INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

PAIN AND TACTILE EVOKED ACTIVATIONS IN CEREBRAL CORTEX: BETWEEN AND WITHIN SUBJECT COMPARISONS USING fMRI

A thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Master of Science

by

Brian J. Ha

Department of Physiology
McGill University, Montreal
March, 2000

He will wipe every tear from their eyes. There will be no more death or mourning or crying or pain ...

Revelation 21:4

ABSTRACT

Positron emission tomography (PET) studies of the human brain reveal pain-related activation in several regions of the cerebral cortex. Nevertheless, patterns of activation vary among studies. This study used the more sensitive method, functional magnetic resonance imaging (fMRI), to assess variability between and within subjects, for both pain and tactile-related activation. Four subjects participated in two fMRI sessions each. Thermal and tactile stimuli were applied to the skin on separate runs. Activation maps were generated comparing painful to neutral heat and tactile to rest.

Group analysis revealed pain- and tactile-related activation consistent with the majority of PET studies. Comparison of activation sites across subjects revealed differences in the location of peaks corresponding to anatomical variability in sulcal position. Comparing across sessions for each subject revealed differences in the intensity but not the location of peaks.

These results indicate that pain and touch evoke reliable patterns of cortical activation. Intensity-related differences and intersubject variability could explain the variable results of PET studies.

RÉSUMÉ

Les études de tomographie par émission de positrons (TEP) chez l'humain révèlent une activation liée à la douleur dans plusieurs aires corticales. Toutefois, les sites d'activations varient d'une étude à l'autre. Cette étude utilise l'imagerie par résonance magnétique fonctionnelle (IRMf) pour estimer la variabilité entre les sujets et chez un même sujet dans l'activation cérébrale induite par une stimulation tactile et une stimulation douloureuse. Quatre sujets ont participé à deux séances d'IRMf. Les séances comprennent un scan anatomique et cinq à huit scans fonctionnels. Les stimuli tactiles et douloureux sont appliqués au cours de différents scans au niveau du mollet gauche. Les sujets ont évalué l'intensité du stimulus après chacun des scans. Les cartes d'activations sont générées en comparant la stimulation douloureuse à la situation de repos ainsi que la stimulation tactile à la situation de repos.

Les analyses de groupes ont révélé des sites d'activations pour les stimulations tactiles et les stimulations douloureuses compatibles avec celles obtenues avec les études de TEP. Les analyses individuelles ont révélé des différences dans la localisation des pics d'activation associés avec des variabilités anatomiques. L'analyse de session unitaire a démontré des variabilités chez un même sujet quant à la présence des pics d'activation.

Ces résultats démontrent que la douleur et le toucher évoquent des patrons d'activation corticale cohérents. Les différences dans l'intensité des activations et la variabilité inter-sujet pour une région pourraient expliquer la variabilité des résultats obtenus entre les études de TEP.

ACKNOWLEDGEMENTS

My words cannot adequately express my gratitude to the many who have contributed to this long journey. I have had the privilege of working with exceptional researchers and the pleasure of discovering the genuine people behind the names. I am especially indebted to Dr. Cathy Bushnell for her caring supervision over the past three years. Her support, encouragement and patience have always inspired me to strive for excellence in my work.

I would like to thank members of the brain imaging community at the Montreal Neurological Institute for their help with the technical aspects of this project. Drs. Bruce Pike and Rick Hoge were instrumental from the inception of this fledgling study. Working with Dr. Keith Worsley and his student, Chuanhong Liao, to develop the new fMRI analysis software was a treat, and I am honoured to have been able to contribute in my small way. In particular, I would like to express my deepest gratitude to Vali Petre for her tremendous and steadfast help.

I am truly grateful for being part of such a helpful, selfless lab group. It's difficult to give full recognition for all the help I've received from my peers, since generosity has been so commonplace. In particular, I would like to thank Jen-I Chen and her supervisor, Dr. Gary Duncan, for their collaboration on this project; Leo TenBokum for developing and testing the fMRI compatible thermodes and other trinkets; Chantal Morin for translating the abstract; and Irina Strigo for her help with Excel.

To those outside of the realm of research whom I've played, laughed, cried and simply experienced life with: Thank you so much for your encouragement, your prayers and your love. The impact you have had on me will remain with me forever.

Table of Contents

Chapter 1
INTRODUCTION

The involvement of the cerebral cortex in the processing of pain has been subject to debate for some time. Early in the century, clinical observations of patients with cortical lesions led to the conclusion that the cerebral cortex is not necessary in the processing of pain (Head & Holmes, 1911). This view was further supported by cortical stimulation of conscious patients undergoing brain surgery (Penfield & Boldrey, 1937). Electrical stimulation of the cerebral cortex rarely evoked the sensation of pain, leading to the conclusion that "pain has little, if any true cortical representation". It was generally accepted that pain entered consciousness at the level of the thalamus, without conveyance to the cortex being necessary. However, other clinical observations demonstrated that circumscribed cortical lesions result in the localized loss of pain perception (Marshall, 1951) and furthermore, removal of cortical regions have been found to effectively alleviate pain (Lewin & Phillips, 1952).

Pain is a complex, multidimensional experience that consists of sensory-discriminative (location, quality, intensity, etc.) and motivational-affective (unpleasantness, desire to withdraw, etc.) components (Melzack & Casey, 1968). In contrast to the concept of a single, fixed pain center in the brain, originally proposed by Descartes (1662), there is now a significant body of evidence supporting the role of multiple cortical regions in the perception of pain. Clinical, anatomical and physiological evidence indicate that this network of brain regions is functionally segregated into systems that correspond to the sensory-discriminative and the motivational-affective components of pain. Several lines of investigation, suggest that primary (S1) and secondary (S2) somatosensory cortices are involved in the discriminative aspect of pain, while anterior cingulate (ACC) and anterior insular (IC) cortices are involved in the affective aspect of pain.

An overview of the pain system will be presented, after which the roles of four cortical regions – S1, S2, ACC and IC – will be discussed in light of the clinical, anatomical and physiological evidence. The blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) technique will be introduced and it's advantages over PET in imaging brain activity will be discussed.

1.1 THE PAIN SYSTEM

1.1.1 Peripheral Structures

Painful stimuli are first detected by nociceptive receptors, or *nociceptors*, located in the skin, muscles, joints, viscera, and the meninges around the spinal cord and brain. These nociceptors are unmyelinated free nerve endings of small-diameter C-fibers, and less commonly, thinly myelinated Aδ fibers (Bishop, 1946; Burgess & Perl, 1973). C-fiber activation characteristically produces a sensation of slow, dull, burning pain (Ochoa & Torebjork, 1989), whereas Aδ activation results in a faster sensation of sharp, pricking pain (Konietzny *et al.*, 1981).

The Aδ and C fibers, whose cell bodies are located within the dorsal root ganglia, subsequently carry nociceptive information to the spinal cord. As the dorsal root enters the spinal cord, the nociceptive afferents separate from the large diameter Aα and Aβ fibers, and send ascending and descending branches that penetrate the dorsal horn in one or two adjacent spinal segments. These collateral branches make up Lissauer's tract (Coggeshall *et al.*, 1981).

Nociceptive afferents primarily terminate in the superficial layers of the dorsal horn, which consists of the marginal zone (lamina I) and the substantia gelatinosa (lamina II). Some Aδ fibers project deeper into the spinal cord and terminate in

lamina V. Nociceptive fibers form connections with three types of neurons in the dorsal horn, including projection neurons (send incoming sensory information to higher brain regions), local excitatory interneurons (relay sensory input to projection neurons), and inhibitory interneurons (regulate the flow of nociceptive input to higher centers). Lamina I contains a large number of projection neurons that receive direct nociceptive and thermoreceptive input from Aδ fibers and indirect input from C-fibers via the interneurons of lamina II (Cervero & Iggo, 1980; Christensen & Perl, 1970). These projection neurons have small receptive fields and response characteristics that enable them to distinguish the location and quality of noxious stimuli. Lamina V projection neurons receive convergent input, directly and indirectly, from both nociceptive small-diameter fibers (Aδ, C) and innocuous large-diameter fibers (Aβ) (Willis, 1985). As a result, these cells respond to a wide range of noxious and non-noxious stimuli and are involved in encoding the intensity of noxious stimuli.

