and rostrally to areas including the lateral reticular nucleus and nucleus gigantocellularis (Mehler, Federman, & Nauta, 1960). Neurons within this tract are activated preferentially by noxious stimuli. The primary role of the SRT is thought to be the signaling of homeostatic changes to the brainstem's autonomic centers (Casey, 1969; Casey, 1971; Foote, Berridge, Adams, & Pineda, 1991; Guilbaud, Besson, Oliveras, & Wyon-Maillard, 1973; Wolstencroft, 1964). Input within this tract also stimulates endogenous analgesic systems (Bouhassira, Bing, & Le Bars, 1990; Cechetto, Standaert, & Saper, 1985). A subset of SRT neurons composes the spino-reticulo-thalamic tract, which terminates in the medial thalamus (Peschanski & Besson, 1984). It is then thought that nociceptive information is relayed to ACC and IC to trigger affective-motivational responses (Musil & Olson, 1988).

1.2.3.3 Spinomesencephalic tract

The spinomesencephalic tract is located in the anterolateral quadrant of the spinal cord. Neural projections from this pathway extend to the periaquaductal grey (PAG), the anterior pretectal nucleus, superior colliculus, and the parabrachial nucleus (PBN) of the pons. One of the primary roles of this pathway is thought to be to limit nociception. This is suggested by the anatamo-functional projections of this tract. Reynolds (1969) demonstrated that electrical stimulation of the PAG in rat produced powerful analgesia. Similarly, Rees and Robert (1993) determined that stimulation of the anterior pretectal nucleus in rat produced antinociceptive effects as demonstrated by increased tail-flick withdrawal latency. In addition, the role of the superior colliculus in pain is thought to orient the organism toward a painful stimulus in order to mobilize a response (Wang et al., 2000). It is believed that the function of the PBN is to

initiate autonomic arousal and cardiovascular processes to mobilize a response to the pain (Allen & Pronych, 1997; Bernard, Bester, & Besson, 1996).

1.2.3.4 Spinocervicothalamic tract

This tract is prominent in certain animals, such as cats, but may have minimal importance in man (Truex, Taylor, Smythe, & Gildenberg, 1965). Neurons within the spinocervicothalamic tract relay information from the dorsal horn to the lateral cervical nucleus in segments C1 and C2 and then decussate to project to several thalamic nuclei (VPL, P_{om}; Smith, Apkarian, & Hodge, Jr., 1991; Berkley, 1980; Boivie, 1980). This tract contains mostly tactile neurons, which respond to low threshold mechanoreceptive stimuli, however, there are nociceptive neurons which respond to thermal stimuli (Downie, Ferrington, Sorkin, & Willis, 1988; Kajander & Giesler, Jr., 1987).

1.2.3.5 Dorsal column postsynaptic pathway

The dorsal column pathway is the major primary afferent pathway for transmitting tactile information (including graphesthesia, 2-point discrimination and position sense). In 1932, Foerster and Gagel demonstrated that stimulation of the dorsal column resulted in referred pain to the sacral region and the perineum. More recently it was discovered that a subset of axons in the dorsal column pathway originate from cells in the dorsal horn. These axons are known as the dorsal column post-synaptic pathway (DCPS). Al-Chaer and his colleagues (1996) provided evidence that projection cells in the DCPS respond to chemical and mechanical irritation of the viscera. This work has led to the discovery of a major visceral pain pathway. Afferent fibres from the viscera synapse on cells near the central canal. The subsequent cells project ipsilaterally to the nucleus gracilis, where they synapse and decussate and project onward to the VPL (Al-Chaer, 1996). It is speculated that this pathway is important for transmitting visceral information, as lesions of the midline dorsal column pathway alleviate abdominal pain (Nauta, Hewitt, Westlund, & Willis, Jr., 1997).

1.2.4 Thalamus

Almost all information that makes its way to the cortex must pass through the thalamus. Grossly speaking, the thalamus can be classified into 3 divisions: anterior, medial, and posterior. These categories can be further subdivided into many nuclei. The major nociceptive nuclei receiving projections from laminae I and V are the ventroposterior lateral and medial nuclei (VPL and VPM; Bushnell & Duncan, 1987; Bushnell, Duncan, & Tremblay, 1993a; Casey & Morrow, 1983; Kenshalo, Jr., Giesler, Leonard, & Willis, 1980), VM_{po} of the posterior thalamus (Craig, Bushnell, Zhang, & Blomqvist, 1994), and the ventrocaudal portion of the medial dorsal (MD_{vc}), central lateral (CL), central median (CM) and parafascicular (Pf) nuclei of the medial thalamus (Dong, Ryu, & Wagman, 1978; Bushnell & Duncan, 1989).

Thalamic neurons can be dissociated along lateral and medial lines representing the sensory-discriminative and affective-motivational components, respectively (Albe-Fessard, Berkley, Kruger, Ralston, & Willis, 1985). Generally speaking, the VPM nucleus contains neurons with small receptive fields, which are constant across behavioural states and repeated stimulation (Bushnell et al., 1993). VPM neurons have a sensitive stimulus-intensity response functions. Consequently, primates are very adept at detecting intensity changes of noxious stimuli, be it large or as small as 0.2°C (Bushnell, Taylor, Duncan, & Dubner, 1983). This ability is compatible with the sensory-discriminative aspect of pain perception. Further, blocking VPM activity with lidocaine microinjection disrupts monkeys' ability to discriminate stimulus intensity (Bushnell et al., 1993). In contrast to cells of the VPM, cells in the MD_{vc}/Pf have large, bilateral receptive fields that respond in an irregular fashion to noxious stimuli (Peschanski, Guilbaud, & Gautron, 1981; Dong et al., 1978; Benabid, Henriksen, McGinty, & Bloom, 1983; Albe-Fessard & Kruger, 1962; Perl & Whitlock, 1961; Pearl & Anderson, 1980). Since activity of cells in the medial thalamus is highly modifiable by behavioural state, these neurons may be involved in the affectve-motivational dimension of pain (Bushnell & Duncan, 1989; Bushnell et al., 1993).

The role of specific thalamic nuclei in pain processing can further be described by examining their cortical connections. The probability is weak that the VPL or the VPM is implicated in the affective-motivational components of pain since they project to SI, which is thought to be involved in the sensory processing. VM_{po} and MD_{vc}/Pf may subserve the emotional and behavioural reaction to pain though their projections to the rostral insula and ACC, respectively (Musil et al., 1988; Vogt, Pandya, & Rosene, 1987; Devinsky, Morrell, & Vogt, 1995). Finally neural imaging studies have been used to confirm the importance of the thalamus in the pain perception. Results from human brain-imaging studies consistently demonstrate an increase in thalamic activity during acute experimental pain (Casey et al., 1994; Casey, Morrow, Lorenz, & Minoshima, 2001; Coghill, Sang, Maisog, & Iadarola, 1999; Davis, Kwan, Crawley, & Mikulis, 1998; Tracey et al., 2000).

1.2.5 Cortical regions

1.2.5.1 Primary somatosensory cortex (S1)

During much of the 20th century, many neurologists believed that the primary somatosensory cortex is not involved in pain perception. This idea was promoted by Head and Holmes (1911) who concluded that after widespread cortical injury there was no disruption to pain perception. Penfield and Boldrey (1937) doubted the role of SI as an area involved in pain perception since electrical stimulation during neurosurgical procedures did not yield pain.

However, recent data have lent support to the importance of these structures in pain perception. Single-unit recording data have implicated SI in pain processing despite the paucity of nociceptive neurons obtained from many recordings (Kenshalo, Jr., Chudler, Anton, & Dubner, 1988; Kenshalo, Iwata, Sholas, & Thomas, 2000; Tsuboi et al., 1993). Single-unit recordings in SI in the awake monkey revealed that nociceptive-specific neurons contained small receptive fields, which coded well the intensity of noxious thermal stimuli. In addition, the activity of these neurons was significantly correlated with the detection speed

(Kenshalo & Isenesee, 1983; Kenshalo et al., 1988). Tsuboi et al. (1993) studied cells that responded to both cold and noxious mechanical stimuli in cat S1 and noted that 19% of cells responded in an incremental fashion to increases in stimulus intensity. Thus, taken together, these results suggest that S1 nociceptive activity could be important in signaling pain intensity perception.

The role of S1 in the conscious appreciation of pain is further supported by data from the human-brain-imaging studies. The first modern PET pain-imaging study implicated S1 as an important structure contributing to the perception of pain (Talbot et al., 1991). Since the publication of this study, however, the function of S1 in pain perception has been a source of controversy, as only about half of all studies obtained S1 activation (Bushnell et al., 1999). Objectively, studies examining both cutaneous and visceral pain have observed activation in S1 (Aziz et al., 1997; Coghill et al., 1994; Hobday et al., 2001; Gelnar, Krauss, Sheehe, Szeverenyi, & Apkarian, 1999). Similarly, when a painful thermal stimulus is used, irrespective of whether it is hot or cold, S1 activation has been observed (Casey, Minoshima, Morrow, & Koeppe, 1996; Tracey et al., 2000). In addition, patients suffering from chronic pain exhibit activity within S1 in response to tactile stimuli (Petrovic, Ingvar, Stone-Elander, Petersson, & Hansson, 1999). Nevertheless, only 50% of brain-imaging studies report S1 activation, most likely due to methodological considerations (see Caveats when using PET and fMRI p. 37).

The importance of S1 for the perception of pain intensity and localization of cutaneous pain has been further strengthened with evidence from lesion studies. Kenshalo et al. (1991) demonstrated that bilateral lesions of SI in two monkeys reduced their ability to detect and discriminate the intensity of noxious thermal stimuli. Similarly, a patient who suffered a cerebrovascular accident encompassing the hand area of S1 & S2 was unable to clearly localize painful cutaneous laser stimulation of the affected hand. The patient described the stimulation as a 'clearly unpleasant' intensity-dependent diffuse sensation,

'somewhere between fingertips and shoulder' that he wanted to escape (Ploner, Freund, & Schnitzler, 1999). In addition, Lewin and Phillips (1952) described three patients who underwent partial resection of the post-central gyrus for the relief of intractable pain. Intra-operative electrical stimulation of the affected area within the post-central gyrus reproduced the patient's pain, in both quality and location. Relief was obtained in all patients following the removal of this area of cortex. These findings taken together suggest that the primary somatosensory cortex plays an important role in the perception of the sensory-discriminative component of the pain experience.

1.2.5.2 Secondary somatosensory cortex (S2)

PET imaging has consistently implicated a region on the upper border of the lateral sulcus, generally defined as S2. Evoked-potential studies have measured sources originating within S2 for both nociceptive cutaneous and visceral stimuli (Hecht et al., 1999; Kunde & Treede, 1993). In monkeys, few nociceptive neurons have been identified in S2 proper (Robinson & Burton, 1980) but Dong et al. (1989; 1994) have found such neurons in a region adjacent to S2, i.e. Area 7b. Initially, they observed that Area 7b cells, which responded to noxious mechanical stimulation, had bilateral receptive fields and were slowly adapting. This result indicated that they could accurately encode the duration of stimulation. In their subsequent study, thermal nociceptive units were discovered that either encoded or did not encode the magnitude of the thermal stimulus. These encoding neurons closely approximated the stimulus intensity-escape frequency functions.

A case study by Greenspan and Winfield (1992) described a patient with a right-sided tumor in area S2/7b who had undergone extensive psychophysical testing. Psychophysical data from this patient revealed laterality differences, with heightened mechanical and heat pain thresholds, and greater cold pain tolerance contralateral to the lesion. The alteration in sensory function resolved following

the removal of the tumor. In a separate study, Greenspan et al. (1999) examined patients following a lesion to the parasylvian cortex and found that only patients with sparing of the parietal operculum had normal thermal thresholds. Taken together, these findings demonstrate deficits in pain perception and increases in thermal thresholds following damage to S2 function.

Evoked-potential, single-unit, lesion-, brain-tumor, and neuroimaging-derived data all point toward a role for S2 in the conscious appreciation of pain and sensorial aspects pertaining to the stimulus parameters of the noxious stimulus. It has been speculated that activity within S1 and S2 was an epiphenomenon related to the tactile properties of the stimulus (Jones, Friston, & Frackowiak, 1992). Recent evidence however, disputes this idea. Painful stimuli lacking a tactile component, namely CO_2 laser, have elicited S2 activity (Svensson, Minoshima, Beydoun, Morrow, & Casey, 1997; Xu et al., 1997). S2 activity has also been seen in response to acute and chronic pain generated from cutaneous (Casey et al., 1996; Coghill et al., 1994; Davis et al., 1998; Petrovic et al., 1999; Peyron et al., 2000a) or visceral (Binkofski et al., 1998; Lotze et al., 2001) stimuli.

1.2.5.3 Anterior cingulate cortex (ACC)

Anatomical and neurophysiological studies support a strong role for the ACC in pain processing. Through anatomical connectivity with medial thalamic nuclei that contain nociceptive units, the ACC receives pain-related input from the nucleus parafascicularis (Pf) and the ventrocaudal part of the nucleus medialis dorsalis (MDvc; Apkarian & Shi, 1998; Craig, 1990). Using single-unit recording, Sikes & Vogt (1992) and Hutchison et al. (1999) located nociceptive neurons within rabbit and human ACC, respectively. Further evidence that ACC is involved in pain processing was derived from studies that recorded evoked potentials emanating from the ACC following application of a painful stimulus (Lenz et al., 1998).

Converging evidence is accumulating to demonstrate a role for the ACC in the processing of the pain affect. There is some anecdotal clinical evidence over the last half century that lesions of the ACC result in an alleviation of the unpleasantness associated with the pain experience but create a slight, if any, deficit in the sensory-discriminative component (Corkin & Hebben, 1981; Talbot, Villemure, Bushnell, & Duncan, 1995; Foltz & Lowell, 1962; Foltz & White, 1968). Patients who have undergone a cingulotomy state that they continue to experience pain, but it is not very bothersome. Consistent with the idea that pain affect is processed in the ACC are data from our laboratory that demonstrate a correlation between subjective ratings of pain unpleasantness and regional cerebral blood flow in the ACC (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Further, Johansen et al. (2001) recently demonstrated a formalin-induced avoidance in rats with intact rostral ACC but not in rats with lesioned rostral ACC, despite normal acute pain-related behaviours. Taken together, these results suggest that neurons within ACC are necessary for the perception of the affective sequelae induced by nociceptive stimuli.

The role of the ACC is not limited to conveying the affective tone of nociceptive stimuli. An additional function for the ACC has been suggested in attentional processing. Cohen et al. (1999) examined patients prior to and following cingulotomy for intractable pain. In addition to achieving moderate pain relief, patients who had undergone cingulotomy demonstrated impairments of focused and sustained attention one-year following the surgery. Studies examining pain and attention within the same subjects have demonstrated a dissociation between pain- and attention-related foci of activations (Davis, Taylor, Crawley, Wood, & Mikulis, 1997; Derbyshire, Vogt, & Jones, 1998). Davis et al. (1997) observed that attention-demanding tasks resulted in an anterior region of activation, whereas pain-related activation was observed more posteriorly. However, Derbyshire et al. (1998) reported the converse. The discrepancy observed in the foci of activation induced by the attentional stimuli could be due to differences in attentional task parameters.

1.2.5.4 Insular cortex (IC)

The anterior insula receives an abundant amount of direct and indirect input from nociceptive areas including S1, S2, Area 24 of the ACC, and VM_{po} (Allen, Saper, Hurley, & Cechetto, 1991; Dostrovsky & Craig, 1996b; Augustine, 1996; Mesulam & Mufson, 1982). Dostrovsky and Craig (1996b) found nociceptive neurons within anterior and mid-IC, consistent with its cortical connections to other nociceptive areas. Finally, it has been demonstrated that the IC sends projections to the limbic lobe, in particular to the amygdala and perirhinal cortex (Penfield & Faulk, 1955).

There is converging evidence to implicate the insula in affective and reactive components of the pain experience. Stimulation of the IC produces mostly visceral and somatic sensations, movement, and sometimes a sense of fear (Feindel, 1961; Penfield & Rasmussen, 1955; Penfield et al., 1955). Insular lesions can lead to a condition called *pain asymbolia*, whereby individuals, in the absence of primary sensory loss, demonstrate an inadequate emotional reponse to a painful stimulus (Berthier, Starkstein, & Leiguarda, 1988).

In addition to the role of IC in pain affect, it also serves a function in thermal sensibility. A thermal-specific nucleus has been located within the posterolateral thalamus (VMpo; Craig et al., 1994). Further, neuroanatomical studies have demonstrated a direct projection from these thermo-receptive thalamic cells to IC (Dostrovsky & Craig, 1996b). Additionally, Craig et al. (2000) recently demonstrated a strong correlation between IC rCBF and the intensity of a graded cool stimulus. Similarly, patients suffering from IC strokes demonstrated an increased cold pain tolerance to the cold-pressor test (immersion of the hand in cold water) on the side contralateral to the lesion. Taken together, these studies suggest a role for IC in the thermal sensibility.

The IC is also known to have a role in autonomic functioning. Studies in rats demonstrate that the IC is involved in cardiovascular modulation (Verberne &

Owens, 1998). In humans, increase in heart rate through active cycling motions has been shown to lead to insular activation (Williamson et al., 1997). Lesions of IC as a result of stroke disrupt autonomic cardiovascular regulation in humans (Oppenheimer, Kedem, & Martin, 1996). Using a single-unit-recording technique in monkey, Zhang et al. (1999) located neurons in the IC which responded to changes in blood pressure and nociceptive stimulation. A high portion of these neurons responded to both the pressor challenge and noxious cutaneous stimulation, suggesting a convergence of autonomic and somatosensory input. The integration of autonomic and nociceptive information might underlie a cortical mechanism for sympathetically maintained pain. These data are also consistent with the role of IC as a necessary structure for homeostasis and interoception (Craig, 1996a; Craig, 1996b).

1.2.5.5 Prefrontal Cortex

The precise role of the prefrontal cortex in the conscious appreciation of pain and its modulation is uncertain. Nevertheless, the prefrontal cortex has been implicated repeatedly in experimental and clinical pain studies using both PET and fMRI in humans (Becerra, Breiter, Wise, Gonzalez, & Borsook, 2001; Casey 1999; Casey et al. 2001; Coghill et al., 1999; Hseih et al., 1995; Svensson et al., 1997). Recent results, however, suggest that the activity seen in the prefrontal cortex following a noxious stimulus is not related to the perceived pain intensity (Coghill et al., 1999).

Studies in rats have shown that electrical stimulation of the prefrontal cortex (PFC) induces analgesic effects through direct connections with the PAG and the midbrain (Hardy, 1985; Hardy & Haigler, 1985; Zhang, Tang, Yuan, & Jia, 1997). Microiontophoretic application of neurotransmitters including methionine-enkephalin, norepinepherine, and acetylcholine replicate the effect of PFC stimulation, suggesting the antinociceptive effects are mediated by these neurotransmitters on the midbrain (Hardy et al., 1985). Taken together these

results suggest an important role for PFC in pain modulation and descending inhibition.

Several investigators have examined the role of the prefrontal cortex in the processing of affect and emotion (Pascual-Leone, Catala, & Pascual-Leone, 1996; Baker, Frith, & Dolan, 1997; Pardo, Pardo, & Raichle, 1993). In a study by Teasdale et al. (1999), subjects were required to look at pictures and captions evoking positive, neutral, or negative feelings. Irrespective of the valence of the emotion induced, medial frontal cortex activation was observed. By their very nature, cutaneous and visceral nociceptive stimuli induce strong changes in mood and affect (Ploner et al., 1999; Binkofski et al., 1998). Therefore, pain-induced changes in affect could be responsible for cerebral changes within the prefrontal cortex.

Recent data collected in our laboratory however, put into question the role of the prefrontal cortex in mediating pain affect. In one group of subjects, painful stimuli were applied to the skin and viscera (Strigo et al., 2001). The painful stimuli, a contact-heat thermode placed on the thorax or a balloon inflatable in the esophagus, were applied to the same dermatome. Subjects rated the visceral stimuli as more unpleasant than the cutaneous stimuli. Interestingly, there was only prefrontal activation (area 10) in response to the cutaneous stimuli. Thus these data suggest activation seen in frontal cortex following a painful stimulus is not directly related to the affective valence of the stimulus.

Alternatively, it is well accepted that the frontal and prefrontal regions play an important role during the encoding and retrieval of information (Burton & Sinclair, 2000; Frey & Petrides, 2000). Most studies require subjects to encode the painful stimulation, retain the event in short-term memory and recall the stimulus properties (such as intensity and unpleasantness ratings) following the scan. These tasks require activation of a short-term memory network within the prefrontal cortex (Buckner, Kelley, & Petersen, 1999; Owen, Milner, Petrides, &

Evans, 1996; Petrides, 2000; Schacter, Buckner, & Koutstaal, 1998). Therefore, activity within the prefrontal cortex might be a secondary effect of the pain and not directly related to the painful stimulus.

1.2.5.6 Cerebellum

The role of the cerebellum in pain perception and modulation is still speculative. However, a number of brain-imaging studies have observed pain-evoked activations in the cerebellum, particularly the vermis (Casey et al., 1994; Casey et al., 2001; Coghill et al., 1999; Paulson, Minoshima, Morrow, & Casey, 1998). Microinjection of morphine into the anterior cerebellum leads to potent analgesia in the rat (Jorum, 1988). Cerebellar-evoked potentials were recorded in cats following C-fibre stimulation, suggesting that noxious stimuli are processed to some degree in the cerebellum (Ekerot, Garwicz, & Schouenborg, 1991). Similarly, colorectal distention in rats exerted both inhibitory and to a lesser extent excitatory effects on the activity of cerebellar Purkinje cells (Saab & Willis, 2001). This overall functional dampening of cerebellar activity supports the idea that the cerebellum might be involved in antinociceptive mechanisms through a negative feedback loop with the ACC and brainstem structures (Schmahmann & Pandya, 1997).

It should be borne in mind that the cerebellum is involved in motor acquisition, discrimination (Gao et al., 1996), and control (Middleton & Strick, 1997). In addition, a recent study demonstrated imagined and executed actions share some of the same central structures, including the cerebellum (Decety, 1996). As such, contemplating an escape strategy or imagining eluding noxious stimuli, could cause an increase in cerebellar neuronal activity, irrespective of whether movement is executed.

1.2.6 Descending modulatory circuits

The ascending pain pathways and cortical structures are important in the perception of pain. Equally important however, are the descending modulatory controls. The first structure discovered to modulate pain perception was the periaquaductal grey (PAG). Reynolds (1969) demonstrated that electrical stimulation applied to the PAG produced profound analgesia in rats. The PAG is innervated by the frontal neocortex, hypothalamus and amygdala. Similarly, microinjection of morphine into these structures produces analgesia (Fields, Heinricher, & Mason, 1991; Helmstetter, Bellgowan, & Tershner, 1993; Burkey, Carstens, Wenniger, Tang, & Jasmin, 1996). The PAG sends a major projection to the rostral ventral medulla (RVM; Vasquez & Vanegas, 2000). From the RVM, projections are sent to cells of the dorsal horn, whereby inhibition of incoming nociceptive information can occur (Fields, Malick, & Burstein, 1995). In addition to the aforementioned endogenous antinociceptive opioid system, there are direct connections between somatosensory cortex, hypothalamus or the subnucleus reticularis dosalis and the dorsal horn (Holstege, 1988; Villanueva, Bernard, & Le Bars, 1995).

1.2.7 Abberant Pain Processing

Pain is an essential sensory experience. However, when acute pain evolves and becomes chronic, it extends beyond its usefulness. Chronic pain occurs as a result of changes within the nervous system. Several physiological alterations take place peripherally and centrally in chronic pain which include, but are not limited to, phenotypic changes in primary sensory neurons (Woolf, 1996), altered connectivity within the dorsal horn (Bester, Beggs, & Woolf, 2000), and hypoperfusion within the thalamus (Iadarola et al., 1995).

Nerve injury leading to chronic pain is preceded by changes in the periphery, which facilitate neuronal firing, nociceptive transmission, and ultimately pain sensation. These changes include increased activity in damaged primary afferent fibres and their sprouts, potentially leading to heightened pain sensation

(Kajander & Bennett, 1992; Laird & Bennett, 1993; Ochoa, Torebjork, Culp, & Schady, 1982). In conditions of neurogenic inflammation, antidromic activation or molecules such as nerve growth factor result in lowering the neuronal threshold for firing (Woolf & Mannion, 1999). Finally, neuronal damage can result in an upregulation of adrenergic receptors, which when activated, produce severe burning pain (Chabal, Jacobson, Russell, & Burchiel, 1992).

Following neuronal injury, the normal connections in the dorsal horn are perturbed. As a result, intact myelinated primary afferent Aβ- fibres sprout collaterally and extend into the layers of the superficial dorsal horn (Mannion, Doubell, Coggeshall, & Woolf, 1996; Doubell, Mannion, & Woolf, 1997). Bester et al. (2000) examined c-Fos expression, a transcription factor and functional marker of neuronal activity, in the superficial dorsal horn of rats following nerve crush injury. Pain thresholds, as measured by paw withdrawal, were reduced for both mechanical and thermal stimuli. Interestingly, allodynia the perception of a non-painful stimulus as painful still remained one year following injury. Additionally, c-Fos expression was seen in laminae I-II in response to tactile stimulation of the affected, but not the non-affected paw. These results suggest mechanoreceptors produce allodynia by gaining access to nociceptive-specific regions of the dorsal horn.

In addition to peripheral changes, central changes have been observed within thalamus and S1 in patients with chronic pain. Consistently, studies observe thalamic hypoperfusion in patients suffering from both peripheral neuropathic and central pain (Iadarola et al., 1995; Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Di, V et al., 1991). Pagni & Canavero (1995) documented a case of central pain associated with thalamic hypoperfusion in a patient with an intramedullary cyst. Following removal of the cyst, pain and thalamic hypoperfusion resolved. Studies examining thalamic stimulation lend further support to the idea that reduced thalamic activity may contribute to chronic pain. Chronic neuropathic pain has been effectively treated with an implantable

thalamic stimulator (Davis et al., 2000; Duncan et al., 1998; Kupers, Gybels, & Gjedde, 2000). The stimulator works by restoring the lost thalamic activity, possibly arising from mechanisms that can include central disinhibition and deafferentation. In contrast to a thalamic hypoexcitability, Flor et al. (1997) demonstrated an enhanced cortical reponse to stimulation of the lower back in patients with chronic back pain of this region compared to healthy control subjects. The enhanced cortical response was positively correlated with the chronicity of the pain. Further, reorganization of S1 has been confirmed in patients with elimination of painful phantom limbs following regional anesthesia. However, cortical reorganization was not observed in patients whose pain was not alleviated by regional anesthesia (Birbaumer et al., 1997). As a whole, these results suggest that pain of a chronic nature can be due in part to neuroplastic changes not only in CNS, but also in the periphery.