1.1.2 Ascending Nociceptive Pathways

Dorsal horn projection neurons carry nociceptive information to higher subcortical and cortical regions through several ascending fiber tracts that terminate at different levels. There are five major pathways including the spinothalamic tract, the spinoreticular tract, the spinomesencephalic tract, the spinocervical tract, and the postsynaptic dorsal column pathway (Willis, 1985). The anterolateral ascending

system is made up of the spinothalamic, spinoreticular and spinomesencephalic tracts, and plays a significant role in the transmission of pain and temperature information. The majority of projection neurons in lamina I and deep laminae cross midline to ascend in the contralateral anterolateral quadrant. The spinocervical and the postsynaptic dorsal column pathways, on the other hand, ascend in the ipsilateral dorsal quadrant of the spinal cord.

1.1.2.1 Spinothalamic Tract

Sensory information related to pain and temperature sensation is primarily carried by the spinothalamic tract (STT) (Vierck & Luck, 1979). The STT originates from cells in laminae I, as well as several deeper laminae (Willis *et al.*, 1979; Apkarian & Hodge, 1989), and project to areas within the lateral, medial and posterior thalamus (Willis, 1985; Willis & Coggeshall, 1991). Neurons in the lateral thalamic nuclei, such as the ventroposterior (VP) thalamic nucleus, receive somatotopically organized input from the STT (Hyndman and Van Epps, 1939; Walker, 1940), as well as non-noxious tactile input from the dorsal column nuclei, and subsequently send axons to somatosensory cortices. In general, STT neurons that project to the lateral thalamus have small, contralateral, cutaneous receptive fields and are therefore suitable to encode the sensory-discriminative aspects of pain (Willis *et al.*, 1974). Projections to the medial thalamus terminate in the central lateral nucleus (CL) and other intralaminar nuclei and in turn project to a

diversity of cortical and subcortical regions, including limbic and motor regions. These neurons have very large receptive fields (Giesler *et al.*, 1981) and thus implicate a role in the motivational-affective aspects of pain (Willis, 1985; Willis & Westlund, 1997). The posterior part of the ventral medial thalamus (VMpo) receives dense terminations from lamina I spinothalamic fibers (Craig *et al.*, 1994). These cells originate from pain and temperature specific cells and subsequently send projections to the insular cortex (Friedman *et al.*, 1986).

1.1.2.2 Spinoreticular Tract

The spinoreticular tract (SRT) sends nociceptive information from deep laminae to terminate on cells of the reticular formation (Willis & Coggeshall, 1991). Some of these reticular neurons terminate on cells involved in descending pain modulation and may be involved in the phenomenon of hyperstimulation analgesia. Other SRT neurons make up the spino-reticulo-thalamic tract, which along with STT neurons, terminate in the medial thalamus.

1.1.2.3 Spinomesencephalic Tract

The spinomesencephalic tract (SMT), originating from laminae I, IV, V and VI (Willis & Coggeshall, 1991; Willis *et al.*, 1979), terminates in the midbrain, primarily in the superior colliculus and the periaqueductal gray matter (PAG). Nociceptive activity within the superior colliculus may play a role in the integration of different sensory input, as well as in the behavioral response to pain (McHaffie *et al.*, 1989). Spinomesencephalic projections to PAG are important in activating an endogenous pain-modulating system (Reynolds, 1969). Endogenous opioids are released within this region and PAG neurons are involved in the inhibition of further pain via descending inhibitory pathways. These descending pathways inhibit nociceptive neuronal transmission in the dorsal horn (Basbaum & Fields, 1984).

1.1.2.4 Spinocervical Tract

It is uncertain whether there is a significant spinocervical tract (SCT) in humans. In monkey and cat, however, the spinocervical tract has been found to originate in the contralateral spinal laminae III, IV and V (Willis, 1985). Most respond solely to tactile stimuli, but some are also activated by noxious stimuli. This tract ascends in the ipsilateral dorsolateral quadrant of the spinal cord and synapses with the lateral cervical nucleus (Brodal & Rexed, 1953; Craig *et al.*, 1992). These neurons then cross midline and ascend in the medial lemniscus, projecting to midbrain nuclei and to the thalamus (Berkley, 1980; Willis & Coggeshall, 1991).

Nociceptive transmission via the spinocervical tract may potentially account for the frequent recurrence of pain after anterolateral cordotomy.

1.1.2.5 Postsynaptic Dorsal Column Pathway

Nociceptive neurons in laminae III and IV (Willis, 1985), together with the collaterals of large diameter primary afferents, project their axons through the dorsal column to the dorsal column nuclei. These nuclei then project by the medial lemniscus to the thalamus. Postsynaptic dorsal column cells respond to both mechanical and chemical irritation of viscera, suggesting that this pathway may play a key role in the transmission of visceral pain (Al-Chaer *et al.*, 1996).

1.1.3 Thalamus

Nociceptive information is transmitted both directly and indirectly to the thalamus via the various ascending pathways discussed above. Traditionally, the thalamus is functionally divided into lateral and medial components, which are thought to correspond to the sensory-discriminative and affective-motivational components of pain, respectively (Albe-Fessard *et al.*, 1985). Several thalamic nuclei receive dense projections from spinal nociceptive fibers. These include the ventroposterior lateral and medial nuclei (VPL and VPM) (Bushnell & Duncan, 1987; Bushnell *et al.*, 1993; Casey & Morrow, 1983a; Kenshalo, Jr. *et al.*, 1980), the posterior division of the ventromedial nucleus (VMpo) (Craig *et al.*, 1994), and

the medial dorsal (MD), central lateral (CL), central median (CM) and parafascicular (Pf) nuclei of the medial thalamus (Dong *et al.*, 1978; Bushnell & Duncan, 1989). These nuclei differentially project to a number of cortical areas, including S1, S2, ACC and IC.

1.1.4 Cortical Regions

1.1.4.1 Primary somatosensory cortex (S1)

Contrary to early human lesion and stimulation studies, there is mounting evidence that S1 cortex plays a key role in the perception of pain. Regions of the thalamus containing nociceptive cells have been shown to project to S1 (Gingold *et al.*, 1991; Rausell & Jones, 1991) and in several species, researchers have found S1 neurons that respond to noxious stimuli (Casey & Morrow, 1983b; Chudler *et al.*, 1990; Kenshalo, Jr. *et al.*, 1988; Kenshalo, Jr. & Isensee, 1983). Clinical evidence also implicates the involvement of S1 in pain perception. Observations of patients with superficial injuries to the post-central gyrus were found to have localized loss of pain perception (Marshall, 1951). In some cases, surgical removal of S1 successfully alleviates pain (Lewin & Phillips, 1952b). Similarly, S1 was found to be the most common site of epileptic foci in patients who experience painful unilateral seizures (Young & Blume, 1983).

Other evidence indicate that S1 is involved in the sensory-discriminative component of pain processing. Clinically, removal of S1 has been observed to impair localization while leaving the ability to perceive pain intact (Penfield & Jasper, 1954). Single-unit investigations in primates have identified a population of S1 neurons that encode the intensity of noxious stimuli (Chudler *et al.*, 1990; Kenshalo, Jr. & Isensee, 1983; Kenshalo, Jr. *et al.*, 1988). These neurons have small, restricted, contralateral receptive fields – properties ideal for encoding the sensory-discriminative aspects of pain, including localization. In addition, most of these cells are wide-dynamic-range neurons and thus respond in a graded manner to varying intensities. The responses of these neurons correspond with the ability of the monkey to discriminate intensities of noxious stimuli (Kenshalo, Jr. *et al.*, 1988), as well as with human ratings of pain intensity during identical conditions (Chudler *et al.*, 1990). Upon bilateral removal of S1, monkeys lose the ability to detect changes in noxious stimulus intensity (Kenshalo, Jr. *et al.*, 1991).