1.3 Functional imaging of the human brain

Until recent advances in human brain imaging techniques, the cerebral mechanisms of pain perception could not be directly addressed. The advent of powerful brain imaging techniques, such as SPECT (single-photon computed tomography), PET (positron emission tomography), and fMRI (functional magnetic resonance imaging) offer alternative tools to study pain through anatomic and physiologic mapping.

Imaging techniques allow for insight into the functioning of the active human brain with varying levels of invasiveness. Various brain imaging techniques can measure functional activities or radio-ligand binding, but each differs in its approximation of neurovascular coupling.

1.3.1 Positron emission tomography (PET)

1.3.1.1 Image acquisition

The basic premise behind the use of PET to measure functional brain activity is that there is a tight spatial and temporal coupling of synaptic activity with regional cerebral blood flow (Lindauer, Villringer, & Dirnagl, 1993). With this principle in mind, a radioactive tracer is injected into venous circulation prior to the task and taken up by brain tissue active in the task. Commonly used radiotracers are easily diffusible and short-lived, including ^{15}O-H_2O, $C^{15}O_2$ gas, or ^{15}O-butanol. Once in the brain tissue, the radiotracer begins to decay by positron emission. The emitted positron will encounter an electron and yield two gamma rays from an annihilation event. These two gamma rays are released at 180 degrees to each other. An event is then recorded when two gamma rays are simultaneously absorbed by a circumferential array of scintillation detectors which line the interior of the PET scanner. The events can then be reconstructed into a cross-sectional image using conventional mathematical algorithms. It is then possible to generate back-projections and determine the site of origin of the signals.

1.3.1.2 Image analysis

Initially all data collected from individual subjects are reconstructed and aligned to remove differences in the subjects' head position and ensure that all data are in the same orientation. PET images are first registered to the other PET images of the same subject and then to the MRI image of the subject. The data can then be smoothed using a filter and placed in stereotaxic space using the Talairach (1988) atlas. This procedure allows for the reduction of high-frequency noise obtained during the acquisition, as well as to decrease the inter-individual variability in the location of anatomico-functional units. This technique allows for inter-subject averaging which increases the signal-to-noise ratio and standardizes reporting of activation foci. Subsequently, the data are normalized to global blood flow, which is important to reduce inter-scan differences in dose of tracer and inter-subject differences in global CBF.

1.3.1.3 Statistical analysis

Following these corrections, statistical analyses of data can be performed either by looking at differences between experimental conditions (subtraction) or correlating CBF-change within the brain with an independent measure such as pain ratings, heart rate, or rCBF in a specific cerebral structure (regression).

1.3.1.3.1 Subtraction

Subtraction PET CBF images are generated by determining the difference between two CBF images for each subject, usually under baseline and activation conditions. Images are then averaged into standardized space to enhance the signal-to-noise ratio. Statistically generated t-maps are derived by calculation of subtracted PET cerebral blood flow (CBF) images on a voxel-by-voxel basis, typically the difference between two CBF images reflecting baseline and activation conditions across subjects. Comparison of means of the two conditions is performed using the t-statistic with pooled variance while correcting for multiple comparisons (Worsley, Evans, Marrett, & Neelin, 1992).

1.3.1.3.2 Regression

Regression analyses are performed to determine the strength of the relationship between a given measure (pain intensity ratings, heart rate, or CBF within a given brain structure) and rCBF across conditions of an experiment. The variable of interest is regressed with rCBF levels across all subjects and all scans. The slopes of the correlation coefficients are then estimated at each voxel, and t-statistics are derived using the standard deviation of the slope pooled over the volume of grey matter defined by a probability map of grey-white-CSF partitioning.

1.3.2 Functional magnetic resonance imaging

1.3.2.1 Image acquisition

The basic theory behind BOLD (blood oxygen level dependent) fMRI is that neuronal activity can be measured through changes in blood flow and blood

oxygenation (Rees, Friston, & Koch, 2000). When neurons increase their activity oxygen is required. As a result, oxygen is extracted from the blood and oxyHb (oxygenated hemoglobin) is changed locally to deoxyHb (deoxygenated hemoglobin). Within a few seconds a microvascular response occurs to reperfuse the area, which raises oxyHb levels and rapidly increases oxyHb/deoxyHb ratio. Since deoxyHB is paramagnetic it causes a small inhomogeneity within the magnetic field, which can be detected by radiofrequency coils as a weaker signal than oxyHb. However, areas that are more active during a task have a higher oxyHb concentration and less signal dilution than deoxyHb, resulting in an increase in signal intensity. The precise basis of the BOLD signal remains uncertain. Therefore, to further understand the origin of the BOLD signal, Logothetis et al. (2001) examined the correlation between the BOLD signal, local field potentials, and single- and multi-unit arrays. Results suggest that the BOLD signal reflects incoming cortical information and its local processing, namely local field potentials within a given area rather than neuronal activity as recorded by a single- or multi-unit array.

1.3.2.2 Image analysis

FMRI data provide very detailed anatomical and functional neuroimaging data. Unfortunately, this information comes at a cost -- it is easily susceptible to motion-associated signal corruption. As a result functional data must be motion corrected. Motion correction is performed to remove subject movement during a scan or spatial distortion due to inhomogeneities in the static magnetic field. FMRI signals are also subject to degradation by spatial and temporal noise. As such, temporal and spatial filtering is required to increase the signal-to-noise ratio and improve image quality. Temporal filtering aids in reducing noise induced by cardiac and respiratory frequencies whereas spatial filtering diminishes misregistration artifact by lowering the resolution of the image.

1.3.2.3 Statistical analysis

Once all the preprocessing of the data is completed, the statistical analysis can begin. The statistical analysis of the fMRI data is based on a linear model with

correlated errors (Worsley et al., 2000). For each scan, the design matrix of the linear model is first convolved with a gamma hemodynamic response function with a mean lag of 6 seconds and a standard deviation of 3 seconds, timed to coincide with the acquisition of each slice (Lange & Zeger, 1997). Drift is removed by adding polynomial covariates in the frame times. At each voxel, the autocorrelation parameter is estimated from the least square residuals using the Yule-Walker equations, after a bias correction for correlations induced by the linear model. The resulting t-statistic images are thresholded using the minimum given by a Bonferroni correction and random-field theory (Ries & Puil, 1999). For a given task, the t-statistic image reflects the difference in activation between the task and the baseline condition.

1.3.3 Comparison of PET and fMRI

PET and fMRI techniques are both excellent tools to examine the living brain. They are both capable of determining anatomico-functional relationships during cognitive and sensory tasks. PET allows for examination of receptor binding by identifying the distribution and concentration of radioactive ligands, an option not available with fMRI. Since there are no magnetic fields created during PET scanning, there are no risks to subjects or patients with implanted ferromagnetic appliances or testing apparatuses. Unlike PET, fMRI does not use any radiation, thus there are no limitations to the number of repeated studies with the same individual subject, ideal for case studies. Additionally, with no radioactive tracer, there is no need to wait for its decay and have a protracted inter-scan interval. Since fMRI provides very high spatial resolution, studies can be undertaken with fewer subjects, and in some cases reducing the need for averaging across the group.

1.3.4 Caveats when using PET and fMRI

Often in the literature, investigators are quick to point out that there was no activation in a given brain region. For example, lack of significant activation

within S1 following painful stimulation has been seen in several brain-imaging studies (Jones, Brown, Friston, Qi, & Frackowiak, 1991; Apkarian et al., 1992; Silverman et al., 1997; May et al., 1998). It is always possible that following the application of a painful stimulus, there is no increase in neural activity within S1. However, extreme discretion should be used when suggesting this interpretation with a small sample size and without performing a power analysis. It is equally, if not more probable, that there is lack of detection of a true signal change. Not discovering the existence of a true activation can arise from a reduced signal-to-noise ratio. This situation might occur due to lack of an adequate number of subjects or scans. Slight anatomical differences between peak activation sites among subjects can lead to a reduced signal following averaging and filtering of scans (Ha, Chen, Pike, Duncan, & Bushnell, 1998a).

The sensory experience following application of a noxious thermal stimulus is highly modifiable. As a result, there are parameters that must be controlled for during a pain study. First, attention must be paid to the stimulus, since recent studies have demonstrated distraction can lead to reduced pain-evoked cerebral activation (Carrier, Rainville, Paus, Duncan, & Bushnell, 1998; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000). As well, it has been shown that stress and anxiety are capable of altering pain sensitivity; as such they must be controlled (Thomas & Weiss, 2000). Since subjects remain immobile for extended periods of time while lying in the PET or fMRI scanner, attempts must be made to reduce and measure any discomfort felt by the subjects. Therefore, it is important when designing and carrying out studies to take into account that the cognitive state of the subject impacts on the cerebral responsiveness to noxious stimulation.

1.4 Alteration of pain perception by conscious state

Presently, which structures are important and their relative contributions to the experience of pain are still under investigation. However, since there is a common agreement as to what is meant by pain, there should be a common brain mechanism that signifies pain. The following three chapters will present studies, in which I will address:

1. What cortical structures are involved in the conscious experience of pain?
2. When the percept of pain is changed, is activity in these cortical structures altered or does it remain the same?
3. How does chronic pain change the cortical representation of pain?

The response of the individual to these manipulations will be examined in the living human brain using both PET and fMRI methodologies.

CHAPTER 2 – PROPOFOL-INDUCED PAIN MODULATION

Hofbauer, R. K., Fiset, P., Plourde, G., Backman, S.B., & Bushnell, M. C. (unpublished manuscript). Effect of propofol-induced sedation and loss of consciousness on pain-related activity in the human forebrain.

2.1 Chapter Overview

The literature indicates that there are numerous brain regions implicated in the perception of pain (Casey, 1999). However, which brain regions are at the core of pain perception is not known. Not all brain structures activated by PET and MRI may be required for the conscious appreciation of pain, but instead they could be concerned with functions that include autonomic or reflexive reactions to the painful stimuli. Thus, the present chapter reports on an experiment in which we used propofol, a non-analgesic anesthetic, to alter consciousness and determine which components of the cerebral pain network are important for the conscious appreciation of pain. Secondarily, we will be able to determine, despite reduced levels of consciousness or even unconsciousness, if nociceptive signals are still reaching the brainstem, thalamus and cortex.

With the advent of brain-imaging techniques, we are able to probe the effects of anesthetics in the living human brain. Studies have been conducted examining the effect of general anesthetics on cerebral activity (Alkire et al., 1995; Alkire, Haier, Shah, & Anderson, 1997; Alkire et al., 1999; Fiset et al., 1999), sensory transmission (Antognini, Buonocore, Disbrow, & Carstens, 1997; Bonhomme et al., 2001), and task-related cognitive abilities (Heinke & Schwarzbauer, 2001). It is thought that anesthetic-induced reduction of sensory transmission occurs at the level of the thalamus (Alkire, Haier, & Fallon, 2000). However, recently Angel and Arnott (1999) demonstrated that etomidate administration resulted in a dose-dependent reduction in cortical responsiveness without altering thalamic or cuneate activity.

How does propofol alter sensory transmission? Results examining vibration in subjects under propofol anesthesia established that rCBF initially decreased in cortical structures followed by a reduction in the thalamus (Bonhomme et al., 2001). Pain, however, is a more complex sensory experience that encompasses a larger cortical and subcortical network than does vibration. Thus, the purpose

of the current study is to assess which brain structures are necessary for the conscious experience of pain and whether following unconsciousness, nociceptive signals still reach the brain. In the present chapter, I provide evidence that only a subset of cerebral structures are necessary for the conscious appreciation of pain, and suggest that neuronal information is still received within the cortex following loss of consciousness.

2.2 Abstract

Anatomical and physiological data show that multiple regions of the forebrain are activated by pain. The relative importance of each of these areas to the conscious experience of pain has yet to be delineated. To address this issue, positron emission tomography (PET) was used to indirectly measure pain-evoked cerebral activity at various doses of propofol, a general anesthetic. Fifteen volunteers were scanned while tonic warm and noxious heat stimuli were presented to the volar forearm using a contact thermode during four experimental conditions: alert control, moderate sedation, deep sedation, and unconsciousness. Similar to results of previous brain-imaging studies, regional cerebral blood flow (rCBF) in the thalamus, brainstem, and parietal and posterior cingulate cortices was inversely correlated with plasma propofol concentrations. In addition, we observed that at sedative doses, subjects' pain perception was increased, along with an associated increase in pain-evoked activation in thalamus and cortico-limbic areas. In contrast, when subjects lost consciousness and stopped responding to the painful stimulus, pain-evoked activation in thalamus and cortical regions (particularly anterior cingulate cortex (ACC)) was dramatically reduced, whereas cerebellar activation remained intact. These data suggest that thalamo-cortical limbic circuits are important for the conscious appreciation of pain.

2.3 Introduction

Recent advances in human-brain-imaging techniques have led to staggering progress in understanding the neural correlates mediating pain responsiveness. Numerous neuroimaging studies have now described functional changes that occur within multiple cortical regions following painful stimulation (Talbot et al., 1991; Coghill et al., 1994; Casey et al., 2001; Davis et al., 1998; Tracey et al., 2000; Apkarian, Darbar, Krauss, Gelnar, & Szeverenyi, 1999). Images acquired using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) reflect not only neuronal activity related to the painful perception, but may also display coupled epiphenomena of the pain experience, such as autonomic function, homeostasis or behavioural reactions. Little is known of which structures are necessary and/or sufficient for the conscious appreciation of pain.

Anatomical and physiological evidence repeatedly points toward a network of cortical regions which subserve the pain experience. Data suggest that nociceptive input is communicated via the somatosensory thalamus to the primary and secondary somatosensory cortices (S1 and S2; Friedman & Murray, 1986; Rausell & Jones, 1991), where information relating to the stimuli's intensity, location, and temporal aspects are thought to be encoded (Chudler, Anton, Dubner, & Kenshalo, 1990; Kenshalo & Isensee, 1983; Kenshalo et al., 2000). Two other structures important in conveying information regarding the affective valence of the pain experience are the anterior cingulate cortex (ACC) and insular cortex (IC), structures within the limbic system. Both ACC and IC receive direct input from medial thalamic nuclei (Apkarian & Shi, 1998; Craig, 1990; Dostrovsky et al., 1996a). Single-unit recordings within the ACC have revealed nociceptive neurons (Hutchison et al., 1999), but the ACC has also been implicated in cognitive processing such as attention (Davis et al., 1997; Derbyshire et al., 1998). The IC has been implicated in thermal processing, but other data suggest its importance in autonomic regulation, cardiovascular

functioning and homeostatic regulation (Augustine, 1996; Craig, 1996a; Craig, 1996b; Craig, Chen, Bandy, & Reiman, 2000).

The structures and mechanisms through which anesthetics block pain responsiveness remain uncertain. It has been hypothesized that their underlying mode of action is to induce thalamocortical hyperpolarization which occurs at the same time as unconsciousness either by direct cellular hyperpolarization, inhibition of excitement, enhancement of inhibition or any coupling of these mechanisms (Alkire et al., 2000). Several brain-imaging studies have investigated anesthetic (Alkire et al., 1995; Fiset et al., 1999; Wessen et al., 1997) and analgesic (Alkire et al., 1997; Alkire et al., 1999; Adler et al., 1997; Firestone et al., 1996; Gyulai, Firestone, Mintun, & Winter, 1996) modulation of cerebral blood flow, and a few have examined its effect on sensory transmission (Antognini et al., 1997; Bonhomme et al., 2001; Gyulai, Firestone, Mintun, & Winter, 1997). Concomitant with loss of consciousness induced by general anesthesia, there is a decrease in blood flow within the thalamus (Fiset et al., 1999). Nevertheless, when somatosensory stimuli are presented with increasing doses of propofol, initially there is a decrease in blood flow within the somatosensory cortices, and only with unconsciousness is there a decrease of somatosensory transmission to the thalamus (Bonhomme et al., 2001).

As described above, pain activates a complex, distributed cortical network, including limbic and sensory regions. In contrast, vibrotactile stimuli preferentially activate sensory cortex (Bonhomme et al., 2001). Thus, although it has been shown that propofol-induced loss of consciousness disrupts thalamo-cortical vibrotactile transmission, it is not known if all cortical pain transmission is interrupted by loss of consciousness. Any pain-evoked activation that remains after loss of the conscious experience of pain would not be likely to subserve that experience, but would more probably reflect other correlates of pain, such as changes in autonomic function. Thus, in the present paper, we examine the influences of propofol-induced loss of consciousness on pain-evoked neural

activation to determine which structures are most likely involved in the conscious experience of pain. A subset of the current data have been described in abstract form (Hofbauer et al., 1999).

2.4 Methods

2.4.1 Subjects

Fifteen normal subjects (6 men, 9 women; all right-handed) aged between 18 and 33 years old (mean=24.0 years) participated. Prior to the study all subjects underwent a thorough medical evaluation. They were pain-free and had no history of neurological disorders. Subjects signed a written consent form, attesting that they could withdraw from the study at anytime. All procedures were approved by the Ethics and Research Committee of the Montreal Neurological Institute and Hospital.

2.4.2 Stimulation Procedures

During each 1-min PET scan, thermal stimuli were delivered to the subject's left volar forearm using a contact thermode ($1cm^2$ for 11 subjects or $9cm^2$ for 4 subjects). Twelve 5-sec stimuli were presented to six spots on a 3x2 matrix with two non-consecutive stimulus presentations at each spot. The thermode temperature was either slightly warm (35°C) or painfully hot (43.5 to 49.5°C). For the painfully hot condition, the thermode temperature was individually determined in a pre-experimental session, to obtain a verbal pain intensity rating between 40 and 80 on a 100-point magnitude-estimation scale. Immediately after each scan except Unconsciousness, subjects rated both pain intensity and unpleasantness using separate magnitude-estimation scales of 0 to100. Verbal descriptor endpoints were given for each scale. For the intensity scale, "0" was defined as "no burning, pricking, stinging sensation", the most frequently chosen words describing the sensory aspect of heat pain in an independent study (Morin & Bushnell, 1998), and "100" indicated an "extremely intense sensation." For the unpleasantness scale, "0" was designated as "not at all unpleasant," and "100" denoted "extremely unpleasant." To avoid ceiling effects, subjects were instructed that responses could surpass "100" if larger values were needed to describe sensations relative to previous ratings (Rainville, Feine, Bushnell, & Duncan, 1992; Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999a). If the

stimulus was not rated as painful the subjects rated warmth intensity on a 0-100 magnitude-estimation scale. For the warmth scale, "0" was defined as "no warm sensation", and "100" indicated "just hot, barely painful."

2.4.3 Experimental Design

Subjects received one trial each of painful heat and warm stimulation during each condition: alert control, moderate sedation, deep sedation and unconsciousness (Table 2-1). An additional painful heat scan was added during the alert-control condition with subjects being told, "to withdraw their arm every 2-3 stimulations" to mimic withdrawal responses that sometimes occur during moderate propofol doses. This condition was used to determine areas mediating stimulus-evoked movement under propofol anesthesia. During all conditions, subjects were instructed to rest quietly with their eyes closed and to focus on the stimulation. The alert-control condition was always presented first, followed by the moderate sedation, deep sedation, and finally unconsciousness (see Table 2-1). The stimulus order of the warm (35°C) and painfully hot (43.5 to 49.5°C) scans was counterbalanced across subjects within each condition.

2.4.4 Propofol Infusion

In addition to the alert-control condition (baseline, 0.0 μg/ml of propofol in plasma), three levels of propofol were targeted: moderate sedation (0.5 μg/ml of propofol in plasma), deep sedation (1.5 μg/ml of propofol in plasma), and unconsciousness (2.5 μg/ml of propofol in plasma and increased in 0.5μg/ml increments until unconsciousness was achieved). Propofol was infused using a computer-controlled infusion pump (for details see Bonhomme et al. 2001). In order to rapidly achieve the desired plasma and effect-site concentration, a bolus was initially given followed by an infusion with an exponentially declining rate. At the first concentration of propofol, the subjects were awake and mildly sedated and promptly followed commands.

Table 2-1: Experimental conditions

Scan	Stimulus*	State
1	Warm	Alert control
2	Pain	Alert control
3	Pain & Movement	Alert Control
4	Warm	Moderate sedation
5	Pain	Moderate sedation
6	Warm	Deep sedation
7	Pain	Deep sedation
8	Warm	Unconsciousness
9	Pain	Unconsciousness

*Stimulus order in scans 1-2, 3-4,5-6,7-8 were counterbalanced across subjects and sessions.

At the second concentration, the subjects were deeply sedated, their speech was sluggish and responses to verbal commands were slow. At the third concentration, the subjects were unconscious and did not respond to verbal commands. Subjects breathed spontaneously throughout. Heart rate and blood pressure were recorded every 10 seconds for the 1-minute periods prior to, during and after the PET scan.

To ensure subjects' safety they were under the care of a board-certified anesthesiologist. Standard monitoring (electrocardiogram, invasive blood pressure, pulse oximetry, end-tidal CO_2) was observed. Throughout the course of the experiment subjects wore a non-rebreathing oxygen mask, which had a flow rate of 3L/min. Resuscitation equipment was immediately available.

Arterial blood samples were drawn at least 5 minutes after the target effect site concentration was reached and 2 minutes prior to the initiation of each scan. High-performance liquid chromatography (HPLC) was used to determine the plasma concentration of propofol (Plummer, 1987).

2.4.5 Scanning Procedures

Regional cerebral blood flow (rCBF) was measured using 3-D high resolution PET (Siemens ECAT HR^+, 63 slices) following bolus injection of $H_2{}^{15}O$ (10 millicuries) without arterial blood sampling (Fox & Raichle, 1984; Fox & Mintun, 1989; Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, Herscovitch, Mintun, & Markham, 1983). Stimulus onset was simultaneous with bolus injection and 1-minute scans started approximately 15 seconds post-injection. Data were collected in two sequential frames of 40 and 20 seconds. Results reported here are for the entire 60 seconds of data acquisition, which we found to produce the highest signal-to-noise ratio in preliminary analyses. An inter-scan interval of 12-15 minutes allowed the tracer to decay to background levels and minimized sensitization to repeated thermal stimulation. Subjects wore insert-earphones connected to a microphone through which they received instructions

prior to each scan. During each scan, the microphone was turned off, and subjects remained immobile and kept their eyes closed. After completing the PET sessions, each subject underwent a high-resolution anatomical MRI (160 1-mm slices acquired on a Philips 1.5T Gyroscan system).

2.4.6 Image processing and analysis

Each PET- and MRI-volume was aligned and transformed (Collins, Neelin, Peters, & Evans, 1994) into a standardised space (Talairach & Tournoux, 1988) to allow for inter-subject averaging and localisation of rCBF changes. PET volumes were smoothed with a 14-mm (full-width, half-maximum) Hanning filter and normalized to the average brain count. Data were analyzed using converging methods. Peak-activation maps of pain-related changes in rCBF for each subject were obtained by subtracting normalised PET data recorded during the warm (35°C) condition from those of the painfully hot (43.5 to 49.5°C) condition during alert control, moderate sedation, deep sedation, and unconsciousness conditions. A peak-activation map was also derived by subtracting the painfully hot (43.5 to 49.5°C) alert-control scans from painfully hot (43.5 to 49.5°C) alert-control movement scans to determine structures involved in stimulus-evoked movement under propofol sedation.

Resulting volumes of pain-related changes in rCBF were averaged across sessions, and statistical t-maps were derived using the methods of Worsley et al. (1992). Directed searches of rCBF changes were performed on the right brain, contralateral to the stimulus, in regions previously shown to be involved in pain processing: S1, S2, ACC, IC, thalamus and cerebellum. The significance threshold for these directed searches was $t=2.63$ ($p< 0.05$, two-tail), after correction for multiple comparisons involving a 6-resel search volume (Worsley et al., 1992).

Global searches were performed within each experimental condition to investigate pain-related changes in activity in other brain areas. The significance

threshold was adjusted for multiple comparisons over the entire brain volume scanned ($t=\pm 4.5$; $p<0.05$). This correction gives an expected false-positive rate of 0.016 over the gray-matter volume, and corresponds to an uncorrected p-value of 0.0001 (Worsley et al., 1992).

To assess the significance of the linear relationship between the plasma level of propofol and normalized rCBF during either neutral or painful stimulation, a propofol regression map was calculated. The following calculations were performed for each of the three-dimensional volume elements (voxels) constituting a volume. The two data sets consisted of normalized rCBF obtained in fifteen subjects, each scanned once during the baseline and each of the three-propofol conditions, yielding a total of 60 CBF volumes. The effect of propofol on CBF was assessed by means of an analysis of covariance (ANCOVA), with subjects as a main effect and the plasma level of propofol as a covariate. The resulting *t*-statistic maps tested whether, at a given voxel, the slope of the regression was significantly different from zero; the presence of a significant peak was tested by a method based on three-dimensional Gaussian random-field theory, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al., 1992). Values equal to or exceeding a criterion of $t=3.5$ were considered significant ($p=0.0004$, two-tailed, uncorrected).

In addition to the above propofol regression, a regional regression map using an analysis of covariance (ANCOVA) was generated to assess the significance of the relationship between rCBF values in the thalamus (x=10.7, y=-15.4, z=2.5) and those obtained at each voxel of the entire scanned volume. This analysis was done to reveal brain regions that showed a coordinated blood flow response with the thalamus when data recorded during the warm condition were subtracted from those of the painfully hot condition at each level of anesthesia. Assessment of significance for this parameter (i.e., generation of a *t* map) was performed in the same manner as for the propofol regression.

2.5 Results

2.5.1 Propofol concentrations

The plasma propofol concentrations were calculated (mean±SD) to be 0.50±0.12; 1.77±0.27; and 3.73±0.84 for the moderate sedation, deep sedation and unconsciousness conditions, respectively and are shown in Figure 2-1. Due to technical constraints, plasma concentrations of propofol were not available for five subjects. We used the mean measured plasma concentrations of the ten available subjects to calculate average plasma concentrations and replaced the missing values at moderate sedation, deep sedation and unconsciousness for further analysis.