Brain imaging studies using a range of techniques and stimuli have provided additional evidence that S1 participates in pain processing. Data from both PET and fMRI studies have shown S1 activation in response to a range of noxious stimuli, including heat, cold, electrical stimuli and injection of capsaicin, which preferentially activates C-fibre specific injection (Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994; Craig *et al.*, 1996; Iadarola *et al.*, 1998; Andersson *et al.*,

1997; Derbyshire *et al.*, 1997; Davis *et al.*, 1995; Porro *et al.*, 1998; Gelnar *et al.*, 1999). This pain-related activation has been found to be somatotopically organized in a fashion consistent with the somatosensory homunculus and a recent PET study (Fox *et al.*, 1987) of S1 somatotopy with vibration (Andersson *et al.*, 1997; Porro *et al.*, 1998). The somatotopic arrangement of pain accounts for the accuracy in localizing painful cutaneous stimuli from pure C-fibre input (mean error ~1cm on the dorsum of the hand (Koltzenburg *et al.*, 1993) and 2cm on the dorsum of the foot (Jorum *et al.*, 1989)).

1.1.4.2 Secondary somatosensory cortex (S2)

There is evidence that S2 participates in the processing of pain but its exact role remains unclear. Primate electrophysiological studies have localized only a small number of neurons in S2 that respond to noxious stimuli (Robinson & Burton, 1980; Dong *et al.*, 1994). However, brain imaging studies, along with clinical observations have affirmed the involvement of S2 in pain processes. S2 activation has been consistently observed in imaging studies of pain (Davis *et al.*, 1998a; Casey *et al.*, 1996; Coghill *et al.*, 1994; Talbot *et al.*, 1991; Xu *et al.*, 1997; Craig *et al.*, 1996; Iadarola *et al.*, 1998), but it remains unclear if there is any related somatotopic organization (Xu *et al.*, 1997; Andersson *et al.*, 1997).

In a case study, a tumor compromising S2 caused contralateral deficits in pain perception – increased pain thresholds for heat, cold and mechanical pain – that normalized upon the removal of the tumor (Greenspan & Winfield, 1992). Pain discrimination was also altered in monkeys with damage to the S2 region (Dong *et al.*, 1996). These findings suggest that S2 may function together with S1 to process discriminative aspects of pain. Since S2 receives direct nociceptive input from the thalamus (Friedman & Murray, 1986), it is possible that S1 and S2 receive and process pain information in parallel, and unlike tactile processes, S2 may not require serial input from S1 (Ploner *et al.*, 1999; Simoes & Hari, 1999). This may explain why surgical lesions of S1 sometimes fail to alleviate chronic pain (White & Sweet, 1969).

1.1.4.3 Anterior cingulate cortex (ACC)

The anterior cingulate cortex is an integral structure of the limbic system that is believed to be involved in the motivational-affective component of pain (Melzack & Casey, 1968b). Anatomical studies have shown that ACC receives direct projections from thalamic nuclei containing nociceptive neurons (Yasui *et al.*, 1988; Musil & Olson, 1988; Vogt *et al.*, 1987; Craig *et al.*, 1994). This has been confirmed by electrophysiological evidence showing that neurons in the ACC respond to noxious stimulation (Sikes & Vogt, 1992; Hutchison *et al.*, 1993). Surgical ablation of the ACC in humans has been observed to reduce the affective

component of pain while leaving localization intact (Foltz & Lowell, 1962; Hurt & Ballantine, Jr., 1973).

Recently, researchers have provided direct evidence for a role of ACC in pain processing. Single-neuron, electrophysiological recordings were carried out in the ACC of awake patients undergoing neurosurgery. ACC neurons were identified that responded specifically to painful thermal and mechanical stimuli (Hutchison *et al.*, 1999).

Opioid analgesics are well known to reduce the affective component of pain. A PET study using a radio-labeled opiate revealed a high concentration of opioid receptors in human ACC (Jones *et al.*, 1991). Furthermore, ACC has been found to be the most consistently activated region in blood flow studies of pain (Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994; Craig *et al.*, 1996; Porro *et al.*, 1998; Iadarola *et al.*, 1998; Andersson *et al.*, 1997; Derbyshire SWG & Jones AKP, 1998; Davis *et al.*, 1997) see also table 1 in (Derbyshire *et al.*, 1997). A recent PET study has provided evidence to support the role of ACC in the motivational-affective component of pain (Rainville *et al.*, 1997). Hypnotic suggestions were used to selectively modulate the affective component of pain without modifying the sensory aspect. Psychophysical measurements confirmed that the unpleasantness associated with the painful stimulus was modified in coincidence with the hypnotic

suggestions, while the intensity remained unchanged. The PET results paralleled the perceptual consequences of these hypnotic suggestions: activity in the ACC was significantly correlated to the perceived unpleasantness, whereas S1 activation was unaltered.

1.1.4.4 Anterior insular cortex (IC)

Bilateral insular activation has been observed in many imaging studies of pain (Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994; Craig *et al.*, 1996; Iadarola *et al.*, 1998; Andersson *et al.*, 1997; Derbyshire *et al.*, 1997). IC receives input from the posterior portion of the spinothalamically activated ventromedial (VMpo) thalamic nuclei (Friedman & Murray, 1986) and has connections with cortical areas implicated in pain perception, including S1, S2, and ACC (Augustine, 1985; Augustine, 1996; Friedman *et al.*, 1986; Mufson & Mesulam, 1982). Evidence suggests that IC plays a role in motivational-affective aspects of pain. Lesions of the insular cortex have been reported to result in asymbolia for pain, which includes increased pain tolerance, lack of withdrawal, and absent or inappropriate emotional responses to painful stimuli (Berthier *et al.*, 1988)(recent ref). Furthermore, IC has been shown to project to regions of the limbic system, including the amygdala and perirhinal cortex (Friedman *et al.*, 1986). Insular association with the limbic system, as well as other areas of the pain processing system, suggest that this region may be involved in the integration of

ongoing pain with mnemonic, motivational and affective processes, thus allowing previous experiences to influence the perception and evaluation of a current pain (Friedman *et al.*, 1986; Coghill *et al.*, 1994).

1.2 FUNCTIONAL BRAIN IMAGING

In 1890, Roy & Sherrington originally proposed that cerebral blood flow (CBF) varies with local neuronal activity. Since then, various physiological stimulation and measurement procedures have confirmed that local changes in CBF are coupled to regional brain activity. Functional brain imaging tools take advantage of this "activation-dependent coupling" in order to map neuronal activity.

The majority of brain imaging studies of pain have been performed using positron emission tomography (PET). This technique uses intravascular injections of a freely diffusible radioactive tracer, typically radioactive water ($H_2{}^{15}O$), to measure changes in regional CBF. In recent years, it was discovered that magnetic resonance imaging (MRI), the standard tool for imaging structural properties of the brain, can be applied to detect brain activity. Functional MRI (fMRI) has since become a valuable tool, if not the most powerful, for imaging activity in the brain and it will likely replace PET in brain activation studies.

1.2.1 Advantages of fMRI

fMRI offers a number of advantages over PET for imaging activity in the brain. Unlike PET, fMRI does not require the injection of radioisotopes to detect neural activity, thus eliminating many tracer-related drawbacks. In order to maintain a safe level of radioactivity within the subject, PET tracers must be allowed to decay between scans. These long interscan intervals, typically around 10 minutes, result in lengthy scanning sessions (~3 hours), with only a limited number of scans acquired (10-12 per subject). This small number of scans per session necessitate the averaging of data over multiple subjects in order to make reliable interpretations. Furthermore, repeated assessments of specific individuals is not possible because any given subject can only participate in 1 or 2 PET sessions in a lifetime. In contrast, fMRI allows for the repeated evaluation of individual subjects and whole-brain functional images can be acquired every 1-4 seconds. In a typical fMRI experimental session, lasting around two hours, hundreds of scans can be acquired so that reliable interpretations can be made. Moreover, the spatial resolution of fMRI, (~1mm) is far superior to that of PET (4-6mm). Finally, the availability of MRI technology also poses a significant advantage over PET.

1.2.2 BOLD fMRI

Originally fMRI experiments used the administration of an exogenous contrast agent in order to measure changes in CBF. This, however, was rapidly replaced by the discovery that deoxygenated hemoglobin can act as an endogenous contrast agent (Ogawa *et al.*, 1990). The blood oxygenation level dependent (BOLD) contrast method has since become the most prevalent approach in fMRI brain mapping studies.

When a brain region is activated, local arteriolar dilation causes a subsequent increase in blood flow to that region. Oxygen metabolism in the activated area increases only slightly and in disproportion to the CBF response. Consequently, the increased blood flow results in an excess of oxygenated HB, reducing the regional deoxy HB content. Because contrast agents, including deoxy HB, are paramagnetic, they act to degrade the homogeneity of the magnetic field and ultimately decrease the MR signal. Therefore, since neuronal activation results in a local reduction of deoxy HB, less signal degradation occurs, effectively increasing the MR signal. In other words, increases in neuronal activity are detected as increases in the MR signal.

1.3 OBJECTIVES

In the past decade, functional brain imaging techniques have provided fresh insight into the cortical processing of pain. These imaging tools, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have allowed for the simultaneous observation of global activity within the normal brain in response to painful stimuli. They have demonstrated that multiple, discrete cortical regions are involved in the perception of pain. Regions observed to be consistently activated by transient heat stimuli include S1, S2, ACC and IC. These areas, however, are not found across all studies or research groups. This is not surprising considering the numerous methodological differences amongst groups (Bushnell *et al.*, 1999).

Still, there may be other sources that contribute to the variability. The majority of brain imaging studies of pain have been performed by PET – the results of which, by nature, are the product of multiple subject analysis. Therefore, any idiosyncratic patterns of neuronal activation from individual subjects are lost in the averaging process. These differences may arise due to functional or anatomical differences across the population. The effect of the scanning day is also unclear in PET studies, as each subject may only participate in one PET session, and hence, it is not known how data from individual sessions contribute to averaged analysis.

Furthermore, it may not possible to differentiate adjacent sites of activation, due to the large blurring kernel used in PET analysis.

The ability of fMRI to repeatedly evaluate individual subjects, as well as it's superior spatial and temporal resolution, allows for a more detailed look at individual differences and how they have contributed to our current understanding of pain processing in the brain. A few fMRI studies of pain have examined intersubject differences and have demonstrated that different patterns of activation are elicited in different individuals during identical stimulation (Davis *et al.*, 1998a; Becerra *et al.*, 1999; Gelnar *et al.*, 1999). However, none have looked at within subject differences – how patterns of activation vary in the same subject on different scanning days.

In this study, fMRI has been used to examine both between and within subject differences in pain- and tactile-related cortical activation. Subjects were scanned on two separate days for both painful thermal and non-painful brush stimuli. Cortical activation maps were generated on multiple levels, from individual session analysis to group analysis across all subjects.

Chapter 2
METHODS

2.1 SUBJECTS

Four normal right-handed volunteers (3 male, 1 female), age 23-27 years old, participated in the study. Subjects were informed of the basic procedures of the study upon which signed consent was obtained. The study was performed according to the Declaration of Helsinki and all procedures were approved by the Research Ethics Committee of the Montreal Neurological Institute.

2.2 DATA ACQUISITION

All images were acquired using a 1.5 Tesla Siemens Vision scanner with a standard quadrature head coil. BOLD fMR images were obtained using a T2*-weighted gradient echo (GE) echo planar imaging (EPI) sequence (TR = 3.36 s, TE = 51 ms, flip angle = 90°, FOV = 300 mm, matrix = 128 x 128); the scanned area covered the brain from the vertex to the base of the thalamus using ten to

thirteen 7 mm contiguous axial slices parallel to the AC-PC line (2.3 x 2.3 mm in-plane resolution). One hundred twenty whole-brain volumes (or 'frames') were acquired during each functional scanning run (3.36 s/frame, ~7 min/run). High resolution T1-weighted anatomical scans (TR = 22ms, TE = 20ms, flip angle = 30°, FOV = 256 mm) were acquired for all scanning sessions and later superimposed with the respective functional activation maps in order to localize regions of activation.

2.3 STIMULATION PROCEDURES

All subjects participated in at least two scanning sessions, each of which included a high-resolution anatomical scan and 5-8 functional scanning runs. Each subject underwent preliminary testing in order to become familiar with the experimental protocol, as well as to determine a tolerable temperature for the thermal stimuli. During this preliminary session, ratings for both the intensity and the unpleasantness of thermal stimuli were obtained on a five-point verbal scale. For ratings of pain intensity, zero represented no pain sensation and five represented the most intense pain sensation imaginable; for ratings of unpleasantness associated with the painful stimuli, zero represented no unpleasantness and five represented the most pain unpleasantness imaginable. The stimulus temperature was determined by finding a temperature that elicited a rating of four on the intensity scale. Brush stimuli were also presented and rated on a similar five-point scale, where zero

represented no sensation and five represented a very intense, but non-painful, sensation.

Before being placed into the scanner, subjects were instructed to attend to the stimuli, to keep their eyes closed and their head as still as possible throughout the scanning session. Head position was further stabilized using an immobilization apparatus that prevented rotational and translational head movements. This apparatus included: a foam headrest; a fixed, plastic bar placed on the bridge of the nose; padded ear-muffs clamped over each ear; and in some cases, a bite bar. The subject held an emergency escape switch so that he could withdraw, for any reason, from the scanner.

Thermal and tactile stimuli were presented to the skin over the medial aspect of the left calf during separate runs. Thermal stimuli were applied using two 9-cm^2 contact thermodes at noxious (46-47.5°C) and neutral (35-36°C) temperatures; thermal runs consisted of ten alternating cycles of rest, noxious heat, rest, and neutral stimulation periods (~10 s each). Tactile stimulation was presented to the same area of the leg using a 2-cm wide soft artist's paint brush. The brush was manually moved back and forth, in a proximal-distal orientation, over a 10-cm region of the skin at a speed of 20 cm/s; tactile runs consisted of twenty alternating cycles of no stimulation and brush (~10 s each). Three whole-brain volumes were acquired for

each 10 s stimulation period, yielding 120 volumes for an entire run. At the end of each run, subjects were asked to rate the stimuli in the same manner as described above. To assess whether there were any changes in perception during the course of each run, subjects were required to give ratings of the stimuli for the beginning of the run, as well as the end of the run. Subjects were also asked to rate any discomfort arising from sources other than the stimulus. In order to minimize head movement, all ratings were given non-verbally, using the fingers of one hand.

2.4 DATA ANALYSIS

fMRI volumes were corrected for head motion by registering all frames of a run to the third frame. Volumes were also low-pass filtered with a 6 mm full width half maximum (FWHM) Gaussian kernel in order to increase the signal to noise ratio. Frames 1 and 2 were excluded to assure steady state magnetic resonance signal. Statistical activation maps were generated using software developed at the Montreal Neurological Institute (Worsley *et al.*, 2000), and were subsequently merged with each subject's anatomical MRI. All images were resampled into stereotaxic space using an automated registration method based on multiscale, three-dimensional cross-correlation with the average of 305 normal MR scans registered into Talairach space (Collins *et al.*, 1994). Activation maps were then examined for regions of globally significant activation.

The statistical analysis of the fMRI data was based on a linear model with correlated errors. For each run, the design matrix of the linear model was first convolved with a gamma hemodynamic response function with a mean lag of six seconds and a standard deviation of three 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 three degrees, to the design matrix. The correlation structure was modeled as an autoregressive process of one degree (Bullmore *et al.*, 1996). At each voxel, the autocorrelation parameter was estimated from the least squares 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.

In a second step, runs were combined using another linear model for the run effects (as data), weighted inversely by the square of their standard errors. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with 15 – 30 mm FWHM Gaussian filters. The variance of the effect was then estimated by the smoothed ratio multiplied by the fixed effects variance to

achieve higher degrees of freedom. This step was repeated combining the sessions of each individual subject and finally, combining all the sessions of all subjects (group analysis).

In order to replicate PET data, raw fMRI volumes were blurred using an analogous 14.3 mm FWHM kernel. The individual subject and intersubject analysis was repeated for these data sets.

The threshold t-values for significant activation ($p = 0.05$) were calculated using the minimum given by a Bonferroni correction and random field theory (Worsley *et al.*, 1996; Worsley *et al.*, 1999).

Chapter 3

RESULTS

All subjects rated thermal stimuli as painful (3.7 ± 0.2) and there were no differences between the beginning and the end of runs ($p>0.05$, student t-test). Tactile stimuli were always rated as non-painful (1.6 ± 0.1).