2.5.2 Magnitude-estimation ratings

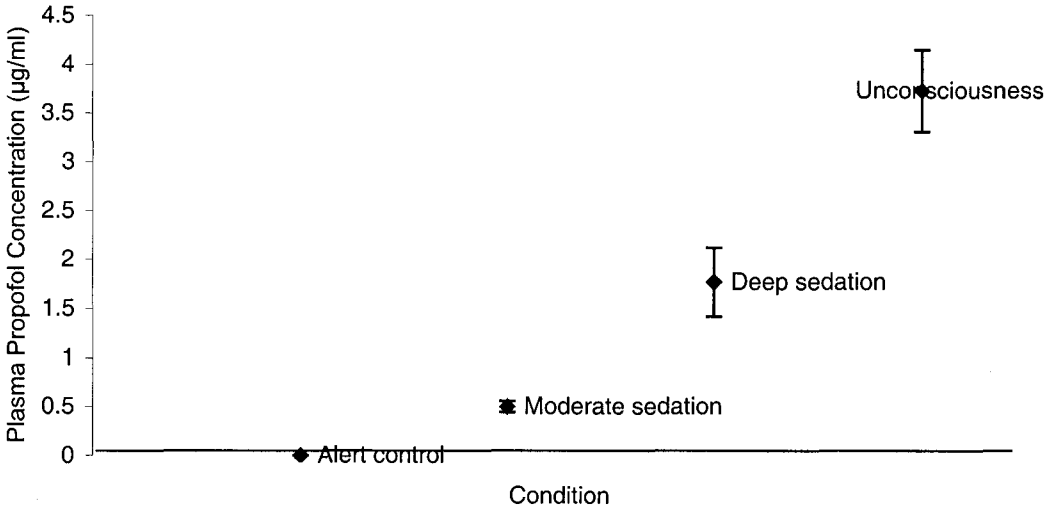
Magnitude-estimation ratings of pain intensity and unpleasantness (n=11) are shown in Figure 2-2. Ratings of pain intensity ($F=56.75$, $p<0.001$) and unpleasantness ($F=73.65$, $p<0.001$) were significantly different across conditions. Post-hoc analysis revealed that pain intensity ratings were higher during moderate sedation than alert control ($p<0.05$), suggesting propofol is hyperalgesic at the low dose (moderate sedation). Further, pain unpleasantness ratings were also higher during moderate sedation than deep sedation ($p<0.05$). Magnitude-estimation ratings were not available for four subjects who were unresponsive during deep sedation.

2.5.3 Vital signs

To examine the effect of propofol on cardiovascular and respiratory function, blood pressure (systolic and diastolic), heart rate (HR), respiratory rate (RR), oxygen saturation (SPO_2), and end-tidal carbon dioxide ($ETCO_2$) were measured. There was no significant change in HR, RR, SPO_2, and $ETCO_2$ before, during, or after painful stimulation across propofol levels (ANOVA, $p>0.05$). Systolic blood pressure (SBP) decreased with increasing sedation and painful stimulation (ANOVAs; $p<0.05$). Post-hoc analysis revealed a lower SBP during

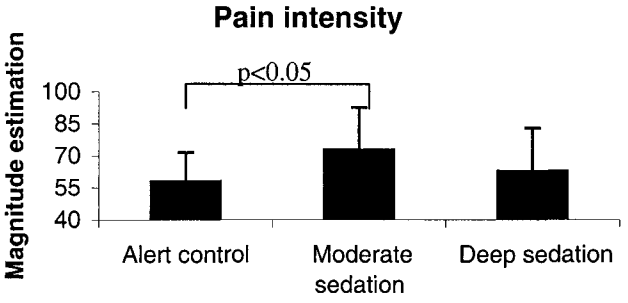
Unconsciousness compared to all other conditions (Tukey; $p<0.05$). Further, SBP was lower during painful stimulation versus non-painful stimulation. There was also a significant difference in systolic BP across all conditions compared to Unconsciousness 47°C (see Figure 2-3;Tukey; $p<0.05$).

Figure 2-1: Plasma propofol concentration

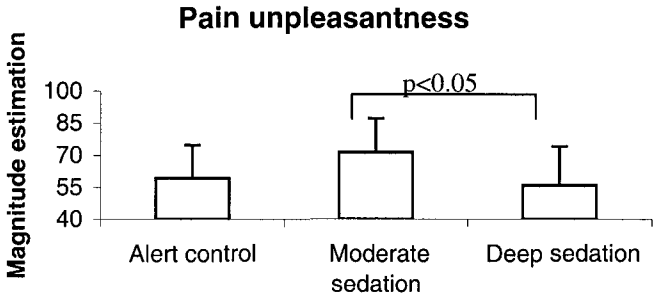


Mean concentration of plasma propofol expressed as the mean concentration of propofol (µg) per ml of blood plasma (± SD).

Figure 2-2: Magnitude-estimation ratings for pain intensity and pain unpleasantness

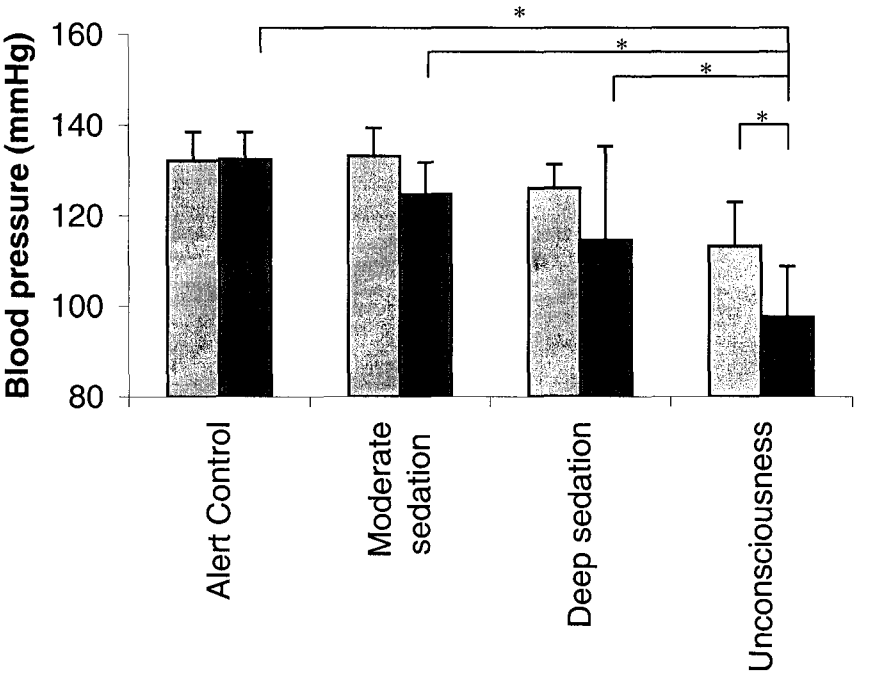


Ratings of pain intensity evoked by a 47°C thermal stimulus on subjects' volar forearm across conditions (±SD). Data are presented for the 11 subjects who rated the pain during all three conditions.



Ratings of pain unpleasantness evoked by a 47°C thermal stimulus on subjects' volar forearm across conditions (±SD). Data are presented for the 11 subjects who rated the pain during all three conditions.

Figure 2-3: Systolic blood pressure across conditions



Systolic BP evoked by a 35°C (gray) and 47°C (black) thermal stimulus on subjects' volar forearm across conditions (±SD; *$p<0.05$).

2.5.4 Brain imaging

2.5.4.1 Pain-related changes in rCBF during Alert-Control condition

To assess the effects of painful thermal stimulation on rCBF, the painful stimulation data were compared with those of the 35°C non-painful stimulation. Results of directed searches performed on S1, S2, ACC, IC, thalamus and cerebellum and global searches are summarized in Table 2-2. In the alert-control condition (Table 2-2A, Figure 2-4) there were significant pain-related increases in ACC, thalamus and cerebellum. A directed search failed to find significant peaks in S1, S2 and IC but peaks with non-significant trends toward significance were observed in these regions (Table 2-2). A global search revealed an additional pain-related increase in rCBF in the brainstem.

2.5.4.2 Movement-related changes in rCBF during Alert-Control condition

To assess the effects of movement on rCBF, the painful stimulation/movement scan data were compared with those of the painful stimulation (see Table 2-3, Figure 2-5). A global search revealed movement-related increase in rCBF in the primary motor cortex (M1), S2, supplementary motor area (SMA), superior parietal lobule, S1, frontal lobe, and cerebellum.

Table 2-2: Pain-related activations

	Region	x	y	z	t-scores
A			Alert Control		
	M1/S1	33	-18	59	2.08
	S2	42	-25	18	2.37
	ACC	4	6.4	38	2.86*
	ACC(mid/post CC)	0	-13	26	4.11*
	IC (mid/post)	44	-7	23	2.51
	Thalamus	13	-16	0	3.39*
	Cerebellum	17	-59	-23	4.38*
	(hemisphere)	4	-49	-8	2.64*
	Cerebellum (vermis)				
	Brainstem	*-5*	*-37*	*-18*	*4.61**
B			Light Sedation		
	S1		No activation above 2.0		
	S2/Post. insula	33	-14	12	2.43
	ACC	15	17	36	4.11*
		4	-6	44	2.90*
	IC (mid/post)	29	-8	10	2.34
	(rostral)	32	6	17	2.74*
	(ipsi rostral)	-27	9	16	3.36*
	**Thalamus*	*9*	*-11*	*6*	*6.01*
	Cerebellum (vermis)	4	-54	-14	2.69*
	Cuneus	*-1*	*-78*	*17*	*-5.26*
C			Moderate Sedation		
	S1	*40*	*-28*	*56*	*-2.68**
	S2		No activation above 2.0		
	ACC		No activation above 2.0		
	IC		No activation above 2.0		
	Thalamus	*9*	*-19*	*2*	*5.08*

	Cerebellum	*24*	*-61*	*-23*	*4.82*
	(vermis)	*17*	*-64*	*21*	*4.77*
		-13	*-56*	*-18*	*7.17*
		-28	*-66*	*-21*	*5.54*
D			High Sedation		
	S1		No activation above 2.0		
	S2	41	-16	17	2.24
	ACC		No activation above 2.0		
	IC	31	-6	11	2.92*
	Thalamus		No activation above 2.0		
	Cerebellum (vermis)	0	-49	-11	2.32

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas.

[B] T=2.5 (see Methods)

[C] Control 47°C - Control 35°C;

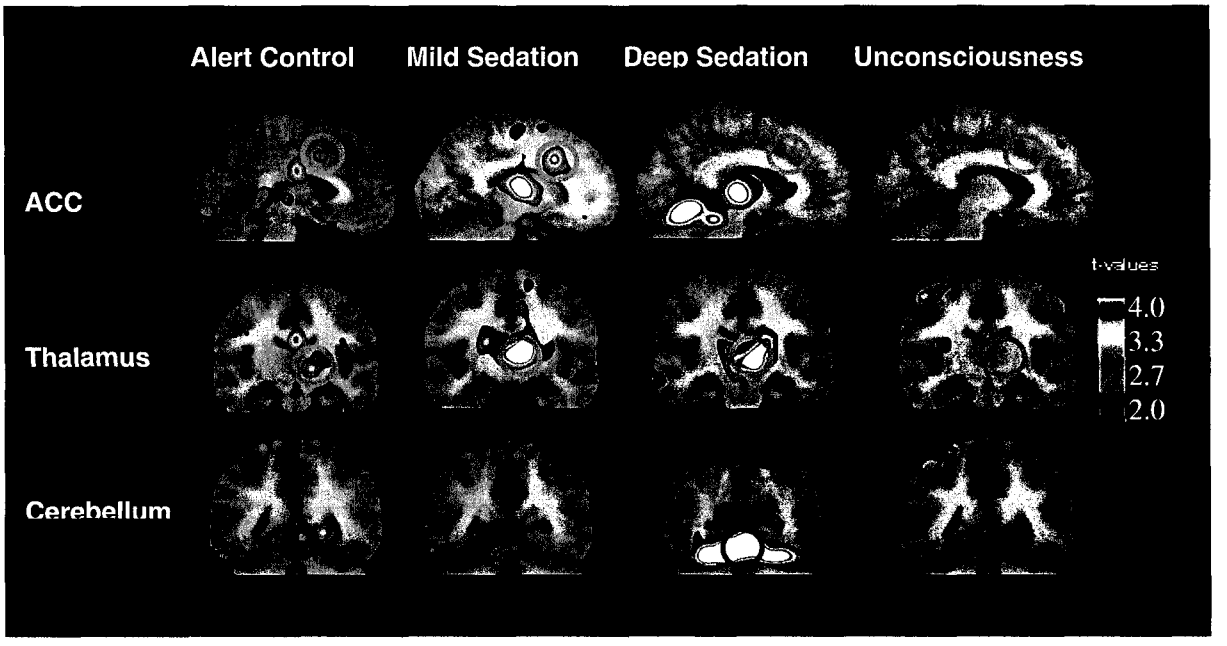
[D] Moderate sedation 47°C - Moderate sedation 35°C;

[E] Deep sedation 47°C – Deep sedation 35°C ;

[F] Unconsciousness 47°C - Unconsciousness 35°C.

Significant global search ($t\alpha=4.5$; $p<0.05$); *= significant directed search, ($t\alpha=2.5$; $p<0.05$

Figure 2-4: Pain-evoked activations



RCBF changes in pain-related activity within ACC (green), Thalamus (blue) and Cerebellum (red) associated with Alert Control, Mild sedation, Deep sedation and Unconsciousness. Pain-related activity is revealed by subtracting PET data recorded during the warm condition from the pain condition for the relevant state of consciousness. Coronal and sagittal slices are centered at the activation peaks.

Table 2-3: Movement related changes during alert-control condition

Region	x	y	z	t-scores
		Positive peaks		
M1	-1	-2	60	8.31
S2	58	-35	27	7.93
	-48	-37	30	6.20
Superior parietal lobe	9	-57	62	7.84
	-8	-57	63	6.72
S1	28	-33	63	7.52
Frontal lobe	27	-13	63	7.49
SMA	28	39	38	5.01
	40	-1	54	4.80
Cerebellum	-27	-52	-24	4.79
	-7	-54	-17	4.67
		Negative peaks		
Medial front-orbital gy	1	24	-18	-7.37
Frontal Lobe WM	31	37	-8	-5.68
Middle temporal gy	64	-30	-11	-4.75
Middle frontal gy	40	53	5	-4.61
Cingulate region	9	41	-8	-4.50

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas. [B] T=2.5 (see Methods). [C] Control 47°C movement - Control 47°C.

Figure 2-5: Movement-related activations

RCBF changes in movement-related activity within M1 (yellow), parietal cortex (aqua), cerebellum (red), S1 (pink) and S2 (green). Movement-related activity is revealed by subtracting PET data recorded during Alert Control 47°C from Alert Control Movement 47°C.

2.5.4.3 Pain-related changes in rCBF during propofol sedation

To assess the effects of propofol on pain-related activation, scans were performed following propofol induction. The painful stimulation data were compared with those of the 35°C non-painful stimulation at each level of propofol sedation. During moderate sedation (Table 2-2B, Figure 2-4), a directed search revealed significant increases in ACC, IC, thalamus and cerebellum. A directed search failed to find significant peaks in S1 and S2. A global search revealed a significant decrease in rCBF in the cuneus (Brodmann Area 17).
As in alert-control- and moderate-sedation conditions, pain-related activation during deep sedation in S1 and S2 was still absent, along with a lack of activity in ACC and IC (Table 2-2C, Figure 2-4). A directed search revealed significant pain-related activation in thalamus and cerebellum.

A directed search of pain-related activation sites during unconsciousness revealed a significant site of activation in IC. However a directed search of the other brain regions did not reach significance nor were any significant global activations observed. Nevertheless sub-threshold activations were observed in the cerebellar vermis and S2 regions.

2.5.4.4 Regression propofol vs. regional cerebral blood flow

Separate regression analyses were performed to determine the strength of the relationship between the plasma propofol concentration and rCBF during the Alert Control and sedation scans during either non-painful or painful stimulation. The results of the regression of propofol levels versus rCBF during the non-painful conditions are displayed in Table 2-4 and data from the painful conditions are summarized in Table 2-5 and Figure 2-6. As the plasma concentration of propofol increased, normalized rCBF decreased in the thalamus, brainstem, posterior cingulate cortex and partial cortex. On the other hand, significant positive correlations between propofol and rCBF were observed in a number of regions, including the cerebellum and ACC.

Table 2-4: Correlation of propofol dose with blood flow during the 35°C conditions

Region	x	y	z	t-scores	r-values
		Positive peaks			
Cerebellum	8	-49	-11	10.33	0.77
	-12	-50	-14	8.08	0.74
Frontal lobe WM	-19	34	14	8.07	0.80
Frontal lobe WM	27	-11	39	8.04	0.84
Frontal lobe WM	-28	-13	35	7.91	0.84
Temporal lobe WM	29	-42	21	7.84	0.84
Frontal lobe WM	-23	20	27	7.59	0.79
Frontal lobe WM	21	34	17	7.40	0.81
Frontal lobe WM	-17	12	36	7.36	0.75
Frontal lobe WM	16	10	38	7.19	0.79
Lateral ventricle	-31	-52	3	6.97	0.73
Superior temporal gy	-40	-6	-18	6.28	0.78
Medial frontal gy	-3	-11	59	6.28	0.59
Parahippocampal gy	32	-28	-20	6.25	0.70
Temporal lobe WM	39	-42	-5	6.00	0.78
Insula	39	1	-20	5.85	0.70
Temporal lobe WM	-23	-47	24	5.79	0.74
Superior temporal gy	-42	10	-20	5.36	0.74
Cuneus	23	-66	5	5.32	0.50
Temporal lobe WM	28	-61	12	5.17	0.65
Frontal lobe WM	40	-14	56	4.93	0.54
Precentral gy	60	1	30	4.31	0.61
		Negative peaks			
Precuneus	3	-66	38	-13.24	-0.80
Angular gy	46	-52	47	-11.51	-0.81
Thalamus	7	-18	9	-10.83	-0.65

Angular gy	-44	-52	48	-10.66	-0.80
Superior parietal lobe	-35	-62	48	-10.50	-0.80
Inferior frontal gy	44	46	3	-8.59	-0.72
Middle frontal gy	38	49	20	-8.10	-0.77
Middle temporal gy	63	-37	-6	-7.11	-0.64
Inferior temporal gy	-58	-33	-18	-7.05	-0.56
Middle frontal gy	-42	44	17	-7.00	-0.68
Inferior temporal gy	59	-28	-18	-6.62	-0.64
Putamen	-19	6	3	-5.80	-0.54
Frontal lobe WM	17	30	-20	-5.51	-0.60
Posterior limb of internal capsule	16	12	3	-5.29	-0.56
Inferior frontal gy	42	20	0	-4.64	-0.51
Cerebellum	-22	-78	-24	-4.57	-0.48

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas. [B] T_{α}=2.5 (see Methods). [C] Correlation of Alert control 35°C, Moderate sedation 35°C, Deep sedation 35°C and Unconsciousness 35°C with plasma propofol levels.

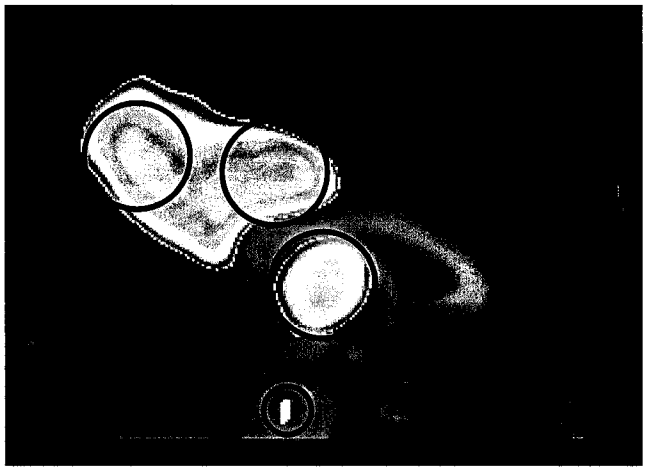
Table 2-5: Correlation of propofol dose with blood flow during the 47°C conditions

Region	x	y	z	t-scores	r-values
		Positive peaks			
Cerebellum	3	-50	-9	9.57	0.69
Cerebellum	13	-47	-14	9.53	0.73
Frontal Lobe WM	-27	-13	35	8.56	0.80
Temporal Lobe WM	31	-40	20	8.30	0.88
Frontal Lobe WM	24	-9	39	8.26	0.79
Frontal Lobe WM	-19	36	9	8.16	0.83
Insula	38	5	-20	7.99	0.80
Frontal Lobe WM	-19	8	39	7.53	0.76
Parietal Lobe WM	-28	-35	32	7.47	0.79
Frontal Lobe WM	20	27	24	7.44	0.79
Lateral occipitotemporal	-31	-37	-18	7.15	0.67
Temporal Lobe WM	-27	-44	17	7.13	0.76
Superior Temporal gyrus	-43	5	-18	6.30	0.68
Temporal Lobe WM	35	-49	-2	6.30	0.69
Medial Frontal gyrus	-8	-7	53	6.26	0.76
Medial Frontal gyrus	4	-6	59	5.88	0.59
Precentral gyrus	-54	-6	33	5.80	0.72
Postcentral gyrus	52	-6	32	5.73	0.69
		Negative peaks			
Precuneus	-1	-68	38	-13.80	-0.84
Cingulate region	1	-44	35	-12.60	-0.86
Thalamus	7	-16	9	-12.53	-0.74
Angular gyrus	48	-49	47	-12.14	-0.81
Thalamus	-4	-18	9	-11.63	-0.70
Superior Parietal Lobule	-39	-59	48	-11.13	-0.83
Middle Frontal gyrus	40	48	18	-8.90	-0.72
Middle Frontal gyrus	40	46	21	-8.90	-0.73
Middle Frontal gyrus	42	49	9	-8.74	-0.72
Inferior Frontal gyrus	31	58	3	-7.63	-0.69
Middle Temporal gyrus	63	-31	-9	-7.40	-0.68
Middle Frontal gyrus	-42	44	15	-7.23	-0.69

Middle Temporal gyrus	-60	-31	-15	-7.04	-0.61
Inferior Frontal gyrus	43	18	3	-6.12	-0.45
Frontal Lobe WM	-16	30	-21	-5.54	-0.61

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas. [B] T=2.5 (see Methods). [C] Correlation of Alert control 35ºC, Moderate sedation 35ºC, Deep sedation 35ºC and Unconsciousness 35ºC with plasma propofol levels.

Figure 2-6: Correlation of rCBF and propofol concentration



Negative correlation between normalized rCBF (during all neutral thermal stimulations) and propofol concentration is observed in the thalamus, brain stem, posterior cingulate cortex and parietal lobule during painful stimulation.

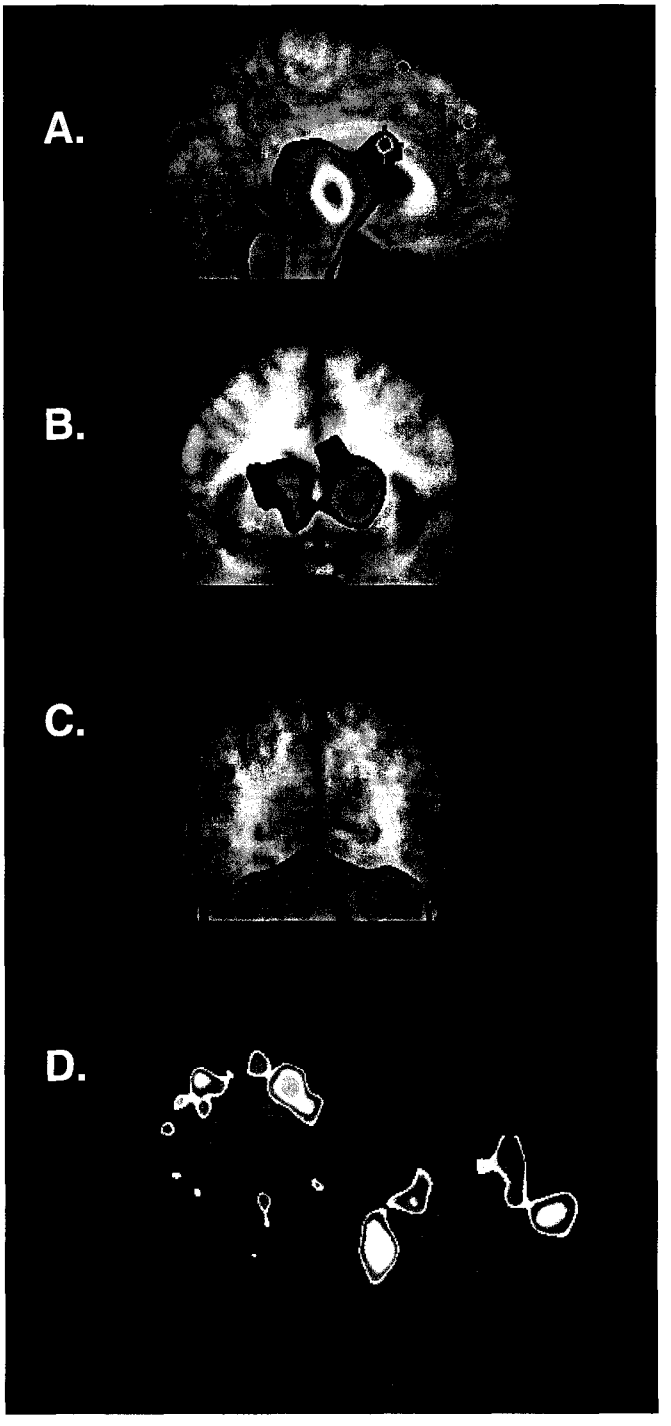
A second regression analysis was conducted to assess the power of the relationship between thalamic activation and rCBF in other brain structures across the experimental conditions. The thalamus-based regional regression revealed a positive correlation between thalamic CBF and the ACC, basal ganglia and cerebellum and negative correlation with activity in the frontal cortex (Figure 2-7, Table 2-5).