3.1 GROUP ANALYSIS

3.1.1 Pain-related sites of activation

Intersubject analysis produced patterns of activation similar to those commonly found across brain imaging studies. Consistent with previous observations using PET, painful stimulation elicited a distributed network of significant activation. However, no activation was observed in S1 cortex. S2 cortex was activated contralateral to the stimulation, along the upper bank of the lateral sulcus (figure 1b), and there was an ipsilateral peak that approached significance (table 1a).

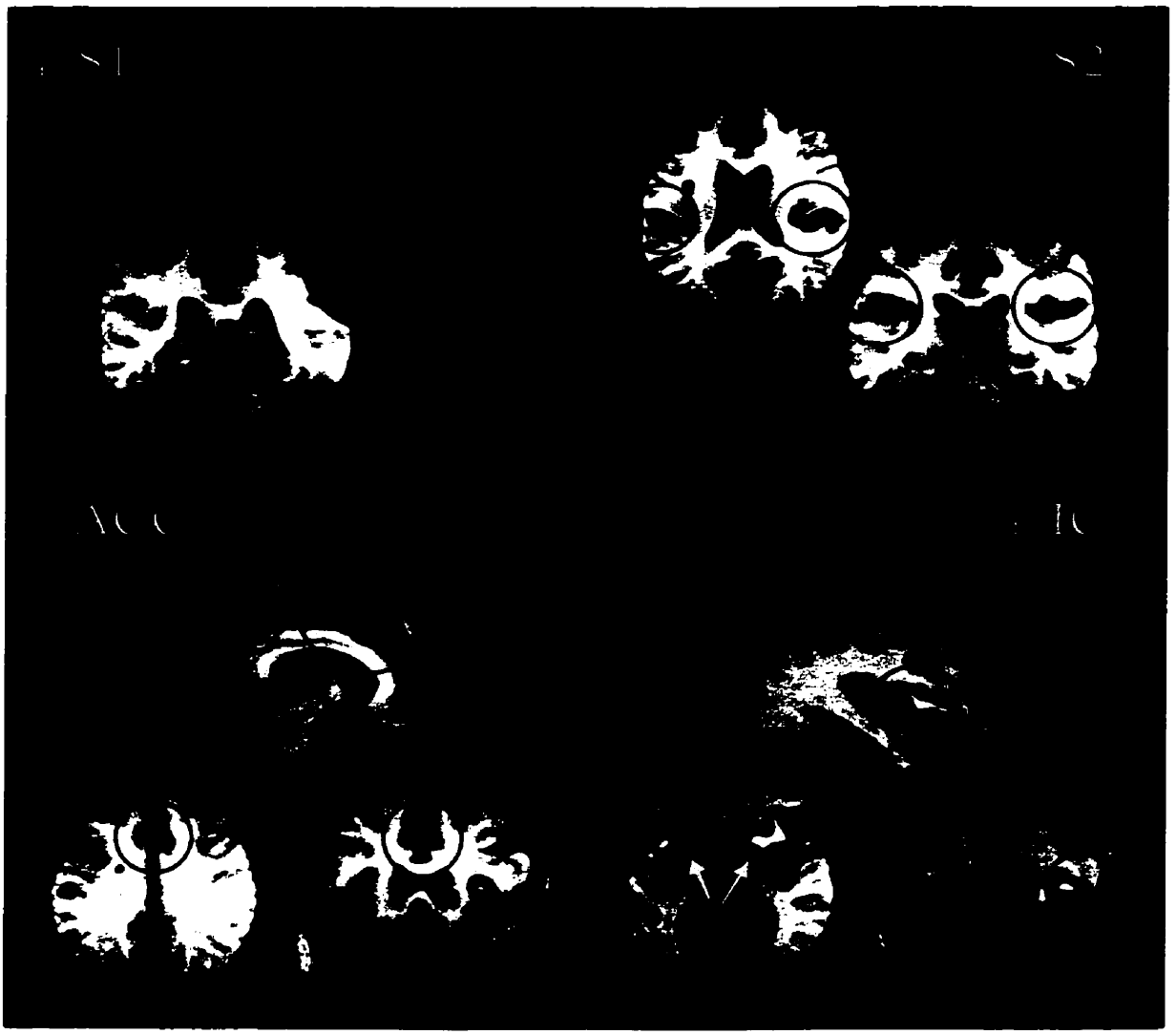

Figure 1. Statistical activation maps of grouped analysis across 4 subjects, showing peaks of pain- (red) and tactile (blue) activation. a) Only brush stimulus elicited significant activation in contralateral S1. b) Both pain and tactile stimuli produced bilateral activation within S2. c) Only pain stimuli produced activation in ACC. Multiple peaks of the midcingulate region were observed. d) Only pain stimuli produced bilateral activation in the anterior portion of the insular cortex. There was also bilateral activation in the basal ganglia (arrows) in response to painful stimulation.
Coordinates of image planes are expressed in millimeters. The anatomical images were constructed by averaging all MR volumes and are thus less detailed than individual images.

Peaks of activation were observed in multiple, bilateral regions of the mid ACC, with stronger activation contralateral to the stimulus (figure 1c, table 1a). A band of activation was observed bilaterally in the rostral portion of the insular cortex (IC) and the adjacent frontal operculum were also activated bilaterally (figure 1d, table 1a).

Table 1a. Pain-related activation sites for grouped analysis across 4 subjects

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	-	-	-	*none*
S2 (contra)	36	-20	16	5.3
S2 (ipsi)	*-56*	*-28*	*18*	*4.1*
i. parietal lobule	56	-34	26	5.1
ACC (contra)	8	16	34	5.9
	8	*-6*	*42*	*4.1*
	0	22	42	5.0
ACC (ipsi)	*-6*	*10*	*40*	*4.4*
IC (contra) band of activation	34	14	4	7.3
	32	26	2	6.7
	34	4	12	6.1
IC (ipsi)	-40	8	4	6.9
operculum (contra)	54	8	6	6.7
operculum (ipsi)	-48	0	6	6.7
SMA	*2*	*12*	*60*	*4.3*
m. frontal gyrus	28	44	24	5.3
basal ganglia (contra)	22	10	4	7.6
basal ganglia (ipsi)	-22	8	-2	6.5
precuneus (area 7)	2	-58	40	-5.5
occipital	40	-70	38	-5.3
s. frontal gyrus (area 9)	*-12*	*56*	*38*	*-4.5*

df = 133, global threshold t-value = 4.79, p = 0.05

b. Pain-related activation sites for blurred (14 mm) group analysis across 4 subjects

S1	*20*	*-42*	*74*	*3.8*
S2 (contra)	26	-16	16	4.8
ACC (contra)	6	12	42	5.6
	8	14	36	5.6
IC (contra)	34	12	6	7.5
IC (ipsi)	-40	6	10	7.2
operculum (ipsi)	-46	4	8	7.1
m. frontal gyrus	*28*	*42*	*22*	*4.4*

df = 127, global threshold t-value = 4.59, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior). Negative t values indicate that the MR signal was greater during control stimulation than during pain stimulation. Coordinates in italics are below the threshold of statistical significance.

Other cortical regions. Cortical peaks of activation were found in the contralateral middle frontal gyrus, the contralateral inferior parietal lobule and the supplementary motor area (table 1a).

Subcortical regions. Pain-related activation was observed bilaterally in the putamen of the basal ganglia (figure 1d, table 1a). No significant peaks of activation were detected in the thalamus.

Negative peaks. Painful stimulation produced negative peaks (greater activation during warm than hot stimulation) in two cortical regions contralateral to the stimulus. One peak was located on the medial aspect of the parietal lobe, between the ascending end of the cingulate sulcus and the parieto-occipital sulcus, in area 7 (precuneus), and the other was found in the occipital cortex (table 1a). There was also a trend toward significance (t = - 4.5) in the ipsilateral superior frontal gyrus (area 9) (table 1a).

14 mm Blur. Intersubject analysis of data sets blurred to replicate PET results revealed fewer regions of pain-related activation than 6-mm blurred data sets. Contralateral S1 showed a trend toward activation (t = 3.8) and contralateral S2 was significantly activated (table 1b). Two significant peaks were found in contralateral ACC (table 1b). Blurred analysis also produced activation in bilateral

IC and ipsilateral frontal operculum (table 1b). There was a trend toward activation in the contralateral middle frontal gyrus (t = 4.4)(table 1b).