Table 2-6: Cerebral structures correlated with thalamic activity

Region	x	y	z	t-scores	r-score
		Positive peaks			
Thalamus	-8	-19	11	11.08	0.83
Cerebellum	-16	-56	-20	9.13	0.63
	-30	-64	-23	6.98	0.68
	27	-64	-21	6.90	0.65
Putamen	24	3	5	7.82	0.72
	-23	5	6	4.62	0.50
Caudate nucleus	-13	6	9	4.52	0.59
Cingulate region	5	8	26	3.29	0.57
		Negative peaks			
Middle frontal gy	31	29	44	-5.69	-0.71
	-42	17	26	-5.18	-0.62
Sup. Frontal gy	23	10	59	-4.81	-0.53
	-21	27	51	-4.64	-0.47
Medial frontal gy	7	48	36	-4.72	0-.57
	-1	17	62	-4.53	-0.40
Post. Central gy	-13	-59	63	-4.48	-0.55

Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas. [B] T=2.5 (see Methods). [C] Correlation of Alert control 47°C - Alert control 35°C, Moderate sedation 47°C - Moderate sedation 35°C, Deep sedation 47°C - Deep sedation 35°C and Unconsciousness 47°C - Unconsciousness 35°C with thalamus (x=10.7, y=15.4, z=2.5).

Figure 2-7: Positive correlation between rCBF and propofol concentration



Positive correlation between normalized rCBF (during all pain minus all neutral thermal stimulations) and propofol concentration is observed in the ACC, basal ganglia and cerebellum and a negative correlation is seen in the frontal cortex.

2.6 Discussion

Results of the present experiment demonstrate that increasing doses of propofol alter both pain perception and forebrain pain-evoked activity in a non-linear fashion. At sedative dose levels, both pain perception and activity in ACC and thalamus are enhanced, and then as the subjects begin to lose consciousness, pain-evoked activity in ACC is lost first, followed by the thalamus. Pain-evoked activity in other cortical areas and in cerebellum shows a less regular relationship to the conscious experience of pain.

The finding that pain-evoked activity in ACC shows a close relationship to the conscious experience of pain during graded doses of propofol is consistent with other types of evidence. Nociceptive neurons have been identified in ACC using single-unit recordings in humans (Hutchison et al., 1999), monkeys (Koyama et al., 1998) and rabbits (Sikes et al., 1982). Further, among human brain-imaging studies, ACC is probably the cortical region most reliably activated by pain (Derbyshire et al. 1998; Peyron et al. 2000). Using correlational analyses, investigators have found a strong association between pain-evoked ACC activity and pain perception, particularly pain unpleasantness (Rainville et al., 1997). Studies that used pharmacological manipulations to reduce pain perception also found reduced pain-evoked ACC activity. For example, Casey et al. (2000) observed that fentanyl reduced both pain ratings and pain-evoked ACC activity. Similar to our findings, Gyulai et al. (1997) showed that ACC pain-evoked activity was eliminated commensurate with reduced pain perception following conscious sedation with nitrous oxide.

Pain-evoked activity in IC showed a less systematic relationship to both propofol level and pain perception. Activity in mid-insula showed similar levels during the alert control, moderate sedation, and unconsciousness conditions, but was reduced during the deep sedation, whereas activity in the rostral insula was only present during the moderate sedation condition. This finding suggests that pain-evoked IC activity may not have a pivotal role in the conscious appreciation of

pain. Based on findings that pain activates IC in human brain imaging studies (Aziz et al., 1997; Casey et al., 2000; Coghill et al., 1999; Hofbauer et al., 2001; Iadorola et al., 1998; Svennson et al., 1997), investigators have concluded that IC is important for pain perception. Nevertheless, other evidence shows that IC has a particularly important role in autonomic control and homeostatic change within the body, so that its activation during pain may not underlie perception, but may reflect autonomic changes associated with pain (Craig, 1996a; Craig et al 2000). Oppenheimer and colleagues have demonstrated the importance of IC in blood pressure change (Zhang et al., 1999) and the consequence its disruption following an IC lesion (Oppenheimer et al., 1996). Other studies have implicated IC to alteration in heart rate (Volkow et al., 2000), respiratory function and breathlessness (Liotti et al., 2001; Banzett et al., 2000). In addition, propofol is known to induce bradycardia, hypotension as well as apnea. In the present study, the only significant change of the cardiovascular measures was a change in systolic blood pressure during unconsciousness between the neutral and painful condition. Moreover, the change in BP was coincident with the only significant modulation of IC (see Table 2-2).

Neuroanatomical studies suggest direct connections from nociceptive thalamic nuclei to IC, using anatomical tracing and antidromic activation techniques (Dostrovsky et al., 1996a; Zhang & Oppenheimer, 2000). Consistent with these findings is a study in monkey, which reports single units that respond to nociceptive pinch (Zhang, Dougherty, & Oppenheimer, 1999). Recently, an opioid-responsive site in the rostral agranular insula was delineated, suggesting the importance of this area in pain perception and its subsequent modulation (Burkey et al., 1996). There is also PET evidence that demonstrates the cessation of pain-evoked insular activity following fentanyl administration (Casey et al., 2000). IC is an important structure in the pain experience but due to the lack of IC modulation by conscious state in our study, it is unlikely that it performs a pivotal role in the conscious appreciation of pain.

The somatosensory cortex, namely S1 and S2, is activated by painful stimuli in approximately one half of all PET and fMRI studies (Bushnell et al., 1999). Activation of S1 and S2 was present in the study but greatly reduced (below significance). The diminution of somatosensory activation might be explained by the DNIC (diffuse noxious inhibitory controls) phenomenon; whereby the second presentation of a noxious stimulus is perceived as less painful due to activation of endogenous opioid systems by the first stimulus (Le Bars, Villanueva, Bouhassira, & Willer, 1992). Placement and management of an arterial catheter in the right wrist of our subjects at the beginning of the study is a painful manipulation, which might have generated stress-induced analgesia. Even though pain intensity ratings were between 40 and 80 (average 59) these ratings were considerably lower than a previous study conducted in our lab (~75) (Coghill et al., 1994). A lack of statistical power or variability in somatosensory sulcal anatomy might also explain the reduction of activation in S1 and S2.

The cortical areas discussed above (ACC, IC, S I and S2) all receive their main nociceptive input via the thalamus (Devinsky et al., 1995; Friedman et al., 1986; Musil et al., 1988; Vogt, et al., 1987; Rausell & Jones, 1991). Data from our study show that thalamic pain-evoked activation increased during moderate sedation, when pain ratings were enhanced, then remained highly significant during deep sedation, and abruptly decreased to below significant levels at loss of consciousness. Bonhomme et al. (2001) showed that as long as subjects remained conscious, there was still thalamic activation in response to vibrotactile stimulation. However, this activation disappeared following propofol–induced unconsciousness.

It is well accepted that the cerebellum is involved in motor acquisition, discrimination (Gao et al., 1996) and control (Middleton et al., 1997). With the advent of brain imaging techniques, a role for the cerebellum has been proposed in nociceptive processing, language, learning, memory and cognition (Casey et al., 1994; Saab, Kawasaki, Al Chaer, & Willis, 2001; Desmond & Fiez, 1998; Fiez, 1996). With the use of an opiate, fentanyl, Casey et al. (2000)

demonstrated the reduction (but not complete blockade) of cold-pressor-induced activation within the cerebellar vermis and cerebellar hemisphere. Opiates lead to reduction of both tactile (Brennum, Arendt-Nielsen, Horn, Secher, & Jensen, 1993) and nociceptive signals (Posner, Telekes, Crowley, Phillipson, & Peck, 1985). This is very different than our results with a non-opiate anesthetic. We observed an augmentation in cerebellar rCBF (within the vermis) from the alert-control condition through deep sedation and a return to baseline levels (alert control) during the unconscious condition. As our subjects descended toward unconsciousness, the non-opiate anesthetic propofol could have inhibited the endogenous pain reduction mechanisms, leading to an enhancement of nociceptive cerebellar activation during moderate and deep sedation. At loss of consciousness, however, there could have been a general reduction of nociceptive transmission and a return to baseline activity.

An additional explanation for the increase of rCBF during the moderate- and deep-sedation conditions could be that slight spastic and uncoordinated movement from eight subjects was randomly locked to the stimulus. These results agree with a study by Jenkins et al. (1997), where movement frequency was dependent on increases in rCBF within the cerebellar hemisphere and vermis. Despite the movement of the subjects, there was no activation seen in motor areas (primary motor area, supplementary motor area or basal ganglia) when the neutral condition was subtracted from the painful condition during moderate sedation, deep sedation and unconsciousness. When subjects were told to move following a painful stimulus, activation was seen in M1, SMA, superior parietal lobule and cerebellum (see Figure 2-5). The cerebellar activation was similar in position to the peak activation of the Moderate Sedation condition (x=-13, y=55, z=-18). This same peak correlated with experimenter ratings of subject movement, which was then correlated to rCBF across conditions (47-35°C). As subjects descend into unconsciousness, there could be a desire to stay alert and avoid the loss of consciousness and move. All of these factors could account for the cerebellar activation seen in this study. Our findings

and those of Casey et al. (2000) suggest that nociceptive and motor information is reaching the cerebellum via the spino-cerebellar pathway, an area less sensitive to anesthetic modulation, but failed to reach higher structures. Our results could also be explained with data collected from rat (Rampil, Mason, & Singh, 1993) and sheep (Antognini & Schwartz, 1993) suggesting pain-evoked movement could be due to reflexive spinal cord anti-nociceptive mechanisms.

Earlier work by Alkire et al. demonstrated a global decrease in metabolic rate in the brain following propofol administration, with a preferential decrease cortically (Alkire et al., 1995). In the current study, we observed that concomitant with an increase in plasma propofol concentration, there was a decrease in rCBF activity within the thalamus, brain stem, posterior cingulate cortex, parietal lobe and precuneus. These results support previously published conclusions (Bonhomme et al., 2001; Fiset et al., 1999) and confirm the importance of the thalamus and the ascending reticular activating system (ARAS) in regulating consciousness (Paus et al., 1997; Steriade et al., 1990). Similarly, patients in persistent vegetative states demonstrated reduced regional cerebral glucose metabolism in posterior cingulate cortex and precuneus areas (Laureys, Lemaire, Maquet, Phillips, & Franck, 1999). These changes may be reversible as suggested by a case report by Laureys and colleagues (2000) who described a patient with restored thalamocortical connectivity following return to consciousness from a persistent vegetative state. Finally these results are compatible with our previous correlation analyses of rCBF and propofol concentration (Fiset et al., 1999), rCBF and propofol concentration during somatosensory stimulation (Bonhomme et al., 2001) and extends the relationship to include nociceptive stimulation.

The mechanisms of propofol-induced unconsciousness have been debated. Recent evidence however, indicates that propofol produces antinociception in rats through spinal $GABA_A$ and delta opioid receptors (Nadeson & Goodchild, 1997). Evidence suggests propofol was devoid of, or contained minimal, analgesic properties (Petersen-Felix, Arendt-Nielsen, Bak, Fischer, & Zbinden,

1996; Wilder-Smith, Kolletzki, & Wilder-Smith, 1995; Zacny et al., 1996). Studies by Petersen et al. (1996) and Wilder-Smith et al. (1995) did not observe analgesia following painful electrical and heat stimulations in response to propofol infusion. Hyperalgesia was observed following mechanical pressure pain. Results from our study support these data since there were significant differences in pain intensity or unpleasantness ratings across conditions. Our data suggests that despite deep sedation and loss of consciousness there is still some nociceptive information that reaches cortical and subcortical structures, which include IC and cerebellum. Moreover, these data suggest that thalamo-cortical limbic circuits are important for the conscious appreciation of pain.

2.7 Acknowledgments

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CHAPTER 3 - CORTICAL REPRESENTATION OF PAIN SENSATION

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (2001). Cortical representation of the sensory dimension of pain. J.Neurophysiol., 86, 402-411.

3.1 Chapter Overview

Whereas the previous chapter addressed the cerebral pain network responsible for the conscious appreciation of pain, the present chapter reports on an experiment in which we investigated the role of different cortical areas in the processing of the sensory dimension of pain. The motivation for this study came from previous work in our lab, in which I took part, that demonstrated that pain sensation and affect can be modulated independently using hypnotic suggestions (Rainville et al., 1999a). In the current study, we took advantage of the ability to separately modify different aspects of the conscious pain experience in order to examine the neural structures underlying the perception of pain intensity.

Single-unit-recording studies have attempted to uncover neurons throughout the peripheral and central nervous system that respond to alterations in stimulus intensity. Neurons in the spinal cord, thalamus and primary somatosensory have been demonstrated to respond and encode changes in stimulus temperature (Bushnell et al., 1993; Kenshalo, Jr. & Isensee, 1983; Maixner, Dubner, Kenshalo, Jr., Bushnell, & Olivéras, 1989). However, little is known about the cortical structures necessary for the representation of pain sensation intensity.

Numerous studies have examined hypnotically induced analgesia. A recent meta-analysis reported that hypnotic suggestions for analgesia were effective in reducing both clinical and experimental pain (Montgomery, DuHamel, & Redd, 2000). Kiernan et al. (1995) demonstrated a reduction of the R-III reflex, a spinal nociceptive reflex, following hypnotically induced analgesia, suggesting a partial involvement of an endogenous antinociceptive mechanism. Similarly, the amplitude of the evoked brain potentials decreased during suggestions for analgesia but increased in response to suggestions for hyperalgesia (Arendt-Nielsen, Zachariae, & Bjerring, 1990). Research from our laboratory corroborates and extends these findings, as directed suggestions were able to selectively alter (increase or decrease) pain unpleasantness and intensity ratings (Rainville et al., 1999a).

Melzack & Casey (1968) described pain as a multidimensional experience. However, little has been done to elucidate the neural underpinnings of these components. However, by combining directed hypnotic suggestions and human brain imaging we were able to separate the sensory and affective components of the pain experience and determine the cortical representation. Thus, using PET brain-imaging techniques, a previous study from our lab used hypnotic suggestions to show that the ACC is particularly important for the affective dimension of pain (Rainville et al., 1997). Therefore, the purpose of this study is to establish cortical structures necessary for the appreciation of pain sensation by using directed hypnotic suggestions. In addition to describing the differential neural correlates of affective and sensory dimensions of pain, this work has elucidated the neural circuitry of hypnotic pain modulation and showed the physiological basis for cognitively produced analgesia (Rainville et al., 1999b; Rainville, Hofbauer, Bushnell, Duncan, & Price, 2001).

3.2 Abstract

It is well accepted that pain is a multi-dimensional experience, but how the brain represents these dimensions is little known. We used positron emission tomography (PET) to indirectly measure pain-evoked cerebral activity before and after hypnotic suggestions were given to modulate the perceived intensity of a painful stimulus. These techniques were similar to those of a previous study in which we gave suggestions to modulate the perceived unpleasantness of a noxious stimulus. Ten volunteers were scanned while tonic warm and noxious heat stimuli were presented to the hand during four experimental conditions: Alert Control, Hypnosis Control, hypnotic suggestions for Increased-Pain Intensity and hypnotic suggestions for Decreased-Pain Intensity. As shown in previous brain imaging studies, noxious thermal stimuli presented during the Alert and Hypnosis Control conditions reliably activated contralateral structures, including primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC) and insular cortex (IC). Hypnotic modulation of the intensity of the pain sensation led to significant changes in pain-evoked activity within S1, in contrast to our previous study in which specific modulation of pain unpleasantness (affect), independent of pain intensity, produced specific changes within the ACC. This double-dissociation of cortical modulation indicates a relative specialization of the sensory and the classical limbic cortical areas in the processing of the sensory and affective dimensions of pain.

3.3 Introduction

Pain is a complex sensory and emotional experience that normally signals actual or potential tissue damage. Nevertheless, like other sensory modalities, pain can be highly influenced by psychological state or environmental factors. The experience of pain is described along two main axes: (1) the sensory-discriminative dimension, comprising spatial, temporal and intensity properties; and (2) the affective-motivational dimension, related to the unpleasantness of the stimulus, as well as the behavioral and autonomic reactions it evokes (Fernandez & Turk, 1992; Melzack & Casey, 1968; Price, Harkins, & Baker, 1987).

Consistent with the multidimensional concept of pain are findings from human brain imaging studies, showing that multiple cortical regions are activated during the presentation of painful stimuli (Coghill et al., 1994; Derbyshire & Jones, 1998; Jones, Derbyshire, Apkarian, & Jones, 1995; Paulson et al., 1998; Talbot et al., 1991). Among the cortical regions frequently activated by pain are primary and secondary somatosensory cortices (S1 and S2). These regions receive noxious and innocuous somatosensory input from the somatosensory thalamus (Apkarian et al., 1989b; Rausell & Jones, 1991) and contain neurons that code spatial, temporal and intensive aspects of innocuous and noxious somatosensory stimuli (Chudler et al., 1990; Dong et al., 1994; Kenshalo, Jr. et al., 1983; Kenshalo, Jr. et al., 1988; Shi & Apkarian, 1995), characteristics that could subserve the sensory-discriminative dimension of pain processing.

Two other cortical regions that are reliably activated in human brain imaging studies of pain, the anterior cingulate cortex (ACC) and the insular cortex (IC) (Aziz et al., 1997; Coghill et al., 1994; Craig, Reiman, Evans, & Bushnell, 1996; Davis e al., 1997; Jones et al., 1991; Ploghaus et al., 1999; Talbot et al., 1991; Vogt, Derbyshire, & Jones, 1996), are considered to be components of the classical limbic system (Papez, 1937; MacLean, 1949), and thus potential candidates for processing the affective-motivational dimension of pain. In

primate, ACC receives input from medial thalamic nuclei that contain nociceptive neurons, including nucleus parafascicularis (Pf) and the ventrocaudal part of nucleus medialis dorsalis (MDvc) (Craig, 1990; Apkarian et al., 1998b). Direct pain input to the ACC is further suggested by the observations that painful stimuli evoke potentials over the human anterior cingulate gyrus and that single nociceptive neurons are present in the ACC of humans (Hutchison et al., 1999; Lenz et al., 1998), monkeys (Koyama et al., 1998), and rabbits (Sikes et al., 1992). These data indicate a specific role for parts of ACC in pain processing that is distinct from, although probably related to, the role of ACC in cognitive processes such as attention (Davis et al., 1997; Derbyshire et al., 1998). The IC also receives direct thalamocortical nociceptive input in the primate (Dostrovsky et al., 1996b) and has been implicated in autonomic regulation (Maquet et al., 1999; Augustine, 1996). The possible implication of IC in the subjective experience of pain is consistent with a function of the IC in higher-order processes relevant to homeostatic regulation (Craig, 1996b; Berman, 1995; Adams & Stenn, 1992).

Although anatomical and physiological evidence provides indirect support for the hypothesis that these distinct cortical regions may be preferentially involved in different aspects of pain perception, a direct test of this hypothesis has been difficult to achieve. Under most circumstances the sensory and affective components of pain are highly correlated; as pain becomes more intense it usually becomes more unpleasant, motivates more vigorous escape or avoidance behaviors, and evokes a more robust autonomic activation. However, in certain clinical situations, these dimensions become dissociated (Price 1999). For example, the pain associated with a myocardial infarction and that associated with heartburn may be similar in intensity and quality, but may lead to widely divergent affective and motivational responses. Nevertheless, under normal conditions in an experimental pain paradigm, sensory and affective components of pain are highly correlated and cannot be easily dissociated (Price et al., 1987; Rainville et al., 1992).

We have developed an experimental paradigm to dissociate pain sensation and pain affect using hypnotic suggestions designed to modulate specifically pain intensity or pain unpleasantness (Rainville et al., 1999a). Using this paradigm, we previously have shown that a selective modulation of pain unpleasantness results in a corresponding modulation in pain-evoked ACC activity, with no indication of such modulation in S1 cortex (Rainville et al., 1997). Positron emission tomography (PET) was used to examine changes in regional cerebral blood flow (rCBF) related to pain and to changes in pain induced by hypnotic suggestions that alter perceived pain intensity. Some of the current data have been described in abstract form (Duncan, Rainville, Price, & Bushnell, 1996; Hofbauer, Rainville, Duncan, & Bushnell, 1998; Hofbauer, Rainville, Bushnell, & Duncan, 1998; Rainville, Duncan, Price, & Bushnell, 1996). Effects of hypnosis unrelated to pain-evoked activity have been reported elsewhere (Rainville et al., 1999b).

3.4 Methods

3.4.1 Subjects

Ten normal pain-free subjects (4 males, 6 females; all right-handed) between 20 and 35 years old (mean=24.2 years) participated. All subjects were selected from a larger group (n=22) for their ability to modulate pain sensation reliably (see Rainville et al. 1999a). Subjects were tested for hypnotic susceptibility using the Stanford Hypnotic Susceptibility Scale (Form A), and had scores ranging from 1 to 10 (mean: 6.9). There was a wider range of hypnotic susceptibility for subjects in the current study than for those in the Rainville et al. (1997) study, but there was no significant difference between the two groups of subjects. Subjects gave informed consent acknowledging that they could withdraw at any time without prejudice. All procedures were approved by the Ethics and Research Committee of the Montreal Neurological Institute and Hospital and were in accordance with the Declaration of Human Rights, Helsinki, 1975.

3.4.2 Stimulation Procedures

During each scan, the subject's left hand was immersed up to the wrist in a temperature-controlled circulating water bath (Neslab Instruments Inc., New Hampshire) for 60 seconds. The water temperature was either slightly warm (35°C) or painfully hot (46.0 to 47.5°C). For the painfully hot condition, the water temperature was individually determined in a pre-experimental session, so that the pain intensity was rated between 40 and 80 on a 100-point magnitude-estimation scale.

3.4.3 Experimental Design

Subjects received two trials each of painful heat and slightly warm stimulation during two conditions (Alert Control and Hypnotic Control) and received painful heat during the conditions involving hypnotic suggestions for Increased- or Decreased-Pain Intensity (Table 3-1). In the Alert-Control condition, subjects

were instructed to rest quietly. Prior to the Hypnotic-Control condition, instructions were given to induce a state of hypnosis (see details below), without suggestions to alter perception. Subjects then remained in a hypnotic state during subsequent conditions involving suggestions to increase or decrease pain intensity.

Table 3-1: Experimental conditions

Scan	Stimulus*	State
1	Warm	Alert Control
2	Painful	Alert Control
3	Painful	Alert Control
4	Warm	Alert Control
5	Painful	Hypnosis Control
6	Warm	Hypnosis Control
7	Warm	Hypnosis Control
8	Painful	Hypnosis Control
9	Painful	↑ Pain Intensity
10	Painful	↑ Pain Intensity
11	Painful	↓ Pain Intensity
12	Painful	↓ Pain Intensity

*Stimulus order in scans 1-4, 5-8, and pain-modulation suggestions order in scans 9-12 is reversed in half the subjects and sessions.

Because of possible residual effects of hypnosis and pain-modulation suggestions, the Alert Control condition was always presented first, followed by the Hypnotic-Control condition, and finally by the Increased- and Decreased-Pain Intensity conditions (see Table 3-1). The stimulus order of the warm (35°C) and painfully hot (46.0 to 47.5°C) scans was counterbalanced across subjects within the Alert-Control and Hypnotic-Control conditions, as were the blocks of two trials in the Increased- and Decreased-Pain Intensity conditions.

3.4.4 Hypnotic Induction and Suggestion Procedures

The hypnotic induction and suggestion procedures were adapted from Bourassa et al. (1991) and Kiernan et al. (1995), and are described in Rainville et al. (1999a). In short, the hypnotic state was induced using a modification of the protocol included in the Stanford Hypnotic Susceptibility Scale, Form A (SHSS-A). The hypnotic state was maintained throughout the Hypnotic-Control and Increased- and Decreased-Pain Intensity conditions; although no instructions were given during the scans, sub-tests of the SHSS-A were administered between scans to assess hypnotic susceptibility. Before each scan of the Increased- and Decreased-Pain Intensity conditions (Table 3-1, scans 9-12), subjects were given the additional suggestions to increase or decrease the intensity of the heat pain (Rainville et al., 1999a).

3.4.5 Psychophysical and Physiological Measurement Procedures

Immediately after each scan, subjects rated both pain intensity and unpleasantness using separate magnitude-estimation scales of 0 to100. Verbal descriptor endpoints were given for each scale. For the intensity scale, "0" was defined as "no burning, pricking, stinging sensation", the most frequently chosen words describing the sensory aspect of heat pain in an independent study (Morin et al., 1998), and "100" indicated an "extremely intense sensation." For the unpleasantness scale, "0" was designated as "not at all unpleasant," and "100" denoted "extremely unpleasant." To avoid ceiling effects, subjects were instructed that responses could surpass "100" if larger values were needed to

describe sensations relative to previous ratings (Rainville et al., 1992; Rainville et al., 1999a). If the stimulus was not rated as painful the subjects rated warmth intensity on a 0-100 magnitude-estimation scale. For the warmth scale, "0" was defined as "no warm sensation", and "100" indicated "just hot, barely painful." Psychophysical ratings of stimulus intensity and unpleasantness were compared across the four experimental conditions involving noxious stimuli (ANOVA; Alert Control, Hypnosis Control, hypnotic suggestions for Increased-Pain Intensity, and hypnotic suggestions for Decreased-Pain Intensity).

Heart rate was recorded for one minute before and for one minute during each of the twelve PET scans. Rates were averaged across the two presentations of each stimulus condition and compared within each experiment (ANOVA) to determine the effects of the stimulation (before and during) and the experimental conditions (Alert-Control 35°C and Hypnosis-Control 35°C; Alert-Control 47°C, Hypnosis-Control 47°C, Increased- and Decreased-Pain Intensity).

3.4.6 Scanning Procedures

Regional cerebral blood flow (rCBF) was measured using 3-D high resolution PET (Siemens ECAT HR$^+$, 63 slices) following bolus injection of $H_2{}^{15}O$ (10 millicuries) without arterial blood sampling (Fox & Mintun, 1989; Fox et al., 1984; Herscovitch et al., 1983; Raichle et al., 1983). Stimulus onset was simultaneous with bolus injection and 1-minute scans started approximately 15 seconds post-injection. Data were collected in two sequential frames of 40 and 20 seconds. Results reported here are for the first 40 seconds of data acquisition, which we found to produce a higher signal-to-noise ratio in preliminary analyses and in previous studies (Coghill et al., 1994; Duncan et al., 1998; Talbot et al., 1991). An inter-scan interval of 12-15 minutes allowed the tracer to decay to background levels and minimized sensitization to repeated thermal stimulation. Subjects wore inserted earphones connected to a microphone through which they received instructions or hypnotic suggestions before each scan. During each scan, the microphone was turned off, and subjects remained immobile and kept

their eyes closed. After completing the PET sessions, each subject underwent a high-resolution anatomical MRI (160 1-mm slices acquired on a Philips 1.5T Gyroscan system).