3.1.2 Brush related activation

As expected, brush activated a less distributed pattern of activation, including contralateral S1 and bilateral S2 (table 2). S1 was activated in the medial-superior region of the post-central gyrus – an area consistent with the somatotopic representation of the leg (figure 1a, table 2). Brush-related S2 foci overlapped those associated with the S2 activation observed in response to pain (figure 1b). No significant peaks of brush-related activation were found in ACC or IC.

Other cortical regions. The only other significant activation was located in the post-central gyrus near face region (table 2).

Subcortical activation. No statistically significant regions of activation were observed in subcortical structures.

Negative Peaks. Tactile stimulation elicited negative peaks (greater activation during rest than brush stimulation) bilaterally along the posterior part of the medial surface of the frontal lobe (paracentral lobule – area 5) (table 2). A negative peak was also detected in the contralateral inferior parietal lobule.

Table 2. Brush-related activation sites for grouped analysis across 4 subjects

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	22	-36	74	5.5
	14	-26	78	5.0
S2 (contra)	42	-28	22	5.4
S2 (ipsi)	-50	-24	22	7.0
postcentral gyrus	-56	-20	34	4.8
Lpc (area 5)	2	-30	58	-6.2
Lpc	-10	-40	58	-5.6
GPoC/LPi	42	-28	56	-5.3

df = 134, global threshold t-value = 4.79, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior). Negative t values indicate that the MR signal was greater during rest than during brush stimulation. Coordinates in italics are below the threshold of statistical significance.

3.2 INDIVIDUAL SUBJECT ANALYSIS

3.2.1 Pain related activation

Individual subject analysis over two sessions revealed significant activation in regions consistently reported across imaging studies of pain. Three of the four subjects showed contralateral S1 activation in regions anatomically relevant for each subject (Kido *et al.*, 1980; Sobel *et al.*, 1993). S1 activation was detected on the surface of the contralateral post-central gyrus for two subjects, while one subject showed bilateral activity deep within the central sulcus (figure 2 – SJ). Significant activity was found in S2, with three subjects showing bilateral peaks and one showing only contralateral activation (figure 2, table 3a-6a).

Painful stimulation elicited bilateral activation in multiple regions of ACC in anatomically significant regions for each subject (Vogt *et al.*, 1996) (figure 2, table 3a-6a). All subjects displayed significant pain-related activation bilaterally in rostral IC and frontal operculum (figure 2, table 3a-6a). Midline SMA was significantly activated across all subjects (table 3a-6a). For all subjects, painful stimulation elicited activation in the contralateral (sometimes bilateral) middle frontal gyrus (table 3a-6a).

Other regions of activation. All subjects showed contralateral inferior parietal lobule activation. Other sites of activation were observed less consistently between subjects. Some of these regions include PCC, superior parietal lobules and occipital lobe (see table 3a-6a).

Subcortical regions. Painful stimulation consistently produced significant activation in the basal ganglia; peaks were bilateral in three subjects and contralateral in one (table 3a-6a). Bilateral thalamic activation was observed in only one subject (table 6a).

Table 3-6. Peaks of pain-related activation for individual subjects

Table 3a. Pain-related activation sites for subject HB across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	10	-46	74	5.7
S2 (contra)	50	-26	22	6.2
i. parietal lobule	52	-30	30	5.5
ACC (contra)	8	-6	38	8.3
	8	14	34	7.4
ACC (ipsi)	-4	6	42	7.5
	-2	-2	48	7.3
PCC	10	-24	40	5.0
IC (contra)	36	12	6	7.0
IC (ipsi)	-34	8	10	8.1
operculum (contra)	54	8	4	7.4
operculum (ipsi)	-48	-2	4	7.5
SMA (contra)	4	-8	66	8.6
SMA (ipsi)	-2	-10	66	6.6
m. frontal gyrus	30	48	28	4.8
s. parietal lobule	-18	-54	74	4.8
basal ganglia (contra)	22	12	-2	7.2
basal ganglia (ipsi)	-24	8	-4	6.6

6 runs, df = 305, global threshold t-value = 4.67, p = 0.05

b. Pain-related activation sites for subject HB (blurred to 14mm) across two sessions

S2 (contra)	*50*	*-28*	*24*	*4.2*
ACC (contra)	4	2	42	6.5
ACC (ipsi)	-2	2	42	6.6
IC (contra)	36	12	6	6.4
IC (ipsi)	-34	8	10	6.0
operculum (ipsi)	-46	4	10	5.8
SMA (contra)	4	-10	68	5.9
basal ganglia (contra)	26	8	0	4.8

6 runs, df = 328, global threshold t-value = 4.45, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior). Coordinates in italics are below the threshold of statistical significance.

Table 4a. Pain-related activation sites for subject CJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S2 (contra)	36	-20	18	8.6
S2 (ipsi)	-38	-20	18	6.9
i. parietal lobule	54	-46	46	5.4
ACC (contra)	4	20	42	9.3
ACC (ipsi)	-2	22	42	6.9
	-2	12	44	5.0
IC (contra)	34	14	4	9.3
IC (ipsi)	-36	12	4	7.0
operculum (contra)	54	16	4	9.0
operculum (ipsi)	-56	2	10	5.3
SMA	4	8	60	5.3
	6	-4	62	4.8
m. frontal gyrus	32	40	6	8.4
m. frontal gyrus (ipsi)	-36	46	22	5.5
i. frontal gyrus	54	16	18	7.7
basal ganglia (contra)	*20*	*10*	*4*	*4.5*

8 runs, df = 418, global threshold t-value = 4.65, p = 0.05

b. Pain-related activation sites for subject CJ (blurred to 14mm) across two sessions

ACC (contra)	6	18	42	5.9
IC (contra)	44	10	2	6.3
IC (ipsi)	*-42*	*12*	*6*	*4.4*
operculum (contra)	56	16	12	5.5
m. frontal gyrus	34	46	14	5.6

8 runs, df = 449, global threshold t-value = 4.43, p = 0.05

Coordinates in italics are below the threshold of statistical significance.

Table 5a. Pain-related activation sites for subject BJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	12	-32	72	4.9
S2 (contra)	48	-24	16	6.0
S2 (ipsi)	*-50*	*-30*	*22*	*4.1*
i. parietal lobule	*62*	*-26*	*24*	*4.4*
ACC (contra)	4	-6	46	6.8
	8	14	36	6.6
	8	32	18	5.0
	2	24	36	4.8
ACC (ipsi)	-6	10	44	5.3
	-12	-4	46	5.3
PCC	0	-22	34	4.7
	14	-28	40	4.9
IC (contra)	44	12	4	7.2
IC (ipsi)	-38	0	14	6.1
operculum (contra)	54	10	4	6.7
	50	0	6	6.7
operculum (ipsi)	-48	-6	8	6.7
SMA (contra)	0	-18	64	6.2
	0	12	62	5.2
m. frontal gyrus	24	46	32	6.7
	42	32	40	5.6
	-30	36	34	5.4
s. parietal lobule	24	-44	72	5.1
	-20	-48	68	6.4
occipital lobe	14	-90	10	5.9
	16	-70	12	5.9
	-8	-74	8	5.0
basal ganglia (contra)	28	8	4	6.2
basal ganglia (ipsi)	-24	2	0	4.9

6 runs, df = 305, global threshold t-value = 4.67, p = 0.05

b. Pain-related activation sites for subject BJ (blurred to 14mm) across two sessions

S1	18	-40	74	5.8
S2 (contra)	48	-22	16	4.7
ACC (contra)	4	-4	46	5.8
	10	10	36	4.9
IC (contra)	40	14	4	5.8
IC (ipsi)	-42	0	16	5.3
m. frontal gyrus	26	52	38	6.0
occipital lobe	-4	-80	2	5.3
	20	-68	6	5.2

6 runs, df = 328, global threshold t-value = 4.45, p = 0.05

Coordinates in italics are below the threshold of statistical significance.