3.4.7 Image processing and analysis

Each PET- and MRI-volume was automatically transformed into a stereotaxic space similar to that of Talairach and Tournoux (1998), using the method published by Collins et al. (1994) to allow for inter-subject averaging and localization of rCBF changes. PET volumes were smoothed with a 14-mm (full-width, half-maximum) Hanning filter and normalized to the average brain count. Data were analyzed using the following three complementary methods.

3.4.8 Directed searches of pain-related activity in S1, S2, ACC and IC.

To obtain peak-activation maps of pain-related changes in rCBF for each subject, we subtracted normalised PET data recorded during the warm (35°C) condition from those of the painfully hot (46.0 to 47.5°C) condition during Alert-Control and Hypnosis-Control states. Resulting volumes of pain-related changes in rCBF were averaged across sessions, and statistical t-maps were derived using the methods of Worsley et al. (1992). Directed searches of rCBF changes were performed on the right cortex, contralateral to the stimulus, in regions previously shown to be involved in pain processing: S1 (post-central gyrus), S2 (ventral aspect of the parietal operculum), ACC and IC. The anatomical coordinates used for each directed search were derived by averaging the stereotaxic coordinates across the four experimental conditions from Rainville et al. (1997) and searching for significant peaks within a 15mm radius of these coordinates. The significance threshold for these directed searches was $t=2.5$ ($p< 0.05$, two-tail), after correction for multiple comparisons involving a 4-resel search volume (Worsley et al., 1992).

3.4.9 Contrasts of Increased- and Decreased-Pain Intensity Conditions.

In order to assess the influence of hypnotic suggestions for pain modulation on pain-related activity, PET data acquired in the conditions of Decreased-Pain Intensity were subtracted from those in the conditions of Increased-Pain Intensity. Directed searches were again conducted on S1, S2, ACC and IC to evaluate the significance of the differences noted in pain-related activity.

3.4.10 Global search.

Finally, global searches were performed within each experimental condition to investigate pain-related changes in activity in other brain areas. The significance threshold was adjusted for multiple comparisons over the entire brain volume scanned ($t=4.5$; $p<0.05$). This correction gives an expected false-positive rate of 0.016 over the gray-matter volume, and corresponds to an uncorrected p-value of 0.0001 (Worsley et al., 1992).

3.5 Results

3.5.1 Psychophysical and physiological responses

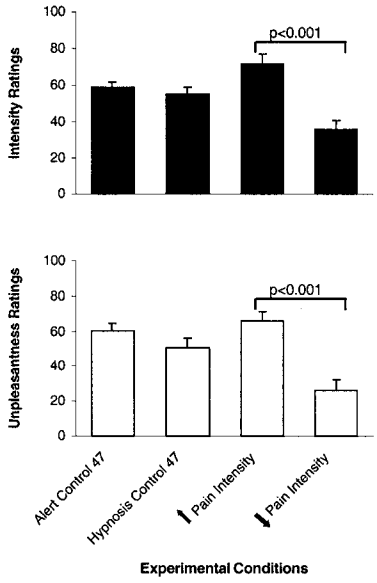
The 35°C stimuli were always rated as warm (Alert Control: mean=18.5; Hypnosis Control: mean= 15.5). In contrast, the 46.0-47.5°C stimuli were rated as clearly painful. Magnitude-estimation ratings of pain unpleasantness and intensity are shown in Figure 3-1. There was no difference in either pain intensity or pain unpleasantness ratings between the Alert-Control and the Hypnosis-Control states (p's > 0.05), suggesting that the hypnotic state itself did not affect pain perception. However, pain ratings were highly modulated by the hypnotic suggestions. Consistent with the hypnotic suggestions themselves, intensity ratings differed between the High-Intensity and Low-Intensity conditions [$F=22.89$, $p < 0.001$]. In addition, although hypnotic suggestions were directed toward pain sensation, unpleasantness ratings were also modulated [$F=11.58$, $p < 0.001$]. Similarly, there was a high correlation between pain intensity ratings and pain unpleasantness ratings ($r=0.812$, $p<0.001$).

Heart rate increased when the noxious thermal stimulus was applied (p's<0.005; Table 3-2), whereas heart rate was not altered upon application of the warm stimulus (p's>0.15). Furthermore, there was no significant effect of experimental condition on heart rate (p's>0.19).

3.5.2 Pain-related changes in rCBF during the Alert-Control condition

In order to assess the effects of thermal stimulation on rCBF, the 47°C pain stimulation data were compared with those of the 35°C non-painful stimulation. Results of directed searches performed on the right contralateral S1, S2, ACC and IC are summarized in Table 3-3. In the Alert-Control condition, there were significant pain-related increases in rCBF within all four areas. A global search of the scanned brain regions revealed additional significant increases in rCBF within the ipsilateral parietal cortex (association area 7) (Table 3-4A).

Figure 3-1: Magnitude-estimation ratings of pain intensity and unpleasantness



Mean magnitude-estimation ratings of stimulus intensity (filled columns) and unpleasantness (clear columns). Error bars indicate SE.

Table 3-2: Heart rate across experimental conditions

Before†	During‡	Before	During
Control 35°C		Control 47°C	
64.4 (3.3)	64.8 (3.9)	65.0 (3.4)	68.9 (4.0)
Hypnosis 35°C		Hypnosis 47°C	
66.2 (4.6)	66.1 (4.6)	66.2 (4.4)	69.5 (4.4)
Increased-Pain		Decreased-Pain	
67.1 (4.2)	70.9 (3.8)	65.8 (3.8)	69.4 (3.7)

* Heart rate in beats per minute (SD); † One-minute period immediately before application of pain stimulus; ‡ One-minute period of hand in painfully hot water.

Table 3-3: Pain-related activation in directed search sites

	Region	x	y	z	t-scores[B]
A			Alert Control[C]		
	S1	34	-18	57	4.13
	S2	42	-16	17	4.49
	ACC	12	-2	44	3.04
		8	3	32	2.72
	IC	30	10	-2	2.80
B			Hypnosis Control[D]		
	S1	39	-25	57	3.35
	S2	39	-19	20	3.06
	ACC	0	3	45	3.11
	IC	32	13	8	3.41
C			Increased-Pain Intensity[E]		
	S1	42	-26	59	5.04
	S2	40	-12	14	3.10
	ACC	8	5	48	3.11
	IC	31	20	-5	2.82
D			Decreased-Pain Intensity[F]		
	S1	36	-25	57	3.90
	S2	47	-16	25	2.64
	ACC	12	17	30	2.81
	IC	31	15	5	3.69
		35	18	0	3.61

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas.

[B] T_{α}=2.5 (see Methods)

[C] Control 47°C - Control 35°C;

[D] Hypnosis 47°C - Hypnosis 35°C;

[E] Increased-Pain Intensity - Hypnosis 35°C;

[F] Decreased-Pain Intensity - Hypnosis 35°C.

Table 3-4: Pain-related activation revealed by global search

	Region	x	y	z	t-scores[B]
A			Alert Control[C]		
	Parietal Lobe	-26	-44	56	4.79
	S2	42	-16	17	4.49
B			Hypnosis Control[D]		
	No significant activations				
C			Increased-Pain Intensity[E]		
	Putamen	28	-2	6	5.31
	S1	42	-26	59	5.04
D			Decreased-Pain Intensity[F]		
	Medial Frontal Gyrus	-1	17	59	4.67
	Frontal Lobe	26	49	15	4.48

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas. [B] T_{α}=2.5 (see Methods); [C] Control 47°C - Control 35°C; [D] Hypnosis 47°C - Hypnosis 35°C; [E] Increased-Pain Intensity - Hypnosis 35°C; [F] Decreased-Pain Intensity - Hypnosis 35°C.

3.5.3 Pain-related changes in rCBF during the Hypnosis-Control condition

In order to assess the effects of hypnosis, itself, on pain-related activation, scans were performed after subjects received hypnotic induction, but before any suggestions were given for pain modulation. Pain-related activation within this hypnotic state was then determined by comparing rCBF observed during the 47°C pain stimulation condition with that of the 35°C non-painful stimulation condition. Results of this comparison demonstrated significant pain-related activation in right contralateral S1, S2, ACC and IC, analogous to that observed in the Alert-Control condition (Table 3-3B). Furthermore a direct comparison of the Hypnosis-Control 47°C condition to the Alert-Control 47°C condition did not reveal significant differences in these areas. These data suggest that hypnosis alone had no effect on cortical pain-related activation. The global search revealed no additional pain-related increases in rCBF during the Hypnosis-Control condition (Table 3-4B).

3.5.4 Effects of hypnotic suggestions to modulate pain perception

As in the Alert Control and Hypnosis-Control conditions, pain-related activation continued to be a prominent feature of the hypnotic suggestion conditions. A subtraction of the 35°C hypnotic control condition from each of the 47°C hypnotic suggestion conditions revealed significant pain-related activity in S1, S2, ACC and IC (Table 3-3C & 3-3D). A direct contrast analysis of the Increased- and Decreased-Pain Intensity conditions revealed, however, a differential effect of hypnotic suggestions on pain-evoked activation within these cortical areas (Table 3-5).

3.5.5 Modulation of S1 activity.

Pain-related activity within S1 was larger in response to hypnotic suggestions for Increased-Pain Intensity, compared with that observed following hypnotic suggestions for Decreased-Pain Intensity (Table 3-3C & 3-3D and Figure 3-2). Direct comparison of the two suggestion conditions (Increased- vs. Decreased-Pain Intensity) confirmed the significantly higher rCBF in S1 during the

Increased-Pain-Intensity condition (Table 3-5 and Figure 3-2). This contrasts with data from Rainville et al. (1997), which demonstrated a non-significant tendency for lower rCBF in S1 in response to suggestions for increased pain unpleasantness (compared with that seen during the Decreased-Pain-Unpleasantness condition; see Figure 3-2). In the present study, separate comparisons of each suggestion condition to the Hypnosis-Control 47°C condition did not yield significant changes in S1 activity, thereby limiting our ability to clarify whether the observed suggestion-related modulation of S1 activity was the result of (1) increased activity in the Increased-Pain condition, (2) decreased activity in the Decreased-Pain condition, or (3) both.

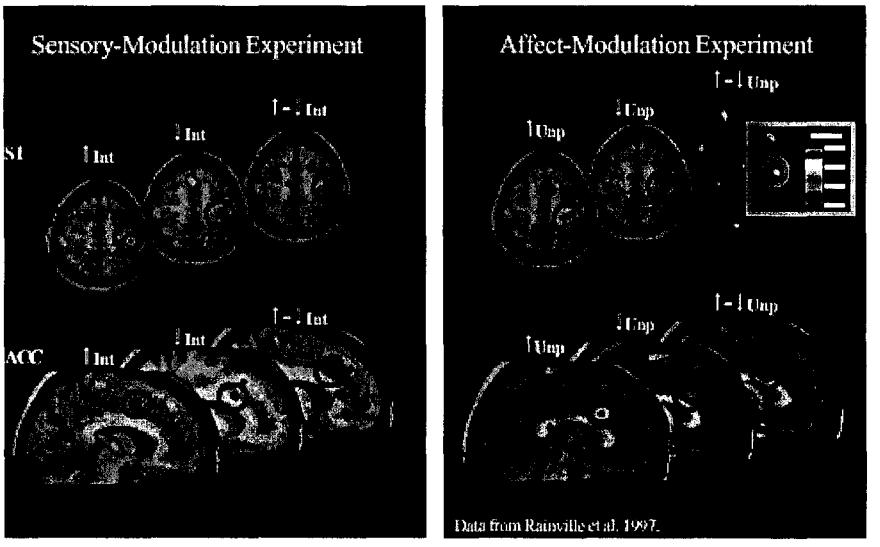
Table 3-5: Sites of differences in pain-related activation during increased- versus decreased-pain intensity

Region	x	y	z	t-scores[B]
S1	48	-21	56	2.91
S2	36	-12	19	2.28
ACC	8	9	45	1.43
Insula	38	6	8	3.00
	28	20	12	-2.62

[A] Stereotaxic coordinates (x = medial – lateral, x>0 denotes right hemisphere; y = anterior - posterior; z = superior - inferior) based on the Talairach and Tournoux (1988) atlas.

[B] T_{α}=2.5 (see Methods).

Figure 3-2: Pain-related activity associated with hypnotic suggestions



rCBF changes in pain-related activity within S1 and ACC associated with hypnotic suggestions for Increased-Pain (↑), Decreased-Pain (↓) and Increased-minus Decreased-Pain (↑-↓) intensity (Int) and unpleasantness (Unp) during the current sensory-modulation experiment and the Rainville et al. (1997) affective-modulation experiment. Modulatory effects of suggestions for ↑ and ↓ Pain (Int or Unp) are revealed by subtracting positron emission tomography (PET) data recorded during the warm hypnosis-control condition from the ↑ pain (Int or Unp) and the ↓ pain (Int or Unp) conditions and the ↑ - ↓ pain (Int or Unp) involved subtracting ↓ pain (Int or Unp) condition from the ↑ pain (Int or Unp) condition. Horizontal and sagittal slices through S1 and ACC, respectively, are centered at the activation peaks observed during the relevant suggestion condition.

3.5.6 Modulation of S2 activity.

Pain-related activity within S2 was observed in both suggestion conditions (Table 3-3C & 3-3D). As was observed in S1, the direct contrast analysis showed a greater pain-related activity following suggestions for Increased-Pain Intensity, compared with that seen for Decreased-Pain Intensity; however, this difference in S2 did not reach significance (Table 3-5). However, rCBF levels in S2 were significantly lower in the Decreased-Pain condition compared with those observed in the Hypnosis-Control 47°C condition (t=-2.6), whereas no significant differences were observed between the Increased-Pain and Hypnosis-Control 47°C conditions.

3.5.7 Modulation of ACC activity.

Pain-related activity was evident in ACC during hypnotic suggestion conditions for both Increased- and Decreased-Pain Intensity (Table 3-3C & 3-3D and Figure 3-2). However, in contrast to the significant modulation of pain-related activity observed within S1 during suggestions to alter perceived pain intensity, such suggestions did not significantly alter pain-related activity within the ACC (Table 3-5). Whereas in the Rainville et al. (1997) study, the direct contrast analysis revealed greater pain-related activity following suggestions for Increased-Pain Unpleasantness, there was no significant difference in ACC activity between suggestions for Increased- Pain Intensity and Decreased-Pain Intensity (Figure 3-2).

3.5.8 Modulation of IC activity.

Pain-related activation was observed in IC during suggestions for Increased- and Decreased-Pain Intensity (Table 3-3C & 3-3D). The direct contrast of the Increased- and Decreased-Pain Intensity conditions revealed a mixed pattern of activation, suggesting higher rCBF in the middle IC in the Increased-Pain Intensity condition and higher rCBF in the most rostral part of the IC in the Decreased-Pain Intensity condition (see Table 3-5).

3.5.9 Global search analysis.

A comparison of the hypnotic suggestion conditions for Increased- or Decreased-Pain to the Hypnosis 35°C Control condition revealed a few additional pain-related activation sites (Table 3-4). Using the more stringent criterion of global searches, we found significant S1 activation only in the Increased-Pain Intensity condition (Table 3-4C). This is consistent with the results described above showing modulation of S1 related to suggestions for increased or deceased pain intensity. A single additional peak was found in the right putamen in the Increased-Pain Intensity condition, and peaks were observed in the frontal cortex during the Decreased-Pain Intensity condition. Some significant pain-related decreases in rCBF were observed in this study but are not addressed in this report.

3.6 Discussion

Results of the present experiments and those of previous human brain imaging studies increasingly point toward a cerebral substrate for pain perception that involves a distributed network of cortical and subcortical regions that participate in the processing of noxious stimuli. The present findings, in agreement with our previous studies and those of others, show that this cerebral nociceptive network includes such regions as S1 and S2, ACC and IC, in addition to subcortical regions, such as thalamus and basal ganglia. Data from the present study and those of Rainville et al. (1997) extend those findings by providing experimental evidence in healthy human subjects for a preferential treatment of sensory-discriminative and affective dimensions of pain perception within somatosensory and limbic structures, respectively.

The present study and that of Rainville et al. (1997) took the unique approach of using hypnotic suggestions as a cognitive manipulation to modulate, and therefore separate, the unpleasantness and intensity of the pain evoked by an experimental stimulus. In the Rainville et al. (1997) experiment, hypnotic suggestions directed toward altering the affective dimension of pain sensation produced significant changes in the perceived unpleasantness of painful heat stimuli without commensurate changes in its perceived intensity. Correspondingly, this manipulation produced significant modulation in pain-evoked activity within ACC, but no significant changes in the activity within somatosensory structures, S1 or S2. In the current experiment, hypnotic suggestions directed toward pain sensation produced significant changes in S1 (with a similar trend in S2 cortex), but not in the ACC. This double dissociation of the modulation of nociceptive processing provides direct experimental evidence in support of the hypothesis that activity in classical limbic cortices and somatosensory systems contribute differentially to the pain experience.

In the Rainville et al. (1997) study, hypnotic suggestions led to selective changes in perceived pain unpleasantness and modulation of pain-related activity in ACC, but not in S1; correspondingly, pain unpleasantness ratings were significantly correlated with rCBF in ACC but not in S1. By contrast, in the current study, although the suggestions targeted only pain sensation, subjects reported perceptual changes in both pain sensation and pain unpleasantness. A similar modulation of pain affect, secondary to changes in pain sensation, was observed by Rainville et al. (Rainville et al., 1999a) and supports a successive-stage model of pain processing (Wade, Dougherty, Archer, & Price, 1996), in which pain unpleasantness is highly (but not exclusively) dependent upon pain sensation. In the current study, the high correlation between pain intensity and pain unpleasantness ratings precludes the use of regression analysis to distinguish cortical areas involved in each dimension of pain. However, the observation of significant modulation of ACC activity associated with direct suggestions for altered unpleasantness (Rainville et al., 1997), but only a smaller non-significant modulation of ACC activity when affect is changed indirectly following suggestions for altered sensation, indicates that primary modulation of affect may involve both direct and indirect modulatory influences on ACC whereas secondary modulation of affect, such as that observed in the present study, may involve only a subset of modulatory circuits without a predominant (significant) influence on ACC activity.

3.6.1 Role of Somatosensory Cortices in the sensory dimension of pain

The indication by the present data that S1 and maybe S2 participate in processing the sensory dimension of pain is consistent with findings from clinical studies that show deficits in pain sensations after lesions to somatosensory cortices (Greenspan et al., 1999; Ploner et al., 1999; Ploner, Schmitz, Freund, & Schnitzler, 1999). For example, Ploner et al. (1999) observed that a patient who suffered a stroke which encompassed S1 and S2 did not experience a painful sensation when a hot laser stimulus was applied to the affected arm, indicating that intact somatosensory cortices are necessary for the normal experience of

pain sensation. However, the patient reported an ill-localized and ill-defined unpleasant feeling in the absence of a clear pain sensation, suggesting that pain affect was present in the absence of pain sensation.

The role of S1 cortex in pain processing has been disputed, and a number of brain imaging studies have failed to detect pain-related S1 activation (see Bushnell et al. 1999). A recent study by Peyron et al. (1999) concluded that S1 does not code pain intensity. These investigators point out that many of the studies, which report pain-related S1 activity used a painful stimulus that is moved from spot to spot during the scanning session and suggest that the S1 activation is related to the touch component of the stimulus. Such a concept has been suggested previously by Jones et al. (1992) and refuted by Duncan et al. (1992). The current study used a tonic stationary stimulus throughout the pain conditions, as well as the non-painful control conditions, and thus does not support such an interpretation of S1 pain-evoked activity. However, pain-evoked activity in S1 appears to be highly modulated by cognitive factors. Directing attention away from a painful stimulus reduces S1 pain-evoked activity (Bushnell et al. 1999), as do hypnotic suggestions to reduced perceived pain intensity (current study).

The S2 cortex is usually activated by painful stimuli in PET and fMRI studies (Coghill et al., 1994; Ha, Chen, Pike, Duncan, & Bushnell, 1998b; Svensson et al., 1997). This activation was confirmed in all phases of the current experiment, but was absent during the hypnotic suggestion conditions in the Rainville et al. (1997) study. In that report we postulated that the absence of S2 activation could be caused by a habituation of S2 activity to repeated stimulation (Rainville et al., 1997). However, if this hypothesis were true, a similar habituation should have occurred in the current study, but it did not. Thus, the absence of S2 activity in the suggestion conditions of the previous Affect-Modulation Experiment might be explained by the reduced emphasis on pain sensation.

In the current study, we observed a non-significant trend towards more pain-evoked S2 activity during the high pain-intensity suggestion condition, compared with that seen during the low pain-intensity suggestion condition. S2 rCBF was also significantly lower in the Decreased-Pain condition than in the Hypnosis-Control 47°C condition. This result implies that the suggestions for Decreased-Pain had a stronger influence on pain-related activity in S2. This speculation is supported by psychophysical results showing a tendency for larger perceptual effects of Decreased-Pain suggestions (Figure 3-1). Further study is needed to determine if this trend represents a preferential role of S2 in the perception of pain intensity, but other data suggest that it may play such a role. Greenspan et al. (1999) observed changes in pain sensitivity after lesions of the parasylvian cortex, and Peyron et al. (1999) observed S2 activation that they interpreted as being related to pain intensity coding (also see Petrovic et al., 2000).

3.6.2 Role of ACC in the affective dimension of pain

Data from our previous study (Rainville et al. 1997) showed a selective modulation of ACC pain-evoked activity after hypnotic suggestions for changes in pain unpleasantness. This modulation of pain-related activity in ACC by suggestions to alter pain affect and the significant correlation between ACC activity and subjects' ratings of pain unpleasantness strongly implicate the involvement of this region in the affective dimension of the pain experience. These observations are consistent with results of lesion studies suggesting that patients who have undergone a cingulotomy show a reduction in pain-related emotional responses (Corkin et al., 1981; Foltz et al., 1962; Foltz et al., 1968). The findings are also generally consistent with those of Tolle et al. (1999), who used a regression analysis to show that pain-evoked activation of ACC is more related to affective than to sensory components of the pain experience. The peak of affective-related pain activation in ACC was somewhat more anterior in the Rainville et al. (1997) study than in the Tolle et al. (1999) study. Tolle et al. suggest that the more rostral peak of the Rainville et al. study may be related to the influence of the cognitive demands of the hypnotic suggestion task. The

location of ACC pain-related activity in the current study was less anterior than that of Rainville et al. (1997), suggesting that hypnotic suggestions in themselves may not explain the small differences in response locations between studies. As indicated above, in the current experiment, there was a secondary modulation of pain affect when suggestions were given to modify pain sensation. This secondary pain-affect modulation was not accompanied by a significant change in pain-evoked ACC activity. The finding that the changes in pain unpleasantness were not associated with significant modulation in the ACC indicates that secondary changes in pain affect may have a different neural substrate than those associated with the direct and specific modulation in pain unpleasantness. This combination of primary and secondary modulatory mechanisms suggests that the contribution of ACC to pain affect may be most determinant when pain unpleasantness is highly dependent on cognitive factors associated with the meaning of pain and largely independent of variations in pain intensity. On the other hand, when pain unpleasantness is strongly determined by pain intensity, the level of pain affect may be at least partially related to activity in other cortical areas. This would be consistent with the model proposed by Price (2000), which emphasizes the interactions between sensory and classical "limbic" cortices for the experience of pain unpleasantness, especially when it is tightly linked to pain intensity.

Recent observations from lesion and brain imaging studies in humans suggest that S1, S2, and the IC may contribute to some aspects of emotions (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Damasio, Grabowski, Bechara, Damasio, Ponto Parvizi, & Hichwa, 2000). These intriguing findings raise the possibility that somatosensory areas may contribute to pain affect. These results, together with those of the present experiments, suggest that the relative magnitude of pain unpleasantness experienced may be encoded through different levels of activation within areas such as S1 and the ACC, as a function of the factors contributing to pain affect.

3.6.3 Role of IC in pain processing

Our findings of both significant positive and negative differences in IC activation during suggestions for increased and decreased pain intensity suggest that there may be a complicated role of IC in pain intensity coding. Craig et al. (2000) observed a significant correlation between IC activity and intensity of cold stimuli, further suggesting that IC may be involved in coding of noxious and innocuous temperature. Nevertheless, other data indicate that IC activity may be important in pain affect. Neuroanatomical studies demonstrate a direct projection from nociceptive regions of thalamus to the insular cortex (Dostrovsky et al., 1996b), thus indicating that the region receives information regarding noxious stimuli. Behavioural consequences associated with disrupting the flow of this information are revealed following insular lesions and are characterized by the condition of pain asymbolia or Schilder-Stengel syndrome, in which pain sensations appear to be normal but behavioural and physiological responses to the offending stimulus are atypical (Berthier et al., 1988; Ogden, Robert, & Carmichael, 1959; Winklemann, Lambert, & Hayles, 1962). Patients do not realize that a stimulus is painful nor see a need to escape, possibly because the affective component of the stimulus is not conveyed.

In addition to the possible role of IC in pain affect, other studies implicate this area in autonomic control. Studies in rat show that the insula is involved in cardiovascular regulation (Verberne et al., 1998). In humans, exercise can lead to activation of the insular cortex (Williamson et al., 1997), and cardiac autonomic activity is disrupted by lesions to the insular cortex (Oppenheimer et al., 1996). In the present study, we observed pain-evoked change in heart rate, which may be related to the pain-evoked activation in the IC observed during all experimental conditions. In a previous psychophysical experiment, we showed that the hypnotic modulation of pain affect was accompanied by small but significant changes in the pain-evoked heart rate response (Rainville et al., 1999a). However, in the present study, the effect of the suggestion on heart rate

responses did not reach significance, and correspondingly, the activity level within the IC was not modulated consistently.

In the present experiment and in that of Rainville et al. (1997) the peak of IC activation was more anterior in the suggestion conditions in the Alert- and Hypnosis-Control conditions (see Table 3-3). This anterior shift in the peak IC activation may reflect a contribution of anticipation to the pain-evoked IC activity, since more anterior activation in IC has been suggested to reflect the anticipation of pain (Chua, Krams, Toni, Passingham, & Dolan, 1999; Ploghaus et al., 1999). In the suggestion conditions, the suggestions themselves alerted the subjects that the upcoming stimulus was to be painful, whereas in the control conditions warm and painful stimulation were presented in a pseudo-random order. Moreover, this anterior shift was most pronounced in the Increased-Pain Affect Condition of the Rainville et al. (1997) experiment, consistent with a contribution of anticipatory processes to the affective dimension of pain.

3.6.4 Possible Participation of ACC in the Sensory Dimension of Pain

The preferential treatment of affective aspects of pain by the ACC discussed above does not exclude this structure from a potential participation in some sensory-discriminative aspects of the experience. Although there is no evidence for a somatotopic organization of nociceptive response within the ACC, which may limit its specific contribution to spatial discrimination, other data suggest that the ACC (and, indeed, other "limbic medial pain pathways") receives nociceptive information relevant to the encoding of the sensory-intensity aspects of pain perception. Electrophysiological evidence supporting this possible role of ACC in pain intensity has been reported by Sikes and Vogt (1992), who identified ACC neurons coding for the intensity of noxious stimuli in anesthetized rabbit. Similar high-resolution coding of intensity has also been reported in the medial thalamus of awake monkeys performing a task requiring the fine discrimination of the intensity of noxious thermal stimuli (Bushnell & Duncan, 1989). These intensity-

coding neurons were found within an area where thalamo-cortical projections to the ACC originate (Apkarian et al., 1998b; Craig, 1990). More recently, Hutchison et al. (1999) identified similar single neurons in human ACC that code the intensity of noxious heat. Furthermore, changes in pain intensity ratings of noxious thermal stimuli have been reported following an anterior cingulotomy (Davis, Hutchison, Lozano, & Dostrovsky, 1994), and following the disruption of thalamocortical input to the frontal lobe by a capsulotomy including the ACC (Talbot et al., 1995). These observations suggest that, although the activity of the ACC evoked during pain may be more closely related to its affective dimension, the properties of ACC neurons and the effects of lesions affecting this area suggest that the ACC may contribute, to some extent, to the sensory aspects of the experience.

3.6.5 Conclusion

It has been well accepted for many decades that pain is a multidimensional experience, and, likewise, it has become increasingly evident that multiple brain regions are activated during the experience of pain. The task, thus, moved from describing regions activated by pain stimuli to defining what functional significance those regions might have in the various aspects of pain perception. However, the normally strong correlation between sensory and affective components of pain perception has made it difficult to identify potential cerebral correlates for these different pain dimensions. The present experiment and that of Rainville et al. (1997) use a cognitive strategy to manipulate sensory and affective dimensions of pain perception and thus demonstrate a double-dissociation of cortical activity related to the perception of pain intensity and pain affect within somatosensory cortices and ACC, respectively. Further, results of these studies speak against a simple dichotomous description of brain areas underlying pain sensation and pain affect. The association between pain unpleasantness and ACC activity was observed when pain affect was directly modulated, independently from pain sensation. In contrast, changes in pain unpleasantness secondary to changes in pain intensity did not lead to a

significant modulation of ACC activity. These results indicate that the cortical representation of pain affect depends on the specific factors that contribute to this dimension of the experience.

3.7 Acknowledgements

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CHAPTER 4 – ALTERATIONS IN PAIN PERCEPTION RELATED TO CHRONIC PAIN STATES

Hofbauer, R. K., Olausson, H., & Bushnell, M. C. (unpublished manuscript). Central representation underlying allodynia in a nerve injured patient.

4.1 Chapter Overview

In Chapters 2 and 3, the cortical representation of pain-evoked activation and its modulation by pharmacological and cognitive interventions was explored in normal control subjects. While it is extremely important to understand acute and experimental pain, it is vital to comprehend how changes in physiological state induced by chronic pain alter pain perception, as our ultimate goal is to achieve an understanding of chronic pain, in order to provide adequate pain relief for those suffering.

How chronic pain develops from an acute injury is not well understood. There is growing evidence to suggest that peripheral mechanisms mediating chronic pain include the establishment of sensitization within peripheral neurons, collateral sprouting of damaged axons,and increased activity of damaged axons and their sprouts (Woolf & Mannion, 1999). Some central mechanisms that might contribute to chronic pain have been documented and include hyperexcitability in pain pathways (Iadarola et al., 1998), disinhibition (Duncan et al., 1998; Morin, Bushnell, Luskin, & Craig, 2001), and neural reorganization (Birbaumer et al., 1997; Derbyshire, Jones, Collins, Feinmann, & Harris, 1999). Little is known however, about how chronic pain is represented within the brain and if there are similarities with acute pain.

In the final study, a detailed case report, we examine a patient who experienced severe chronic neuropathic pain in her right foot. The purposes of the study is to assess the alterations in pain perception relating to chronic pain states, determine the central representation of chronic pain, and propose potential peripheral and central mechanisms. In the present chapter, I provide evidence that abnormal allodynic pain activates the same cortical neural circuitry as normal pain, and challenge the notion in the literature that a separate neural network mediates clinical pain.

4.2 Abstract

This study examined a patient with chronic ischemic neuropathy of her right foot post-compartment syndrome. Careful psychophysical examination of the patient using thermal, tactile, and mechanical tests suggests severe dysfunction of both large and small fibers in her right foot. Despite elevated pain thresholds and little tactile perception, light touch evoked a deep burning pain in the affected foot. Functional magnetic resonance imaging during brushing of the patient's affected foot activated the same cortical neural circuitry as normal pain, namely S2, ACC, and IC. Brushing of the patient's non-affected foot elicited activity in S1 and S2, brain regions mediating tactile perception. Thalamic activation was greater on the contralateral side during stimulation of the non-affected foot whereas stimulation of the neuropathic foot elicited a greater activation in the ipsilateral thalamus. Region of interest (ROI) analysis of the left and right thalamus during rest did not reveal a hypoperfusion of the hemi-thalamus receiving input from the neuropathic foot. Whether pain in this patient is provoked by anatomical changes such as sprouting related to deafferentation of nociceptive pathways or by central disinhibition of pain pathways through loss of sensory input, there is a signature cerebral neural circuitry that corresponds to the conscious appreciation of pain.

4.3 Introduction

Pain is an essential protective mechanism that signals actual or potential tissue damage. Chronic peripheral neuropathic pain extends beyond its function and can leave patients with pain, typically of a burning quality. The pain may be felt superficially or in deep tissues, may be present intermittently or constantly, and can occur spontaneously or be triggered by various stimuli. Sensory loss in the painful area is common and is often accompanied by a paradoxical increase in pain sensations in response to cutaneous stimuli.

Fields et al. (1998) propose a framework to conceptualize allodynic pain associated with postherpetic neuralgia. The clinical presentation follows one of two paths. Patients with "deafferentation-type pain" have an area of spontaneous pain and variable allodynia with extensive sensory loss. For those patients, allodynia most likely involves changes in the CNS related to reduced sensory input, one possibility is that damaged or intact adjacent myelinated primary afferent Aβ- fibres sprout collaterally from laminae III-IV to laminae I-II of the dorsal horn (Bester et al, 2000; Doubell et al, 1997). The myelinated fibres' new sprouts now have access to ascending nociceptive pathways and provide the basis for tactile allodynia. In addition, Aδ-mediated nociceptive inhibition could be altered. It has been demonstrated that selective compression block of Aδ-fibres in human subjects changes pain threshold and leads to skin cooling causing a burning sensation (Landau and Bishop, 1953; Torebjork & Hallin, 1973).

The second group of patients possess an area of spontaneous pain with minimal if any sensory loss and severe allodynia due to "irritable nociceptors." Damage to a peripheral nerve sometimes leads to sensitization and spontaneous neuronal firing in the affected nociceptor and possibly intact adjacent nerves (Bennett, 1993; Kajander and Bennett, 1992). Patients with allodynia due to an "irritable nociceptor" achieve clear pain relief with intradermal lidocaine unlike patients with "deafferentation-type pain" (Rowbotham and Fields, 1989).

Recently, brain imaging techniques have evolved from describing experimental pain to examining pathophysiological pain states, to reveal the neural foci underlying chronic pain of peripheral (Hsieh et al, 1995; Peyron et al, 1998; Petrovic et al, 1999) and central (Davis et al, 2000; Duncan et al, 1998; Iadarola et al, 1995; Olausson et al, 2001) origins. Imaging studies of allodynia in central and peripheral neuropathic pain patients suggest varying patterns of cortical activation, likely due to different etiologies. Petrovic et al. (1999), examining patients with peripheral neuropathic pain and tactile-evoked allodynia, demonstrated activation patterns similar to those seen with normal acute pain, including S1, S2, ACC, periaqueductal grey, posterior parietal cortex, thalamus, and motor areas. On the other hand, Peyron et al. (1998; 2000a) only observed increased cerebral activity within IC and S2 following cold-evoked allodynia, in central pain patients, and suggested allodynia has a different representation than does normal pain.

In the present case report, we used detailed psychophysical tests and fMRI imaging to characterize the cortical representation of probable deafferentation-type allodynia. In light of the previous studies, we wanted to further characterize the cortical structures necessary for the conscious appreciation of neuropathic pain and determine whether there are commonalities with acute pain. If similarities exist, this would suppose a common cortical neural signature for pain. Some of the current data have been described in abstract form (Hofbauer et al, 2000).

4.4 Methods

4.4.1 Experiment 1

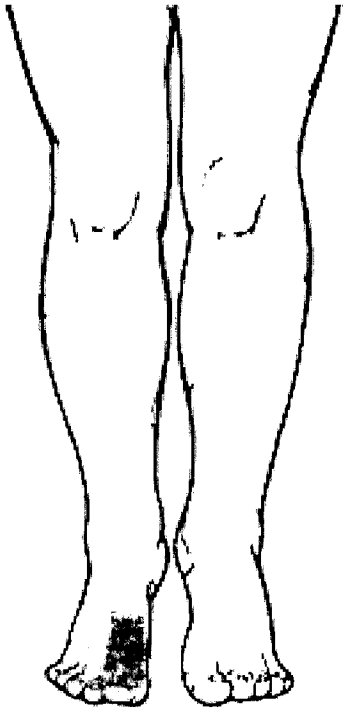
The first experiment evaluated the ability of the patient (J.B.) and control subjects to perceive thermal, tactile and mechanical stimuli. Subjects gave informed consent acknowledging that they could withdraw at any time without prejudice. All procedures were approved by the Institutional Review Board of the Faculty of Medicine, McGill University.

4.4.1.1 Subjects

J.B., a 30-year-old female with insulin-treated diabetes mellitus developed a bilateral lower leg compartment syndrome following a total proctocolectomy to treat ulcerative colitis. She was treated with fasciotomies of the anterior compartment of her non-affected foot and anterior and lateral compartments of her affected foot along with extensive debridement. Immediately following the procedure, she developed a constant, deep ongoing pain burning pain as well as tactile allodynia in her right (affected) foot.

The dorsal aspect of the affected foot innervated by the superficial peroneal nerve demonstrates a circumscribed area, delineated posteriorly by the first and second metatarsal and anteriorly by the first and second phalange (see Figure 4-1), of near-total surface anesthesia. Within this same area was a deep, burning pain, which began following the myectomy and was subsequently unremitting but controlled with a strict pharmacological regimen. The symptoms were stable from 2 months after surgery until at least the time of testing (7-months post-surgery). At the time of testing the subject was taking gabapentin (3000mg/day) and morphine sulfate (as needed) to treat her pain condition. During the testing session, skin temperature was measured on both feet using a monitoring thermometer (Physitemp Instruments Inc., Clifton, New Jersey, USA). No significant differences were found between the affected and non-affected foot

Figure 4-1: Zone of superficial anesthesia and tactile allodynia.



(34.7 and 34.6°C, respectively), nor were there any visible skin changes to the affected foot.

4.4.1.2 Age-matched controls

Ten normal, healthy female subjects between 25 and 35 (mean age 30.3) years old served as age-matched controls. Thermal, brush and Von Frey hair tests were performed in a similar manner with both the patient and control subjects.

4.4.1.3 Psychophysical tests mediated by Aδ and C fibres

4.4.1.3.1 Thermal sensibility

A 3cm x 3cm Peltier thermode (Medoc Ltd., Israel) was placed on the anesthetic zone of the affected foot and the corresponding area of the non-affected foot. Thermal thresholds were determined using a method of limits described by Yarnitsky et al. (1995). The subject underwent four tests, (1) sensory threshold determination for cool, (2) warm, (3) cold pain and (4) heat pain. Each test was repeated five times per foot and the average was taken. During the tests, the thermode was set to a baseline temperature of 30-32°C (Hagander et al, 2000) and increased/ decreased at a variable rate between 0.8°C/s and 1.2°C/s until the subject indicated that she felt a change in temperature for the warm and cool tests, and pain for the pain test, by pressing a button.

4.4.1.4 Psychophysical tests mediated by Aβ fibres

4.4.1.4.1 VonFrey hair sensibility

Five monofilaments (0.9, 5.2, 23, 110 and 800 mN) were utilized to assess mechanical sensibility of both the patient and control subjects. The monofilaments were placed one at a time on different spots, on either the affected foot (in the patient's zone of anesthesia) or non-affected foot (in a comparable area) in a pseudo-random order. The subject had her eyes closed, and each monofilament was placed five times on each foot for 2 seconds.

Following each stimulation, the subject rated the intensity of the sensation on a 10-point scale, "0" signifying no sensation, and "10" indicating "an extremely intense tactile experience". The subject also indicated the intensity of the pain on a 10-point scale, "0" signifying "no pain sensation", and "10" representing the "worst pain imaginable."

4.4.1.4.2 Brush sensibility

Tactile stimuli were presented to the dorsal aspect of the patient's and control subjects' first metatarsal. Tactile stimulation was presented to the same area of both feet using a soft 2-cm wide artist's paintbrush. The brush was manually moved back and forth, in a proximal-distal orientation, over a 10-cm region of the skin at approximately 2Hz. The subject was required to rate the pain intensity and pain unpleasantness of the stimulation every 15 seconds for the duration of the 1-minute stimulus. The control subjects were required to rate the sensation following the 1-minute stimulation. The patient and subjects indicated the intensity of the pain sensation as described above (on a 5-point scale "0" signifying "non-painful stimulation", and "5" representing the "worst pain imaginable.") The patient and subjects also rated the unpleasantness of the stimulation "0" describing "no unpleasantness" and "5" indicating "most unpleasant sensation imaginable." A five point rating scale was used to mimic conditions in the fMRI scanner in which subjects used their fingers to give non-verbal ratings. Following each determination of unpleasantness ratings, the patients completed the short form of the McGill Pain Questionnaire (MPQ; Melzack, 1987) to describe qualitatively the sensations elicited by brushing both feet. In addition, the subject was required to rate the intensity of the tactile sensation following the 60 second stimulation, "0" describing "no tactile sensation" and "5" indicating "most intense sensation imaginable. The task was repeated ten times per foot in the patient and three times per foot with the normal controls.

4.4.1.4.3 Vibrational sensibility

Vibration (100 Hz) was applied by means of a rectangular piece (40 x 12 x 7 mm) of balsa wood connected to a piezo element (Piezo Systems, Inc., Cambridge, Massachusetts, USA) during two tasks. The vibrator was placed in the patient's anesthetic zone of the affected foot and on the symmetrical area of the non-affected foot. Control subjects were not tested. The first test, a two-alternative forced-choice paradigm, required the subject to indicate whether the 1-second vibratory stimulus was on during the first or second 1-s time period (the vibrator was in contact with the skin during both time periods). There were 10 trials per foot, performed in an alternative fashion. After the stimulation, the subject rated the intensity of the vibratory stimulation on a 10-point scale with "0" signifying no vibration, and "10" indicating "an extremely intense vibratory sensation". The subject also indicated the intensity of the pain as described above (on a 10-point scale "0" signifying "no pain sensation", and "10" representing the "worst pain imaginable.") The subject also rated the unpleasantness of the stimulation "0" describing "no unpleasantness" and "10" indicating "most unpleasant sensation imaginable." The second task involved presenting the same vibratory stimulus for 20-seconds, 5 trials on either the affected or non-affected foot in an alternative fashion. The subject rated the intensity of the vibratory stimulation, as well as the pain and unpleasantness of the stimulation following each application using the same verbal anchors as in the previous test.

4.4.1.4.4 Directional sensibility

As a further test of large-fibre function, the ability to tell the movement direction of a tactile stimulus was tested according to the method described by Norrsell et al. (2001). The testing was performed on either the patient's affected foot within the anesthetic zone or on the corresponding location on the non-affected foot. Control subjects were not tested. The patient was required to indicate whether the stimulator (blunt probe, vertical load 16 g) was moved distally or proximally in a pseudo-randomized fashion for 32 consecutive trials per foot. The probe could be moved 3, 6, 10, 18, 32, 58 or 100mm. At the beginning of the experiment the

probe was moved 18mm. Following three correct directional discriminations, the distance of probe movement was reduced one level to a minimum of 3mm. However, following each incorrect response, the distance of the probe movement was increased one level, to a maximum of 100mm. A response profile area (RPA), representing the subject's tactile directional sensitivity, was calculated from the data sheet (Olausson et al. 2000; Figure 4-6).

4.4.1.4.5 Data Analysis

For statistical evaluation of the data, two-way and one-way analysis of variance (ANOVA) with repeated measures, followed by post-hoc tests (Tukey HSD and paired t-tests with Bonferroni correction) were used (StatSoft, Inc., Tulsa, OK, USA). For statistical analysis of MPQ data, Wilcoxon Signed Ranks Test was used.

4.4.2 Experiment 2

In the second experiment brush-evoked cortical activation was studied in the same patient using functional magnetic resonance imaging (fMRI).

4.4.2.1 fMRI stimulation procedures

Tactile runs consisted of three alternating cycles of no stimulation and brush (~60 seconds each). The brush was manually moved back and forth, in a proximal-distal orientation, over a 10-cm region of the skin at approximately 2Hz. Each run was performed three times on each foot in an alternating fashion. At the end of each run, subjects rated the intensity of the tactile sensation, and the pain intensity and pain unpleasantness of the brushing. For the tactile sensation scale, "0" indicated "no tactile brushing component", and "5" designated "an extremely intense tactile sensation". For the pain intensity scale, "0" was defined as "no burning, pricking or stinging sensation", and "5" indicated an "extremely intense sensation." For the unpleasantness scale, "0" was designated as "not at all unpleasant," and "5" denoted "extremely unpleasant." The subject was also asked to rate any discomfort arising from sources other than the stimulus on a 5-

point scale "0" indicated "no discomfort arising from other sources", and "5" designated "extreme discomfort arising from other sources". In order to minimize head movement, all ratings were given non-verbally, using the fingers of one hand.

4.4.2.2 fMRI scanning procedures

MRI was performed using a 1.5 T Siemens Vision scanner with a standard head-coil. The session consisted of one anatomical and 6 functional scans. The anatomical scan was collected using a high-resolution T1-weighted anatomical protocol (TR 22 ms, TE 20 ms, flip angle 30°, FOV 256 mm). The functional scans were collected using a BOLD (blood oxygen level dependent) protocol with a T2*-weighted gradient echo planar imaging (EPI) sequence (TR 3.363s, TE 51 ms, flip angle 90°). Each functional scan consisted of 120 volume acquisitions (10-13 slices, 7 mm thickness, 2.3 x 2.3 mm in-plane resolution). The scanning planes were oriented parallel to the anterior-posterior commissure line and covered from the top of the cortex down to the base of the thalamus.

4.4.2.3 fMRI image processing and analyses

Data processing was performed with software developed at the Montreal Neurological Institute, Montreal, Canada. Functional data were motion corrected by registering all volume acquisitions to the third volume in the scan, low-pass filtered with a 6 mm full-width-half-maximum (FWHM) Gaussian kernel in order to increase the signal to noise ratio, and the first three volumes were excluded to assure steady state condition. All images were resampled into stereotaxic space based on the techniques of Collins et al. (1994).

The statistical analysis of the fMRI data was based on a linear model with correlated errors that has previously been described in detail (Worsley et al, 2000). For each scan, the design matrix of the linear model was first convolved with a gamma hemodynamic response function with a mean lag of 6 seconds and a standard deviation of 3 seconds timed to coincide with the acquisition of each slice (Lange & Zeger, 1997). Drift was removed by adding polynomial

covariates in the frame times, up to 3 degrees, to the design matrix. The correlation structure was modeled as an autoregressive process of 1 degree. At each voxel, the autocorrelation parameter was estimated from the least square residuals using the Yule-Walker equations, after a bias correction for correlations induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing with a 15 mm FWHM Gaussian filter, then used to "whiten" the data and the design matrix. The linear model was then re-estimated using least squares on the "whitened" data to produce estimates of effects and their standard errors.

The resulting t-statistic images were thresholded ($p = 0.05$) using the minimum given by a Bonferroni correction and random field theory (Ries and Puil, 1999). For brush stimulation, the t-statistic image reflects the difference in activation between the brush and no brush conditions on either the affected or non-affected foot. For a global search, the activation threshold for significance is 4.91. Directed searches were performed in S1, S2, IC, ACC and thalamus. These were the only cortical areas that were significantly activated, across a group of normal subjects, by similar brush and pain stimuli in related fMRI studies (Olausson et al, 2001). For a directed search within these volumes the t-values for significant activation were calculated to for S1 (3.64), S2 (3.59), ACC (3.46), IC (3.58) and thalamus (3.51; Olausson et al, 2001).

In order to assess the influence of chronic pain on baseline thalamic activity, a region-of-interest (ROI) analysis was performed. Two ROIs were defined anatomically for each hemi-thalamus. The level of activation was then extracted from the motion-corrected functional runs during the intermediate 30s of the resting cycle, for the hemi-thalamus contralateral to the affected and non-affected foot, by using the corresponding ROI as a selection mask. A paired t-test was performed to examine the level of activity within the left and right thalamus during brushing of the affected and non-affected foot respectively.

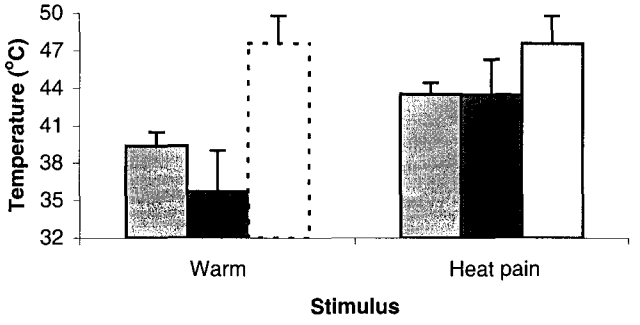
4.5 Results

4.5.1 Experiment 1

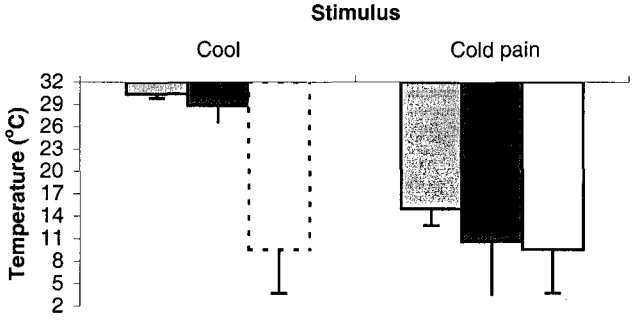
4.5.1.1 Thermal sensibility

Thermal thresholds for warm, cool, heat pain and cold pain are shown in Figure 4-2. In this patient, the thermal threshold for warm on the non-affected foot was 39.4°C which was within 2SD of that of normal controls. On the affected foot, the warm stimuli were not perceived until painful levels were reached. The threshold for heat pain differed significantly between the non-affected and affected foot (43.6°C and 47.6°C respectively; p =0.003; Student's t-test). However, the pain thresholds of both feet are within 2SDs of age-matched controls. The thermal threshold for cool stimuli on the non-affected foot was 30.4°C. Again on the affected foot, the sensation of cool was not perceived until painful levels were attained. There was no significant difference in cold pain threshold on the non-affected and affected foot (14.9 and 9.5°C respectively; p=0.11). Cool thresholds on her non-affected foot and cold pain on both feet are within 2SDs of the data collected from the age-matched controls.

Figure 4-2: **Thermal thresholds**



Thresholds for warmth detection and heat pain (±SD). Left column represents data acquired following brushing of patient's non-affected (left) foot, middle column represents data from normal controls and right column represents data from patient's affected (right) foot.

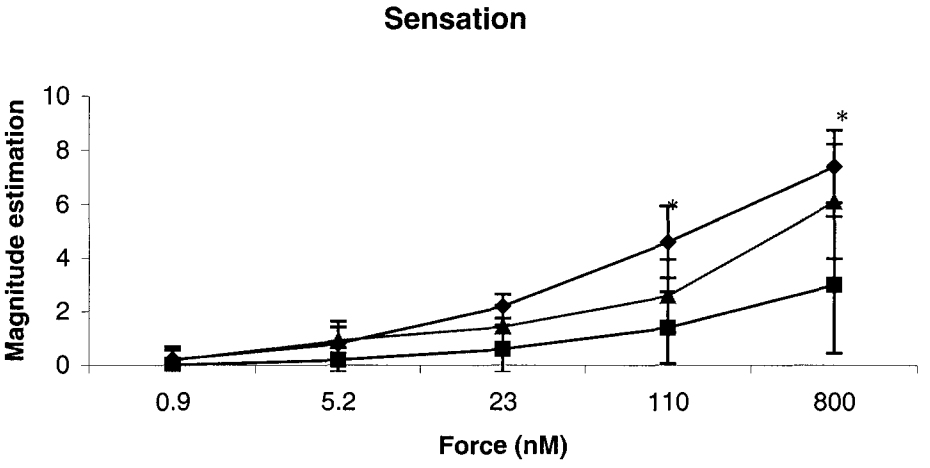


Thresholds for cool detection and cold pain (±SD). Left column represents data acquired following brushing of patient's non-affected (left) foot, middle column represents data from normal controls and right column represents data from patient's affected (right) foot.