Table 6a. Pain-related activation sites for subject SJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	20	-24	62	5.0
	-20	-28	62	4.9
S2 (contra)	36	-24	16	6.7
S2 (ipsi)	-38	-20	14	8.5
ACC (contra)	10	8	36	7.1
	8	28	26	6.8
	2	16	42	5.8
	6	-2	44	5.7
ACC (ipsi)	-10	10	42	5.7
IC (contra)	44	8	4	9.7
	36	14	4	9.4
IC (ipsi)	-44	8	-2	8.5
operculum (contra)	54	4	2	5.6
operculum (ipsi)	-56	4	4	6.3
SMA (contra)	10	4	74	6.2
	0	-4	60	6.2
m. frontal gyrus	28	42	24	6.5
i. parietal lobule (contra)	54	-36	32	7.5
i. parietal lobule (ipsi)	-60	-38	32	5.2
precuneus	6	-52	74	5.9
precentral gyrus	-54	-4	52	6.3
basal ganglia (contra)	22	8	4	7.1
basal ganglia (ipsi)	-26	4	4	6.8
thalamus (contra)	14	10	6	4.9
thalamus (ipsi)	-14	-10	12	5.2

5 runs, df = 249, global threshold t-value = 4.69, p = 0.05

b. Pain-related activation sites for subject SJ (blurred to 14mm) across two sessions

S2 (contra)	*28*	*-24*	*16*	*4.1*
S2 (ipsi)	-36	-24	22	4.8
ACC (contra)	8	4	28	6.5
	8	26	26	5.6
	4	8	42	5.1
ACC (ipsi)	-12	6	28	6.6
	-2	12	42	5.0
IC (contra)	32	12	4	6.7
IC (ipsi)	-36	8	12	5.2
SMA (ipsi)	-2	-4	60	5.4
basal ganglia (contra)	24	6	6	6.6
basal ganglia (ipsi)	-22	-2	14	6.2

5 runs, df = 268, global threshold t-value = 4.47, p = 0.05

Coordinates in italics are below the threshold of statistical significance.

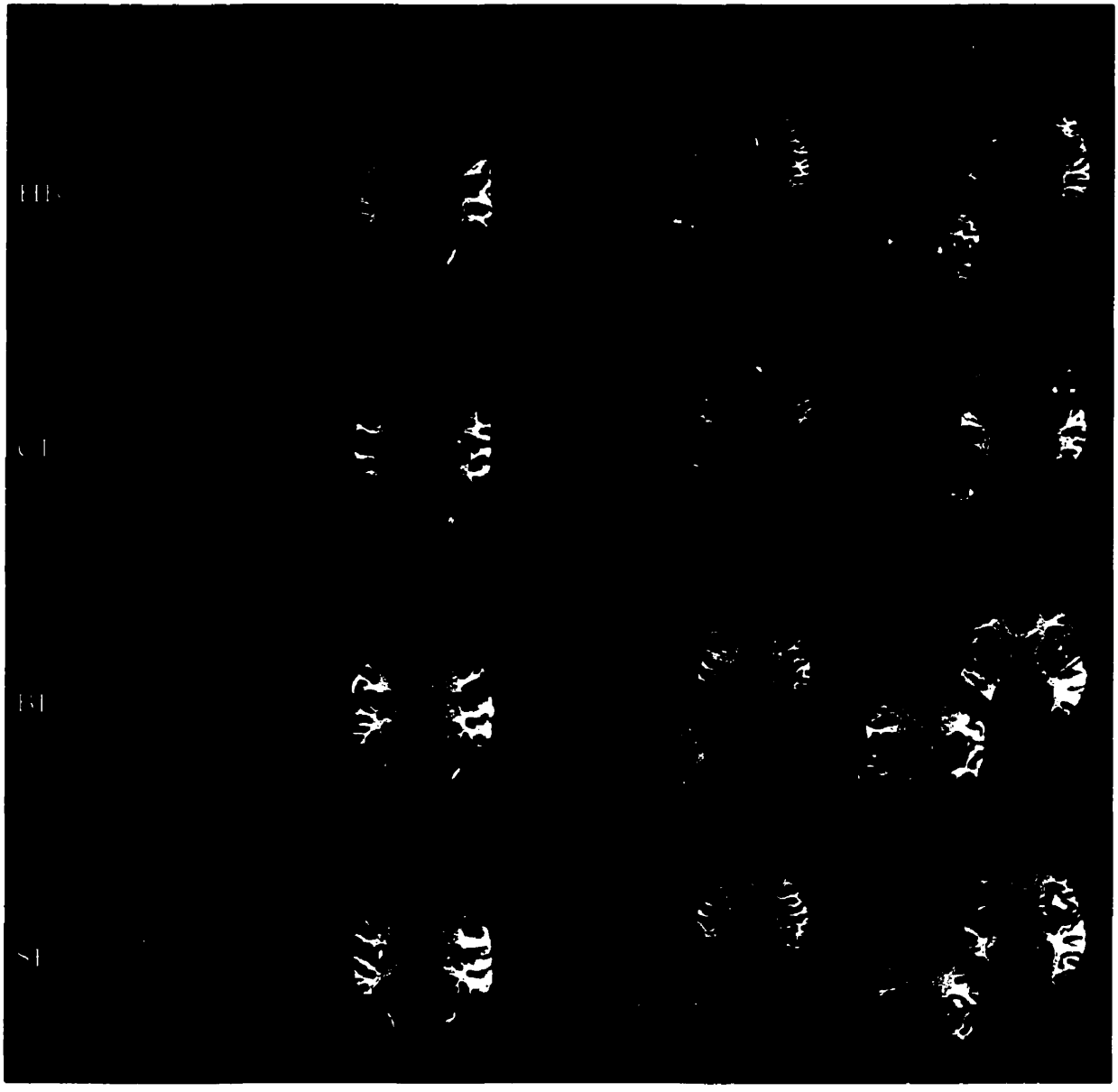

Figure 2. Analysis of individual subjects revealed that areas most commonly observed in PET studies of pain, including S1, S2, ACC, and IC, were activated for each subject. Only one subject did not show activation in S1 (CJ). Coordinates of image planes are expressed in millimeters. Although there is some variability across subjects, the peaks of activation lay within anatomically relevant locations for each subject.

14 mm Blur. For all subjects, the pattern of pain-related activation produced by the analysis of blurred (14mm kernel) data was less distributed than for the 6 mm data sets (see table 3b-6b). Only one subject showed significant S1 activation (table

5b). Contralateral S2 (bilateral for SJ) was activated in all but one subject – CJ (table 3b-6b). All subjects showed contralateral ACC activation, while two subjects (HB – table 3b, SJ – table 6b) showed bilateral ACC activation. IC was consistently activated bilaterally across all subjects. Frontal operculum activation was observed in two subjects (HB – ipsilateral, table 3b; CJ – contralateral, table 4b). Blurred analysis detected activation of SMA in two subjects (HB – contralateral, table 3b; SJ – ipsilateral, table 6b). Other pain-related cortical activation included contralateral frontal gyrus in two subjects (CJ – table 4b, BJ – table 5b) and bilateral occipital lobe in one subject (BJ – table 5b). Subcortical activation was observed in the basal ganglia for two subjects (HB – contralateral, table 3b; SJ – bilateral, table 6b).