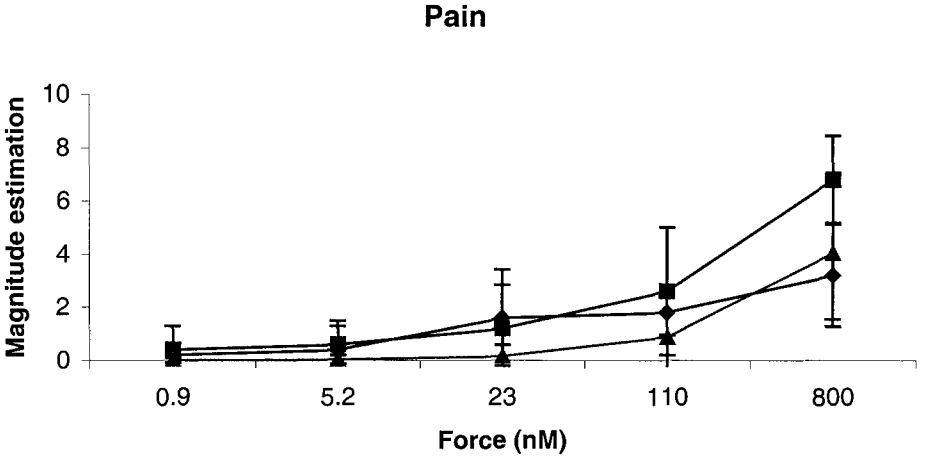
4.5.1.2 Von Frey hair sensibility

Mechanical sensitivity was examined using von Frey hairs of differing strengths placed on the subject's affected and non-affected foot. Figure 4-3 illustrates that the ratings of touch sensation were significantly different between feet ($F=35.71$, $p<0.004$). The 800mN and 110mN von Frey hairs were perceived as more intense on the non-affected foot ($p<0.01$, Tukey's HSD). In addition, the 800mN von Frey hair was felt more intensely than the 23, 5.2, and 0.9mN hairs on the affected foot ($p<0.05$, Tukey's HSD). Ratings of pain sensation were not significantly different between feet ($F=2.70$, $p=0.175$) or between the different von Frey hairs ($F=2.76$, $p=0.064$).

Figure 4-3: Von Frey hair sensibility



Ratings of tactile sensation using von Frey monofilaments on patient's non-affected foot (blue diamond) and affected foot (blue square) and normal control subjects (red triangle; ±SD).



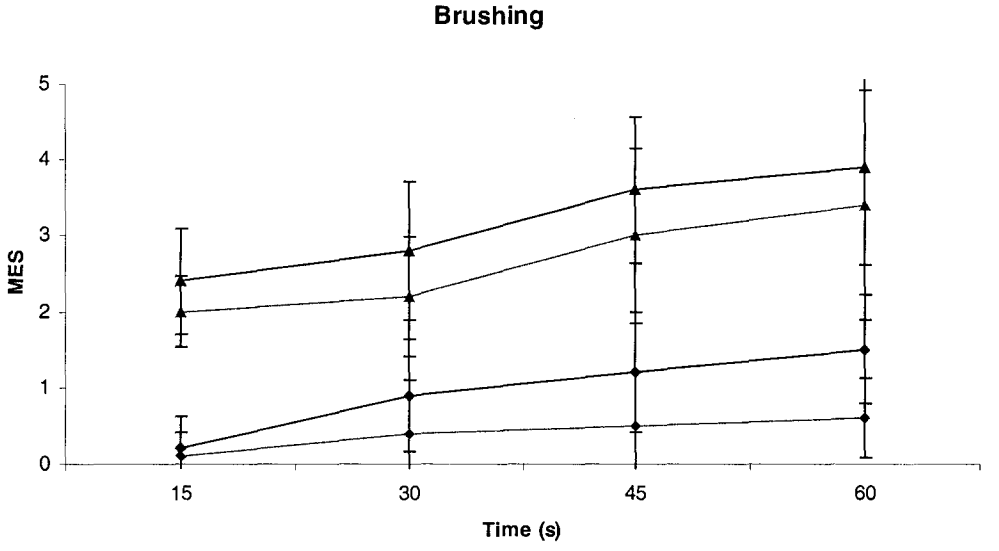
Ratings of pain intensity using von Frey monofilaments on patient's non-affected foot (blue diamond) and affected foot (blue square) and normal control subjects (red triangle; ±SD). Although the pain ratings are quite low, pain ratings on the affected foot using the 5.2 mN monofilament, and on both feet using the 0.9 and 23 mN monofilament were not within 2SDs of the data collected from the age-matched controls, none of whom reported any pain for these stimuli.

4.5.1.3 Brush sensibility

Dynamic tactile allodynia was evaluated by brushing the dorsal aspect of the foot for 1 minute and asking the subject to rate pain intensity and unpleasantness every 15 seconds. Figure 4-4 shows that brushing the affected foot causes a more intense pain and unpleasant sensation than the same brushing on the non-affected foot (p's <0.001, ANOVA). These ratings increase over time ($p<0.05$; ANOVA) independent of foot brushed. The quality of brushing varied between the affected and non-affected foot. Brushing the allodynic foot led to a "deep burning pain" whereas brushing the non-affected foot elicited "an annoying irritation." There was no significant difference in pain intensity ratings when brushing the foot of normal subjects or the non-affected foot of the patient ($p>0.05$). However, there was a significant difference in pain unpleasantness ratings were when brushing the foot of normal subjects and the non-affected foot of the patient ($p<0.05$). In addition, the intensity of brushing of the affected foot was significantly less intense than the non-affected foot ($p<0.05$; t-test).

The MPQ was assessed by analysing the number of words chosen from each of the four categories (sensory, affective, evaluative and miscellaneous) and the total number of words chosen in all categories. The number of sensory words chosen to describe the pain elicited from brushing the feet was greater for the affected than the non-affected foot (Median non-affected foot=0, median affected foot=4; $p<0.05$, Wilcoxon Signed Ranks Test). No differences were found between the affected and non-affected foot in the number of words chosen to describe affective (median non-affected foot=0, median affected foot=0), evaluative (median non-affected foot=0, median affected foot=1) or miscellaneous (median non-affected foot=0, median affected foot=1) categories ($p>0.05$, Wilcoxon Signed Ranks Test). The total number of words chosen in all categories were greater for the affected than the non-affected foot (median non-affected foot=1, median affected foot=5; $p<0.05$, Wilcoxon Signed Ranks Test).

Figure 4-4: Brush sensibility



Ratings every 15-seconds of pain intensity (red) and unpleasantness (blue) evoked by brush stroking patient's non-affected (diamond) and affected foot (triangle) (±SD).

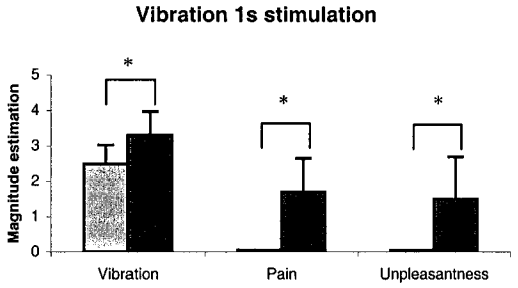
4.5.1.4 Vibrational sensibility

On both the affected and non-affected foot, the patient always correctly determined whether the vibration occurred during the first or second of two possible periods. Figure 4-5 illustrates the magnitude estimation ratings of vibration intensity, pain intensity and unpleasantness. There was a significant difference between ratings of vibration intensity on the affected and non-affected foot ($p<0.05$, Student's t-test). Pain intensity and unpleasantness ratings were significantly greater on the affected than non-affected foot ($p<0.05$). As in the case of the 1-second stimulation, during the 20-second stimulation pain intensity and unpleasantness ratings were significantly greater on the affected than the non-affected foot ($p<0.05$). For vibration intensity there was a tendency for heightened sensation on the affected foot, which did not reach significance ($p<0.07$).

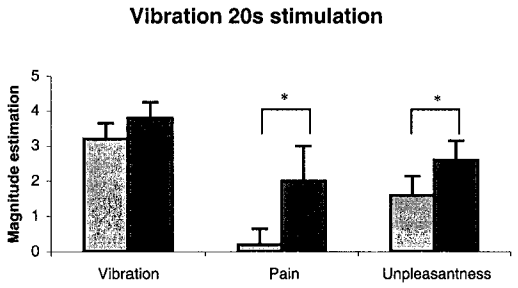
4.5.1.5 Directional sensibility

Since the only primary afferent shown to respond differently to direction of movement of a tactile stimulus in man are the large myelinated (Aβ) mechano-afferents (Olausson et al, 2000), we used a moving stimulus to specifically examine the function of these fibres. A probe was either dragged up or down along the dorsal surface of the foot, and the subject was asked to indicate the movement direction. Figure 4-6 shows the Response Profile Area of the data collected (cf. Methods). The RPA for the non-affected foot (21) was within the normal range [mean±2SD; 38±30]. However, the result of 166 on the affected foot was clearly an abnormal value for the task, indicating a severe disturbance of the myelinated mechanoafferents.

Figure 4-5: Vibrational sensibility



Ratings of vibration intensity, pain intensity and pain unpleasantness evoked by a 1s, 100Hz vibratory stimulus on patient's non-affected (left column) foot and affected (right column) foot (±SD; *p<0.05).



Ratings of vibration intensity, pain intensity and pain unpleasantness evoked by a 20s, 100Hz vibratory stimulus on patient's non-affected (left column) foot and affected (right column) foot (±SD; *p<0.05).

Figure 4-6: Directional sensibility

Left foot

		Start						
		3	6	10	18	32	56	100
1	up				+			
2	down				+			
3	up				+			
4	up			+				
5	down			+				
6	up			+				
7	down		+					
8	down		+					
9	up		+					
10	up	+						
11	up	+						
12	up	+						
13	down	+						
14	down	+						
15	down	+						
16	down	+						
17	up	+						
18	down	-	+					
19	up		+					
20	up		+					
21	down	+						
22	up	+						
23	down	+						
24	down	+						
25	up	+						
26	up	+						
27	up	+						
28	up	+						
29	down	+						
30	down	+						
31	down	+						
32	down	+						

Right foot

		Start						
		3	6	10	18	32	56	100
1	up				-			
2	down					+		
3	up					+		
4	up					-		
5	down						+	
6	up						-	
7	down							+
8	down							+
9	up							+
10	up						-	
11	up							+
12	up							+
13	down							+
14	down						+	
15	down						+	
16	down						+	
17	up					+		
18	down					-		
19	up						+	
20	up						+	
21	down						-	
22	up							+
23	down							+
24	down							+
25	up						+	
26	up						-	
27	up							+
28	up							-
29	down							+
30	down							+
31	down							+
32	down						+	

Quantitative test protocols of directional sensibility for J.B. The left diagram shows test results for the 32 trials on the left foot and the right diagram shows

test results for the 32 trials on the right foot. The stimulation distance (indicated in mm) was decreased one step after three correct responses (marked +). The stimulation distance was increased one step immediately following an incorrect response (marked -). RPA is calculated as the total number of blocks to the left of the marks. RPA>= 68 was considered to be abnormal (mean value + 2 SD of normative data) (Olausson et al. 2000).

4.5.2 Experiment 2

In the second experiment brush-evoked cortical activation was studied in the same patient using functional magnetic resonance imaging (fMRI).

4.5.2.1 Psychophysical ratings of brush

Magnitude-estimation ratings obtained during scanning of brush intensity, pain intensity and pain unpleasantness are shown in Figure 4-7. There was a significant decrease in brush intensity on the affected compared to the non-affected foot. Pain intensity but not unpleasantness ratings were significantly heightened on the affected foot compared to the non-affected foot ($p<0.037$ & $p>0.12$). Despite similar unplesantness ratings, the quality of brushing varied between the affected and non-affected foot. Brushing of allodynic foot led to a "deep burning pain" whereas brushing the non-affected foot elicited "an annoying irritation." Brush intensity but not pain intensity or unpleasantness ratings of both feet are within 2SDs of the data collected from the age-matched controls during the previous experiment.

4.5.2.2 Brush-evoked changes in fMRI signal

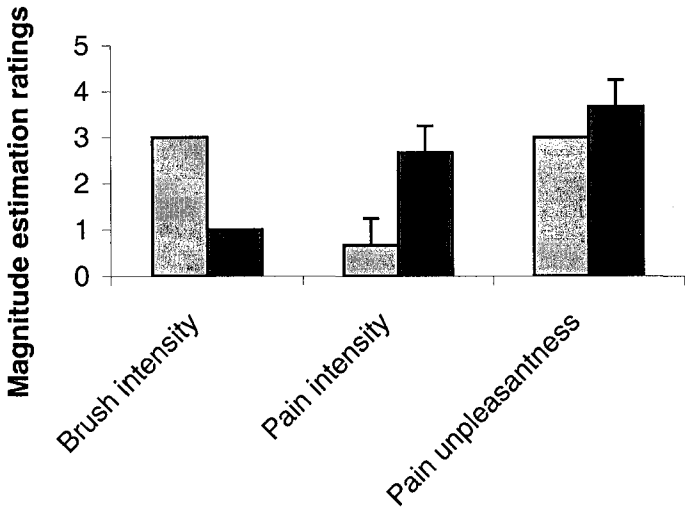
In order to infer the effects of brush stimulation on rCBF, the fMRI signal was correlated to the hemodynamic function. Results of directed and global searches of non-affected foot brushing are summarized in Table 4-1 and Figure 4-8,4-9, 4-10. There were significant activations in somatosensory cortices (contralateral S1 and bilateral S2), IC, and bilaterally in the thalamus. A global search of the scanned brain regions revealed significant increases in the bilateral posterior lobule (Areas 7 and 40) and the frontal cortex. These data are similar to results collected from normal controls in a separate study in our lab (Olausson et al, 2001). Data collected during brushing of the allodynic foot are displayed in Table 4-2. Brain regions activated by brushing of this foot are similar to those observed during experimental pain stimulation in normal subjects (Olausson et al, 2001). Significant brush-evoked activation was observed in bilaterally in S2, ACC and IC

and thalamus (see Figure 4-8, 4-9). There was a strong tendency toward significance for contralateral brush-related activity in S1. Using a more stringent criterion for global searches we found significant bilateral prefrontal cortex (see Figure 4-10) and ipsilateral posterior lobule activation, SMA and medial temporal gyrus and posterior cingulate cortex. Further, a biphasic response was seen within the prefrontal cortex. During painful brushing a robust activation was seen in Area 10 but during non-painful brushing a deactivation was observed. Significant brush-related decreases were observed in the visual cortex.

4.5.2.3 Thalamic ROI analysis

Examination of the ROI analysis of thalamic activation associated with the resting state revealed significant differences in left and right thalamic activity. Independent of whether a circumscribed ROI of the VPL thalamus or an ROI encompassing entire thalamus was analysed, activity was greater on the left side, contralateral to the neuropathic foot (paired t-test, $p<0.001$).

Figure 4-7: Magnitude-estimation ratings during brushing in fMRI



Mean ratings of brush intensity, pain intensity and pain unpleasantness evoked by brush stroking (±SD). Ratings between 0-5 were given after each run. Left columns represent data acquired following brushing of patient's non-affected foot, right columns represent data from patient's affected foot.

Table 4-1: Cerebral structures significantly activated by brushing of the left foot.

Region	***x***	***y***	***z***	***t-value***
S1	18	-36	76	6.17
S2	44	-30	20	5.64
	46	-16	32	5.52
	56	-20	40	5.10
	60	-14	32	5.09
	-56	-24	33	4.38
	-46	-38	20	*3.70
Insula	35	-16	16	*3.65
Thalamus	8	-9	11	*3.99
	-5	-8	11	*3.70
Posterior lobule	42	-36	44	7.44
	44	-40	60	5.59
	-40	-38	44	5.51
Frontal cortex	50	8	20	5.28
	40	36	-10	-4.96
	-58	6	36	5.59

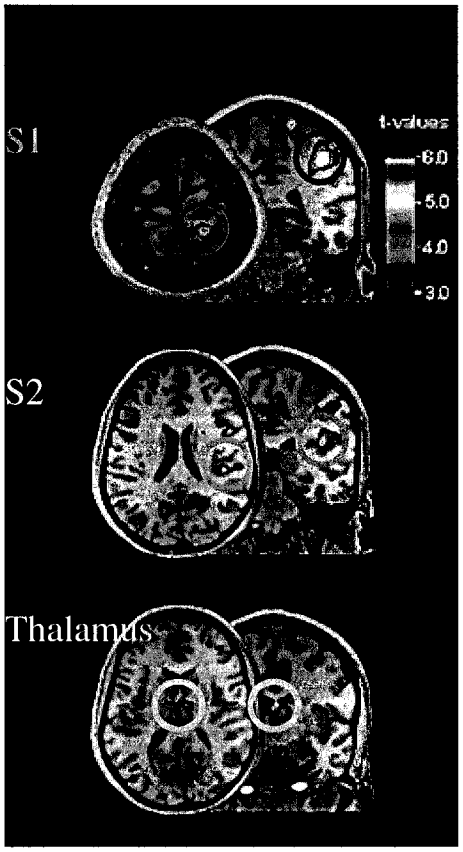
Stereotaxic coordinates (x=medial-lateral, x>0 denotes right hemisphere; y=anterior-posterior; z=superior-inferior) based on the Talairach and Tournoux (Talairach et al., 1988)atlas. * Significant only with directed search

Table 4-2: Cerebral structures significantly activated by brushing of the right foot

Region	*x*	*y*	*z*	*t-value*
S1	-19	-38	76	**3.39
S2	-54	-16	10	7.07
	-48	-36	20	6.38
	-58	-32	20	5.74
	-64	-30	20	5.72
	-66	-22	26	5.14
	-46	-26	18	5.00
	56	-26	18	6.30
	46	-30	26	4.92
ACC	-2	36	14	5.32
Insula	-46	6	-4	4.93
	-38	-20	10	5.10
	36	18	2	*4.05
Thalamus	-11	-21	9	*3.94
	11	-13	8	*4.11
Frontal cortex	-52	8	-4	5.37
	44	46	4	7.02
	34	48	18	5.03
SMA	-56	-6	46	5.23
Medial Temporal gyrus	56	-46	6	5.04
Posterior cingulate cortex	2	-54	8	-6.85
Visual cortex Area 19	4	-78	44	-6.97
Area 18	2	-86	14	-5.95
Area 17	-8	-62	10	-6.18
Area 17	18	-74	12	-5.91

Stereotaxic coordinates (x=medial-lateral, x>0 denotes right hemisphere; y=anterior-posterior; z=superior-inferior) based on the Talairach and Tournoux (1988) atlas. * Significant only with directed search, ** Below significance threshold for directed search

Figure 4-8: Cortical activation evoked by brushing the patient's left foot



The left side of the images corresponds to the left side of the patient. A red circle indicates a region of interest within the S1, a green circle indicates a region of interest with S2 and a turquoise circle indicates a region of interest in thalamus. T-values are between 3.0 and 6.0. Solid-line circles represent activation of contralateral (to the foot stimulated) brain structures.

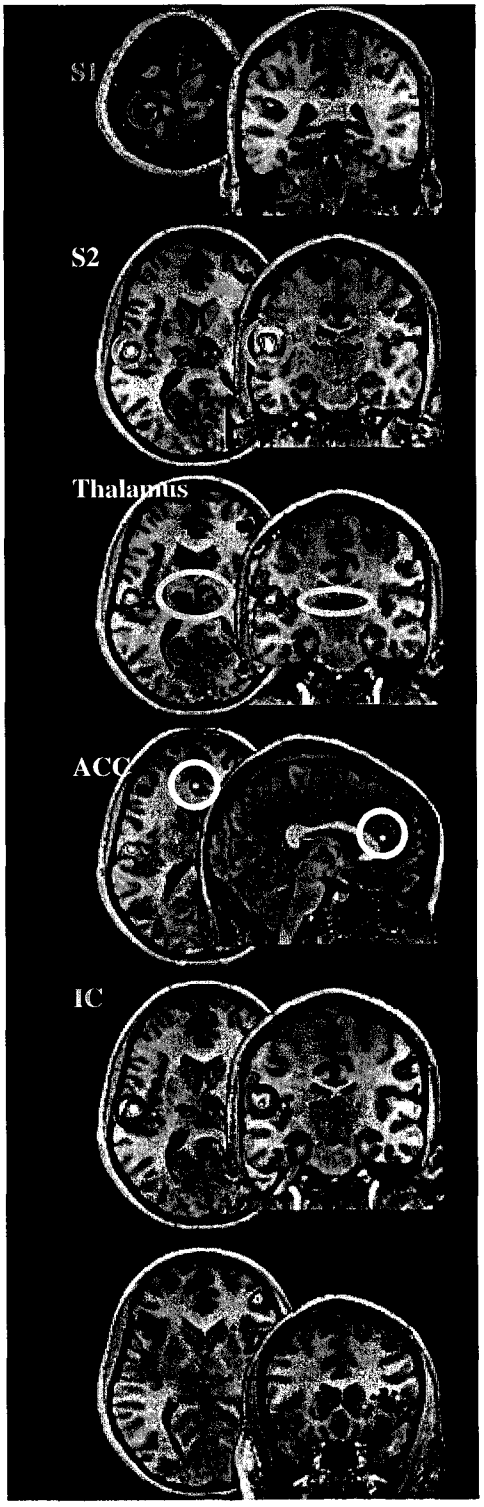
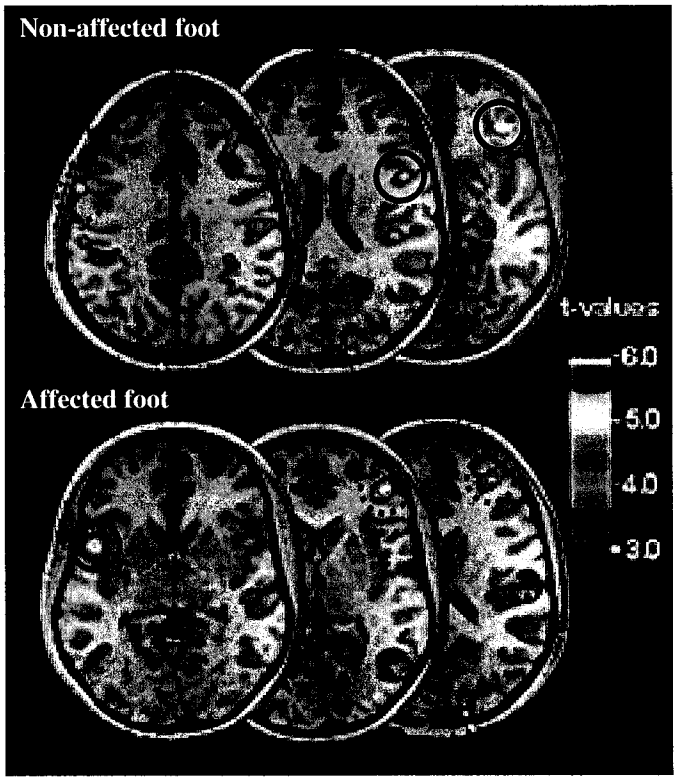


Figure 4-9: Cortical activation evoked by brushing right foot.

The left side of the images corresponds to the left side of the patient. A red circle indicates a region of interest within the S1, a green circle indicates a region of interest with S2 and a turquoise circle indicates a region of interest in thalamus, a yellow circle indicates a region of interest with ACC and a pink circle indicates a region of interest in IC. T-values are between 3.0 and 6.0. Solid-line circles represent activation of contralateral (to the foot stimulated) brain structures and dotted-line circles represent activation of ipsilateral brain structures.

Figure 4-10: Brush-evoked frontal cortex activation of left and right foot



The left side of the images corresponds to the left side of the patient. T-values are between 3.0 and 6.0. Solid-line circles represent activation of contralateral (to the foot stimulated) brain structures whereas dashed-line circles represent activation of ipsilateral brain structures. Red circles represent positive t-values and blue circles represent negative t-values.

4.6 Discussion

Detailed psychophysical assessment of the patient revealed a zone of limited tactile and thermal perception on the affected foot, within which light touch evoked a deep burning pain. Brushing of the allodynic foot during fMRI demonstrated activation in brain regions implicated in pain processing whereas brushing the non-affected foot yielded activation in brain structures normally engaged in tactile perception. The experimental findings of this subject suggest that the allodynia is mediated by partial deafferentation that could lead to a disinhibition of central pain inhibitory mechanisms and not mediated by "irritable nociceptors."

Unmyelinated C fibres and Aδ fibres convey sensations of warmth, cool and heat pain, respectively, and both heat and cold pain-induced information are carried by polymodal nociceptors (Darian-Smith et al, 1973; Konietzny & Hensel, 1975; Torebjork, 1974). Thermal testing of the patient revealed that within the zone of anesthesia on the affected foot there was no sensation of warm or cool. Based on these results, there was probably severe damage to both unmyelinated C fibres and Aδ fibres. Although heat pain thresholds were somewhat heightened, the patient did feel heat and cold pain suggesting that there were some intact nociceptive-specific C fibres, be it fewer in number. Peripheral "irritable nociceptors" as the cause of pain in this patient seems unlikely, due to the reduced C-fibre function.

Additionally, in this patient, tactile-evoked pain could have arisen from damage to C-fibre afferents, which lead to a loss of connections with pain signaling neurons in lamina II. Aβ-fibres would then sprout from layer III & IV to contact the deafferented layer II cells in order to transmit nociceptive information (Castro-Lopes et al, 1990; Shortland and Woolf, 1993; Woolf et al, 1992).

The inability to determine the direction of a moving probe and reduced sensation of von Frey monofilaments on the affected foot suggest significant Aβ-fibre loss. Vibration and brushing are mediated by large, myelinated fibres and under normal circumstances do not evoke pain. As a result of injury to Aβ fibres, tactile inhibitory systems normally in place are damaged, which could clearly add to the pain the patient felt (Hillman and Wall, 1969; Landau and Bishop, 1953). Similarly, touching interleaved warm and cool bars produces an illusionary painful, burning sensation similar to the quality of sensation evoked by tactile allodynia associated with neuropathic pain (Craig and Bushnell, 1994). PET imaging of the thermal grill illusion revealed activation of S2, ACC and IC (Craig et al, 1996). Functional imaging of brush-evoked allodynia of the patient's affected foot also produced activation in the S2, ACC and IC. The brush-evoked allodynic pain was similar to the thermal grill in both quality (burning – based on MPQ) and its cortical activation, suggesting a similar mechanism. Craig and Bushnell (1994) hypothesized that the thermal grill illusion elicits pain through a central disinhibitory (unmasking) phenomenon, which is likely a mechanism mediating our patient's tactile allodynia.

Several studies have observed that patients suffering from chronic neuropathic pain have reduced rCBF at rest within the affected thalamus (Hsieh et al, 1995; Iadarola et al, 1995). ROI analysis of our data did not reveal significantly reduced thalamic activity of the hemi-thalamus receiving nociceptive input from the neuropathic foot, which could reflect a disruption of sensory inhibitory processes. However, we did observe that thalamic activation was greater on the contralateral side than the ipsilateral side during stimulation of the non-affected foot, whereas the activation was greater in the ipsilateral thalamus during stimulation of the allodynic foot. This asymmetrical thalamic activity supports the idea that an imbalance in sensory transmission can lead to abnormal pain processing. Additional evidence in favour of this hypothesis comes from the finding that thalamic stimulation can be an effective treatment for chronic pain (Davis et al, 2000; Duncan et al, 1998; Kupers et al, 2000). The stimulator may

alleviate the patient's pain artificially, by replacing a lack of thalamic activity arising from mechanisms of central disinhibition and deafferentation attributable to the chronic neuropathic pain.

Brain imaging studies examining normal healthy volunteers' responses to tactile stimulation typically reveal activation of contralateral S1 and bilateral S2 (Coghill et al, 1994; Polonara et al, 1999). Our results replicate these findings, with brushing of the non-affected foot eliciting activation within S1 and S2. The indication by the present data that S2, ACC, IC participate in the processing of dynamic mechanical allodynia is generally consistent with the findings from other clinical studies examining peripheral neuropathic pain (Petrovic et al, 1999; Peyron et al, 1998, 2000a). For example, Petrovic et al. (1999) demonstrated brushing an allodynic zone in patients with mononeuropathy generated cerebral activation in S1, S2, IC, ACC, PAG and thalamus. Similarly, Peyron et al. (2000) observed that a patient who suffered a stroke encompassing right S1, S2 and ACC exhibited activation of the IC/S2 region during tactile allodynia. In another study, Peyron et al. (1998) demonstrated that patients who suffered lateral-medullary infacts displayed activation of S1, S2 and IC but not ACC in response to tactile allodynia. Previous studies examining painful neuropathic pain patients with allodynia have failed to find activity within ACC (Peyron et al, 1998, 2000a). Data from our lab have shown that ACC is important in conveying the affective valence of a stimulus (Rainville et al, 1997). Potentially, the other studies lacked the necessary modulation of primary unpleasantness and as such failed to elicit significant ACC activation (Hofbauer et al, 2001). An alternative explanation could be there is a lack of sensitivity in detecting a signal.

The frontal cortex is usually activated by painful stimuli in both PET and fMRI studies (Becerra et al, 1999; Casey et al, 2001; Coghill et al, 1999). Activation was confirmed in the frontal cortex during non-painful and painful brushing of the non-affected and affected foot respectively. It is well accepted that the frontal lobe plays an important role during the encoding of tactile information (Romo et

al, 1999). The precise role of the frontal cortex, however, in the conscious appreciation of pain and its modulation is uncertain, despite numerous studies showing frontal cortex activation by experimental (Becerra et al, 1999; Casey et al, 2001; Coghill et al, 1999) and neuropathic pain (Hsieh et al, 1995). Our patient was required to encode the tactile stimulation, retain the event in short-term memory and recall the stimulus intensity and unpleasantness following the scan. These tasks are performed during both tactile and painful stimuli and require activation of a vigilance, pain-intensity-independent network within the frontal cortex. The bi-phasic activation seen in Area 10 could subserve this function (Coghill et al, 1999). The orbitofrontal cortex plays an important role in the processing of affect and emotion induced by noxious stimuli, which may be responsible for activations seen only while brushing the affected foot (Baker et al, 1997; Paschal-Leone et al, 1996). Similarly, studies in rat have shown that electrical stimulation of prefrontal regions induces analgesic effects through direct connections with PAG (Zhang et al, 1997). This finding could account for increases in frontal cortex activation during painful brushing and deactivation for the period of non-painful brushing seen in our data.

In addition to observing increases in fMRI signal during painful brushing, we observed decreased activation within the visual cortex. Svenson et al., (1997) observed decreases within the visual cortex during both cutaneous and muscular pain. Similarly, Kawashima et al. (1995) demonstrated robust decreases within the visual cortices during attention-demanding tactile tasks. The decrease in visual cortical activity found in these studies may be due to a selective attentional process of diverting information and blood flow not involved in the task at hand to integral cerebral structures. This idea is supported by findings that diverting attention away from a sensory modality reduces activity in the associated cortex (Bushnell et al, 1999; Downar et al, 2000).

In conclusion, detailed examination of the patient showed widespread damage of both large and small fibers in her affected foot. Brushing of the allodynic foot

during fMRI demonstrated activation in brain regions implicated in pain processing suggesting a common cerebral signature mediating both experimental and clinical pain. These results provide the prospect that with detailed psychophysics, the pathophysiology of neuropathic pain can be described and etiology-specific treatments can be designed.

4.7 Acknowledgements

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CHAPTER 5 – GENERAL DISCUSSION

If I can stop one heart from breaking
I shall not live in vain;
If I can ease one life the aching,
Or cool one pain,
Or help one fainting robin
Unto his nest again,
I shall not live in vain.

Emily Dickinson

5.1 General Conclusion

The results of these studies demonstrate that for the conscious appreciation of pain, which is a complicated and multidimensional experience, there is a complex thalamo-cortical neural circuit that is activated. Further, activation of this circuit is not dependent on the application of a specific noxious stimulus, as long as the stimulus triggers the individual meaning of pain for the subject.

Due to the multifaceted nature of pain sensation, there is a need to recruit many different neuronal modules within the cortex to convey the pain experience. This network includes sensory, affective, attentional, motor, memory, and antinociceptive elements. The primary structures that constitute this pain system include, but are not limited to, the primary somatosensory area, the secondary somatosensory cortex, the anterior cingulate cortex, the insular cortex, the frontal cortex, the cerebellum, and the thalamus.

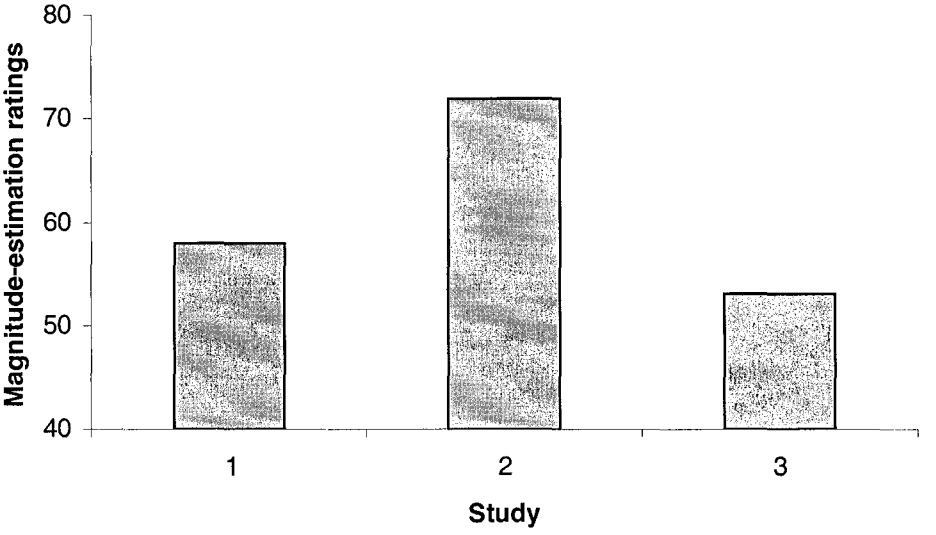
A nociceptive stimulus reliably elicits the same response within a given individual, time and time again. The human body however, is not a static entity; it constantly changes in response to the world around it. Similarly, the pain one perceives is highly modifiable by the state of consciousness of the individual. For example, if an individual focuses on his injury, the pain he feels will be magnified, whereas distracting the individual leads to reduced pain (Bushnell et al., 1999; Butt & Kisilevsky, 2000; Miron, Duncan, & Bushnell, 1989). In addition to psychological modulation of pain, pathophysiological changes due to degeneration of the nervous system (e.g. HIV or diabetic neuropathy) can also lead to severe and debilitating pain conditions. If there is an evident alteration of pain perception, there must also be a commensurate change in activation within the associated neural pain circuitry, peripherally and/or centrally.

5.2 Cortical regions

5.2.1 Primary somatosensory cortex

A debate has intensified in the literature as to whether there is a role for S1 in pain perception, as only half of all studies demonstrate S1 activity (Bushnell et al., 1999). Recent data provide an attractive explanation for the discordant results among studies. Lorenz et al. (2001) examined the neural correlates of heat detection, heat pain threshold and heat pain tolerance. Interestingly, S1 activity was only observed when the thermal stimulus approached heat pain tolerance but was absent at heat detection and heat pain thresholds. These findings are in agreement with results described in the three previous chapters. In Study 2 of this thesis, activity was seen throughout the experiment within S1. Hypnotic suggestions for increased pain intensity lead to an extremely painful sensation (close to heat pain tolerance; see Figure 5-1) with matching activity within S1. Similarly, when hypnotic suggestions were given to decrease pain intensity, subjective ratings were lowered, but the sensation remained objectively painful with reduced S1 activity. In Study 3, brush-evoked allodynia led to severe burning pain in a nerve-injured patient. We observed a non-significant trend toward increased pain-evoked activity within S1 during painful brushing compared to that seen during rest. There was however, reduced touch sensation, suggesting reduced tactile input into S1. Another explanation for the absence of significant S1 pain-evoked activation was the small sample size and the few number of scans performed (as well as other factors mentioned in the *Caveats of PET and MRI* section of the Introduction, p.37). In Study 1, prior to and during propofol anesthesia pain-evoked S1 activation was not observed. To reduce the likelihood of subject movement, which can be observed under propofol anesthesia during extremely painful stimulation, thermal stimuli used during the study were kept above pain tolerance but clearly below heat pain threshold. In light of current results by Lorenz et al. (2001), the absence of S1 activation during the Alert-Control condition and subsequent scans is probably due to the reduced temperature of the thermal stimulus.

Figure 5-1: Magnitude-estimation ratings across studies



1. Propofol study: Alert control 47
2. Hypnosis study: Increased pain intensity suggestion
3. Case study: Painful brushing

These results, together with those of the present experiments, suggest that the relative magnitude of pain intensity experienced may be encoded through different levels of activation within areas such as S1. The activation however, may only become significant using current imaging techniques when the stimulus intensity is approaching pain tolerance.

5.2.2 Secondary somatosensory cortex

There is a large body of evidence to implicate S2 as an important structure involved in tactile perception and evidence is emerging for its role in pain sensation. Data collected from intra-cerebral recordings to painful laser heat and non-painful electrical stimulation suggest that processing of nociceptive and tactile information occurs in close proximity within S2 (Frot, Rambaud, Guenot, & Mauguiere, 1999; Frot, Garcia-Larrea, Guenot, & Mauguiere, 2001; Frot & Mauguiere, 1999). Our findings also demonstrate that whether brushing of the foot elicits a painful burning sensation or normal tactile sensation, similar, if not identical areas of S2 are involved (Study 3). Further, painful brushing yielded higher levels of activation compared to non-painful brushing. We also observed a non-significant trend toward more pain-evoked S2 activity in the hypnosis study (Study 2) during the increased-pain-intensity suggestion condition compared with that seen during the decreased-pain-intensity suggestion condition. Thus, the overlap of tactile and nociceptive areas within S2 could be instrumental in signaling stimulus intensity along an innocuous-noxious continuum consistent with findings by Coghill et al. (1999).

Activation of S2 was present but greatly reduced (below significance) prior to and during propofol administration (Study 1). The lack of significant activation within S2 does not diminish its importance in the conscious appreciation of pain, however, the lack of activity is curious. Nevertheless, it is known that stress alters nociceptive responses in spinal and dorsal horn neurons (McGaraughty & Henry, 1997), and presumably this modulation would be carried to higher levels. Additionally, modulation could occur at forebrain levels, which could differentially

alter cortical nociceptive responses, possibly with S2 being most affected. The invasive, stressful, and anxiety provoking nature of the experiment provides a potential explanation for the absence of S2 activity seen during the study. An alternative explanation for the reduction of activation within S2 could be lack of statistical power or variability in somatosensory sulcal anatomy.

5.2.3 Anterior cingulate cortex

There is converging evidence from lesion (Corkin et al., 1981; Foltz et al., 1962; Foltz & White, 1968; Talbot et al., 1995), single-unit (Hutchison et al., 1999; Koyama et al., 1998; Sikes & Vogt, 1992), evoked-potential (Lenz et al., 1998), and brain-imaging data (Rainville et al., 1997) to implicate the ACC as a pivotal structure in conveying the affective tone of painful stimuli.

First, cingulotomy is an effective treatment in alleviating pain (Corkin et al., 1981; Foltz et al., 1962; Foltz et al., 1968; Talbot et al., 1995). The behavioural consequence associated with a lesion of the ACC is characterized by a reduction of pain-related emotional responses. The patients still report feeling the sensory dimensions of the pain but state it is not bothersome. Second, data from a previous study in our laboratory showed that hypnotic suggestions directed at modulating pain unpleasantness led to increased ratings of pain unpleasantness and greater rCBF activity within the ACC (Rainville et al., 1997). Third, a recent elegantly performed study by Johansen et al. (2001) demonstrated a role for ACC neurons in encoding pain affect. Using a rodent pain assessment model (formalin test) and a place-preference paradigm simultaneously, it was shown that destruction of rostral ACC neurons prevented formalin-induced conditioned place avoidance without reducing acute pain-related behaviours. These results suggest the importance of ACC neurons in the affective/unpleasantness component of the pain experience.

In Study 3, painful brushing led to changes in perceived pain unpleasantness and modulation of activity within the ACC. The large unpleasant component related

to the tactile stimulation lends support to the idea that the ACC is involved in conveying the affective valence of noxious stimuli. The idea is further supported by examining the unpleasantness/ intensity ratios of the magnitude-estimation ratings, which were greater for the painful brushing during Study 3 than the painful thermal stimulus used in Study 2 (1.4 vs. 1.0, respectively). Additionally, evidence from Study 1 suggests a role for the ACC in the conscious experience of pain. Correspondingly, activity was observed in the ACC in response to noxious thermal stimulation during alert-control and moderate-sedation condition, but as subjects began to enter deep sedation and unconsciousness ACC activity was abolished. In study 2, a secondary modulation of pain affect was noted when hypnotic suggestions were given to modify pain sensation, however, alteration of sensation was not accompanied by a significant change in pain-evoked ACC activity. The fact that the changes in pain unpleasantness were not associated with significant modulation in the ACC indicates that secondary changes in pain affect may have a different neural substrate than those associated with the direct and specific modulation in pain unpleasantness. The findings from these three studies, along with data from other groups, suggest that the ACC plays a crucial function in the conscious appreciation of primary pain affect.

5.2.4 Insular Cortex

Despite the overwhelming belief in a role for the insular cortex (IC) in the overall pain experience, its precise function is still in doubt. Currently, there is evidence to implicate IC in autonomic control (Zhang et al., 1999; Zhang et al., 2000; Oppenheimer et al., 1996), anticipation of pain (Ploghaus et al., 1999; Chua et al., 1999), thermal sensibility (Craig et al., 2000), and pain affect (Berthier et al., 1988; Ogden et al., 1959; Winklemann et al., 1962). Qualitatively, these functions describe the overall internal state of the body's physiological condition. Craig et al. (2000) have postulated that the cortical representation of these homeostatic functions reside within the IC.

Results using various anatomical techniques lend support to the role of IC in pain perception. Anatomical tracing and antidromic activation techniques have delineated direct connections from nociceptive thalamic nuclei to the IC (Dostrovsky et al., 1996b; Zhang et al., 2000). Nociceptive neurons responding to nociceptive pinch were located in monkey IC with single-unit recording (Zhang et al., 1999). In addition, IC is usually activated by painful stimuli in PET and MRI studies (Casey et al., 2001; Coghill et al., 1994; Coghill et al., 1999; Lotze et al., 2001).

In addition to its contribution in nociceptive processing, the IC may be involved in autonomic responses to pain. Williamson et al. (1999) demonstrated an elevation in right-sided IC rCBF with increasing exercise intensity, concomitant with a rise in BP. In a separate study, Williamson et al. (2001) utilized hypnotic manipulation to increase effort during constant-load exercise. As a result, HR and BP were both elevated, as well as increased activation in the right insular cortex. A higher preponderance of baroreceptive units were found in right IC compared to left IC in non-human primates (Zhang et al., 1999). Data obtained during the propofol study demonstrated that the only significant change in the cardiovascular measures was a change in systolic blood pressure during unconsciousness between the neutral and painful conditions. This change in BP was coincident with the most robust rCBF modulation of IC in the study. Data from Study 2 indicate that suggestions did not significantly alter subjects' heart rate, and correspondingly, rCBF within the IC was not consistently modulated by the hypnotic suggestions. However, as BP data were not collected, cardiovascular modulation of IC cannot be ruled out. In Study 3, right IC activation was observed in an identical site to that in Study 2 following painful brushing. Nevertheless, the interpretation of this activation as being related to a change in BP remains speculative since we could not monitor BP within the fMRI scanner.

Other studies implicate the IC in the anticipation of pain (Ploghaus et al., 1999; Chua et al., 1999). Ploghaus et al. (1999) demonstrated that the expectation of a painful stimulus activates the anterior IC. The hypnotic suggestions used in Study 2 alerted subjects to the imminent painful stimulus. Likewise, the neuropathic pain patient was told the experimental session would comprise alternating runs of brushing the right and left foot. Therefore, the subjects in both of these experiments could predict and anticipate the painful stimuli, and this may have accounted for some of the IC activation seen in these studies.

5.2.5 Cerebellum

Until the last decade, little thought was given to the role of the cerebellum in nociceptive processing. However, stimulation of cerebellar structures has been shown to elevate nociceptive thresholds for painful tail shocks in monkeys (Siegel & Wepsic, 1974). Similarly, cerebellar stimulation enhances spinal neuronal responses to noxious colorectal distention (Saab et al., 2001). Data from Study 1 showed an increase of cerebellar activity from the alert-control condition through the deep-sedation condition. The amplification of neuronal activity could have been mediated by a propofol-induced disinhibition of cerebellar activation, followed by a general reduction of nociceptive transmission at loss of consciousness and a return to baseline activity.

The enhanced cerebellar activity seen during the moderate- and deep-sedation conditions was coincident with the spastic and uncoordinated stimulation-induced movements. Results correlating rCBF and subjective ratings of movement demonstrated a significant cerebellar focus of activation. Further, all cortical activation normally seen in the production of movement was abolished by the anesthetic. Thus, the cerebellar activity seen could be due to the active suppression of movement or actual subject movement.

Initially, analysis of cerebellar pain-evoked activity was not reported for data collected during Study 2. A retrospective examination of the results revealed

peaks of activation within the cerebellum during suggestions for increased pain and suggestions for decreased pain. However, no peak was observed when the decreased-pain condition was subtracted from the increase-pain condition. Thus, there is no modulation of cerebellar activation by suggestion, which supports the idea that pain-evoked cerebellar activation is not related to the conscious appreciation of pain. This finding is similar to the presence of pain-evoked cerebellar activation following propofol-induced loss of consciousness. Regrettably, the acquisition paradigm used during Study 3 precluded analysis of cerebellar-related activity.

5.2.6 Thalamus

It is not surprising that the thalamus is activated by painful stimuli in PET and fMRI studies (Becerra et al., 1999; Casey et al., 1996; Coghill et al., 1994; Coghill et al., 1999; Davis et al., 1998; Derbyshire & Jones, 1998; Paulson et al., 1998; Xu et al., 1997), as it is the gateway to the cortex for most senses. The role of the thalamus, however, is more important than just a thoroughfare for sensory information.

Thalamic activity proceeds along a spectrum. At one end is robust hyperpolarization, which leads to unconsciousness; on the other end is substantial depolarization, namely action potentials, which for noxious stimulation is perceived as pain. The thalamus is thought to be a key structure in the mediation of consciousness, a highly modifiable reverberating circuit that is in constant contact with the cortex and brain stem (Steriade, 2001). Generating thalamo-cortical hyperpolarization produces loss of consciousness (Steriade et al., 1990). Disruption of thalamic activity has been shown to produce persistent vegetative states (Laureys et al., 2000; Adams, Graham, & Jennett, 2000). Data from Study 1 demonstrates a large decrease in thalamic and thalamic-pain-evoked activity at loss of consciousness, similar to results published by Fiset et al. (1999) and Bonhomme et al. (2001).

There is growing evidence to suspect reduced thalamic activity as a principal mechanism for, or an immediate result of, chronic pain (Di, V et al., 1991; Apkarian, Thomas, Krauss, & Szeverenyi, 2001; Iadarola et al., 1995; Pagni et al., 1995). A reduced level of rCBF has been observed in the hemi-thalamus contralateral to the affected (painful) limb. In our chronic pain patient, brushing of the non-affected foot led to a greater activation of the contralateral than the ipsilateral hemi-thalamus, whereas brushing of the affected foot elicited a greater activation within the ipsilateral thalamus. These results suggest reduced activity in the hemi-thalamus contralateral to the peripheral nerve injury. Chronic pain mediated by thalamic hypoperfusion is effectively treated with an implantable thalamic stimulator possibly by supplementing the missing thalamic activity (Davis et al., 2000; Duncan et al., 1998; Kupers et al., 2000).

As the temperature of a thermal stimulus increases, a commensurate increase of activity is observed in both VP and medial thalamic nuclei (Bushnell & Duncan, 1987; Bushnell et al., 1993; Rosenberg, Harrell, Ristic, Werner, & de Rosayro, 1997). There is a close coupling between thalamic activities and sensory perception (Petrovic et al., 2000). A retrospective look of the data collected during the hypnosis experiment (Study 2) demonstrates a widespread thalamic activation (a strong tendency toward significance t=4.21) when suggestions were given to increase pain, whereas a smaller focus of activation (t=2.99) was observed during suggestions for decreased pain. The results from all three studies suggest a spectrum of behaviour, ranging from unconsciousness to hyperalgesia, depending on the level of thalamic activity.

5.2.7 Prefrontal Cortex

The role of pain-evoked activity within the prefrontal cortex remains enigmatic despite its obvious function in nociceptive processing. The orbitofrontal cortex serves a central function in the processing of affect and emotion, including conveying the aversive salience of stimuli, which might occur along a continuum. (Pascual-Leone et al., 1996; Baker et al., 1997). In addition, electrical stimulation

of the medial prefrontal and ventrolateral orbital cortices have been documented to elicit analgesia (Hardy, 1985) and engage descending inhibitory mechanisms in rat (Hardy & Haigler, 1985; Zhang et al., 1997). Data obtained during brushing of the neuropathic pain patient's foot support these hypotheses. A biphasic response was observed within the prefrontal cortex conditional on the foot being brushed. If the neuropathic foot was brushed, a robust activation was seen in the prefrontal cortex, however, if the non-affected foot was brushed, a deactivation was seen within the same region. Similarly, a post-hoc review of the hypnosis data demonstrated a peak within the same region of the prefrontal cortex when suggestions for decreased pain intensity were subtracted from suggestions for increased pain intensity. These data support the theory that pain-evoked frontal activation is related to the conscious appreciation of pain.

5.3 A conceptual view

An integrative approach to the cortical representation of pain is essential. As such, I developed the idea of a preliminary, interactive network to examine the cortical structures involved in the conscious appreciation of pain. Central to this system is the *sensory-discriminative module*. This unit is responsible for noxious thermal detection and discrimination, in addition it responds in a graded fashion to increases in thermal stimulus intensity (Kenshalo, Jr. et al., 1988; Kenshalo et al., 2000; Kenshalo, Jr. et al., 1991; Tsuboi et al., 1993). The neural correlates relating to the sensorial aspects of the pain experience reside in the primary and secondary somatosensory cortices, and the parietal cortex.

The second component in this network is the *affective module* served by the ACC, prefrontal cortex, and the IC (Rainville et al., 1997; Teasdale et al., 1999). This module is responsible for the affective tone ascribed to the pleasantness/ unpleasantness of the nociceptive stimulus. Following application of the painful stimulus, attention is diverted to the offending stimulus. The *attentional module* engages the ACC, the PCC, prefrontal cortex, and parietal cortex to alert the

individual that danger is imminent (Cohen et al., 1999; Davis et al., 1997; Derbyshire et al., 1998; Paus, 2000).

The application of a painful stimulus leads to *autonomic arousal* resulting in elevated blood pressure as well as an increase in heart rate and respiration. Speculatively, this activity is controlled by structures within the IC, frontal cortex, and brain stem (Harper, Bandler, Spriggs, & Alger, 2000; Oppenheimer et al., 1996; Zhang et al., 1999). Once the individual is aroused, a motor response must be initiated to escape the offending stimulus. The *motor unit* comprises the primary motor area, supplementary motor area, premotor area, cerebellum, and basal ganglia and provides the individual with the ability to escape from the painful stimulus (Jenkins, Passingham, & Brooks, 1997). The *pain reduction module* is now placed into action by activating the descending inhibitory pain mechanisms thought to reside in the frontal cortex and periaqueductal gray (Hardy, 1985; Hardy & Haigler, 1985). *Learning and memory systems* within the prefrontal cortex, temporal lobes, amygdala and hippocampus are also recruited (Alkon et al., 1991; Gallagher & Holland, 1994; Squire et al., 1992; Milner, Squire, & Kandel, 1998). In order to avoid future trauma and injury the individual must learn to avoid the offending stimulus and remember to prevent future contact.

The design of this network requires an intricate interplay between these multiple modules. In some cases of pain, there will be robust input from certain modules while others are in a phase of quiescence. The result is the emergence of different pain experiences, be it acute (thermal, chemical, ischemic pain) or chronic (neuropathic, central, arthritic, or low back pain) all mediated by common structures. In addition, all units are highly modifiable by genetic and environmental factors, in addition to psychological, physiological and pharmacological interventions. One caveat should be kept in mind when viewing this system; the time scale for cortical activity might be extremely brief or

extremely protracted. If this is the case, current imaging tools are inadequate to observe activity at either extreme.

5.4 Conclusion

Pain is a complex, multifaceted sensorial experience, which is heavily determined by physiology, the state of the individual, cultural factors, and the meaning that is given to the sensation. Despite variation within individuals among these determinants, there is a common concept and general agreement as to what constitutes the conscious experience of pain.

Not only is there a general consensus as to what comprises pain, there is also a common cortical neuronal circuitry that signifies pain. Regardless of whether an individual is experiencing acute pain from stubbing his toe or he is experiencing chronic neuropathic pain as a result of chemotherapy, this network of structures is activated. As the quality of the sensation changes, activity within the cortical network is altered. Since the nature of the pain experience is multidimensional, it is not surprising that the cortical correlates are extensive and include S1, S2, ACC, IC, thalamus, cerebellum, and frontal cortex.

Together, these three studies demonstrate that there is a complex thalamo-cortical neural circuit that is activated during the conscious appreciation of pain, and that activation within this circuit can be modulated by conscious state, resulting in altered pain perception.

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