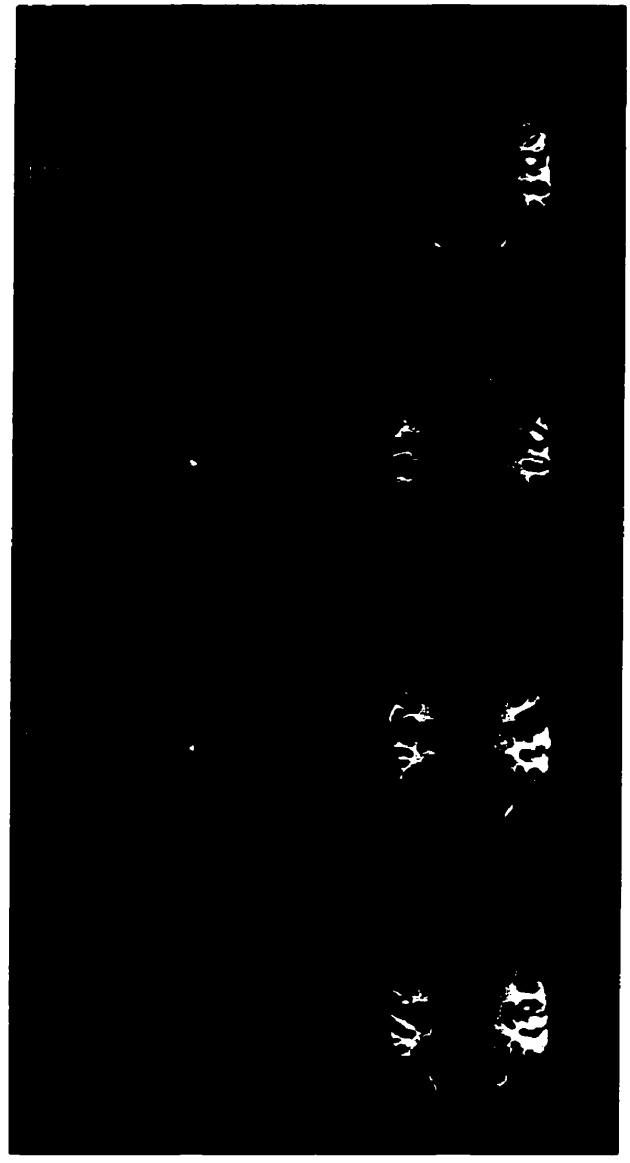

Figure 3. Individual subject analysis showed regions of activation in regions most commonly observed in previous studies of innocuous tactile stimuli. Significant activation was found in the contralateral S1 and bilateral S2 for all subjects. Coordinates are expressed in millimeters.

3.2.2 Brush-related activation

Tactile stimulation produced significant activity within contralateral S1 and bilateral S2 in all subjects (figure 3, table 7-10). There were a number of other cortical areas activated, however these were not consistent across subjects (table 7-10). No subcortical regions of activation were found in any subject.

Table 7-10. Peaks of brush-related activation for individual subjects

Table 7. Brush-related activation sites for subject HB across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	10	-40	70	7.1
	14	-42	74	6.1
S2 (contra)	50	-24	20	8.7
S2 (ipsi)	-48	-34	20	8.7
i. parietal lobule	-60	-22	30	7.3
i. parietal lobule	-54	-26	48	7.2
SMA	-8	-6	60	7.5
operculum (ipsi)	-60	-6	8	6.8
operculum (contra)	60	-4	6	5.3
m. frontal gyrus	50	6	34	5.2
precentral gyrus	-56	-4	46	9.0
s. parietal lobule	-18	-62	56	5.0
occipital	-48	-74	8	5.4

7 runs, df = 363, global threshold t-value = 4.66, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior).

Table 8. Brush-related activation sites for subject CJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	20	-36	74	10.3
	16	-30	78	10.0
S2 (contra)	56	-28	24	9.8
S2 (ipsi)	-52	-38	24	9.1
	-50	-26	22	7.8
SMA	-2	4	64	6.1
frontal gyrus	54	8	32	5.4
m. temporal gyrus	56	-58	12	8.4
	-54	-52	12	5.6
postcentral gyrus	-54	-18	36	5.6

7 runs, df = 363, global threshold t-value = 4.66, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior).

Table 9. Brush-related activation sites for subject BJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	22	-34	74	8.1
	14	-34	80	5.5
	12	-28	78	5.2
S2 (contra)	42	-24	16	5.5
S2 (ipsi)	-50	-24	18	6.3
s. parietal lobule	-22	-42	66	5.2

6 runs, df = 307, global threshold t-value = 4.67, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior).

Table 10. Brush-related activation sites for subject SJ across two sessions

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	22	-40	72	6.7
	20	-36	64	5.4
S2 (contra)	52	-22	16	7.9
S2 (ipsi)	-50	-22	22	8.3
operculum	52	0	6	5.1
m. frontal gyrus	34	66	0	5.9

6 runs, df = 307, global threshold t-value = 4.67, p = 0.05

M-L – medial-lateral relative to midline (positive = right); A-P – anterior-posterior relative to the anterior commissure (positive = anterior); S-I – superior-inferior relative to the commissural line (positive = superior).

3.2.3 S1 activation in individual subjects

Figure 4 shows both pain (red) and tactile (blue) activation within the post-central gyrus of each subject. Three of the four subjects demonstrated consistency in the location of peaks across modalities. Sites of pain- and tactile-related activation lay within anatomically relevant regions for each individual subject (Kido *et al.*, 1980; Sobel *et al.*, 1993). The anatomical variability of the central sulcus contributes to the variability in the location of peaks across subjects (figure 4).

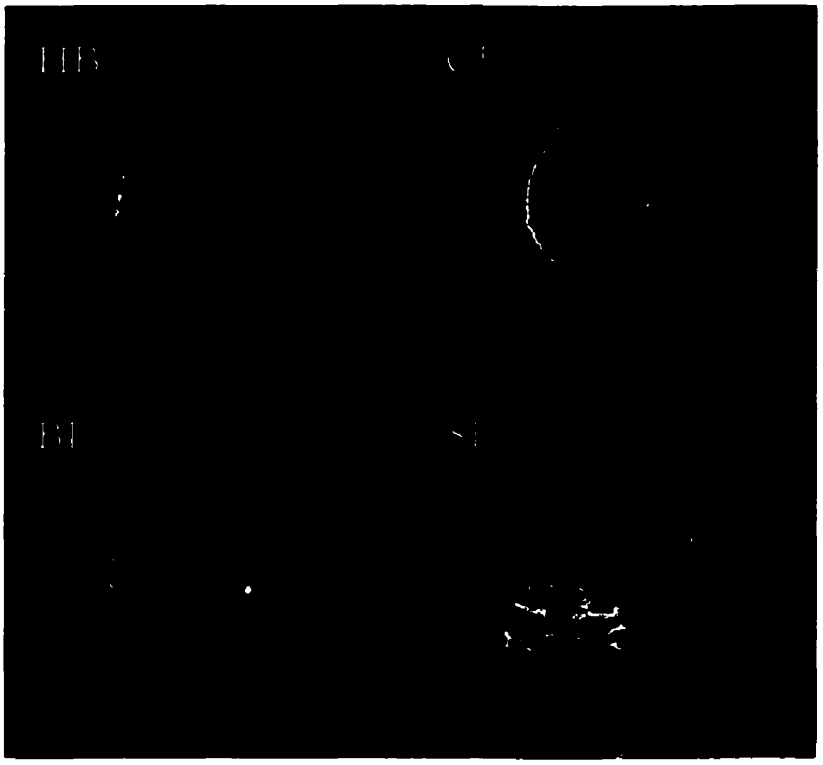

Figure 4. S1 activation was found within the post-central gyrus of each individual subject. Although there is variability in location, activation was found in anatomically relevant positions for each subject. Brush and pain evoked activation in consistent spatial locations for 3 subjects. Note the variability of the central sulcus across subjects. Coordinates are expressed in millimeters. (Pain-related activation was taken from a single session for subject CJ.)

3.3 SINGLE SESSION ANALYSIS

3.3.1 Pain-related activation

Analysis of single sessions for each subject showed inconsistent S1 activation, even within individual subjects (figure 5, table 11a). Contralateral S1 was activated in three subjects during only one of the two scanning sessions for pain (one subject, SJ, showed bilateral activation). The fourth subject also showed a trend toward activation in one session (CJ). S2 was more frequently activated, with all subjects showing either significant activation or trends toward activation, with the exception of one session (BJ_2, table 11a). S2 activation was generally bilateral, but sometimes only contralateral (table 11a).

ACC and IC were consistently activated across subjects and scanning sessions (figure 5, table 11a). Painful stimulation produced bilateral and sometimes contralateral (CJ_2 and BJ_2) activation in multiple regions of ACC for all subjects during each scanning session. A band of activation was detected bilaterally in the rostral portion of IC for all subjects (BJ_2 approached significance, table 11a). The frontal operculi were also activated bilaterally, and sometimes contralaterally, in all sessions (with the exception of BJ_2, table 11a). Consistent activation was detected in the SMA, with all subjects showing activation in at least one session (table 11a).

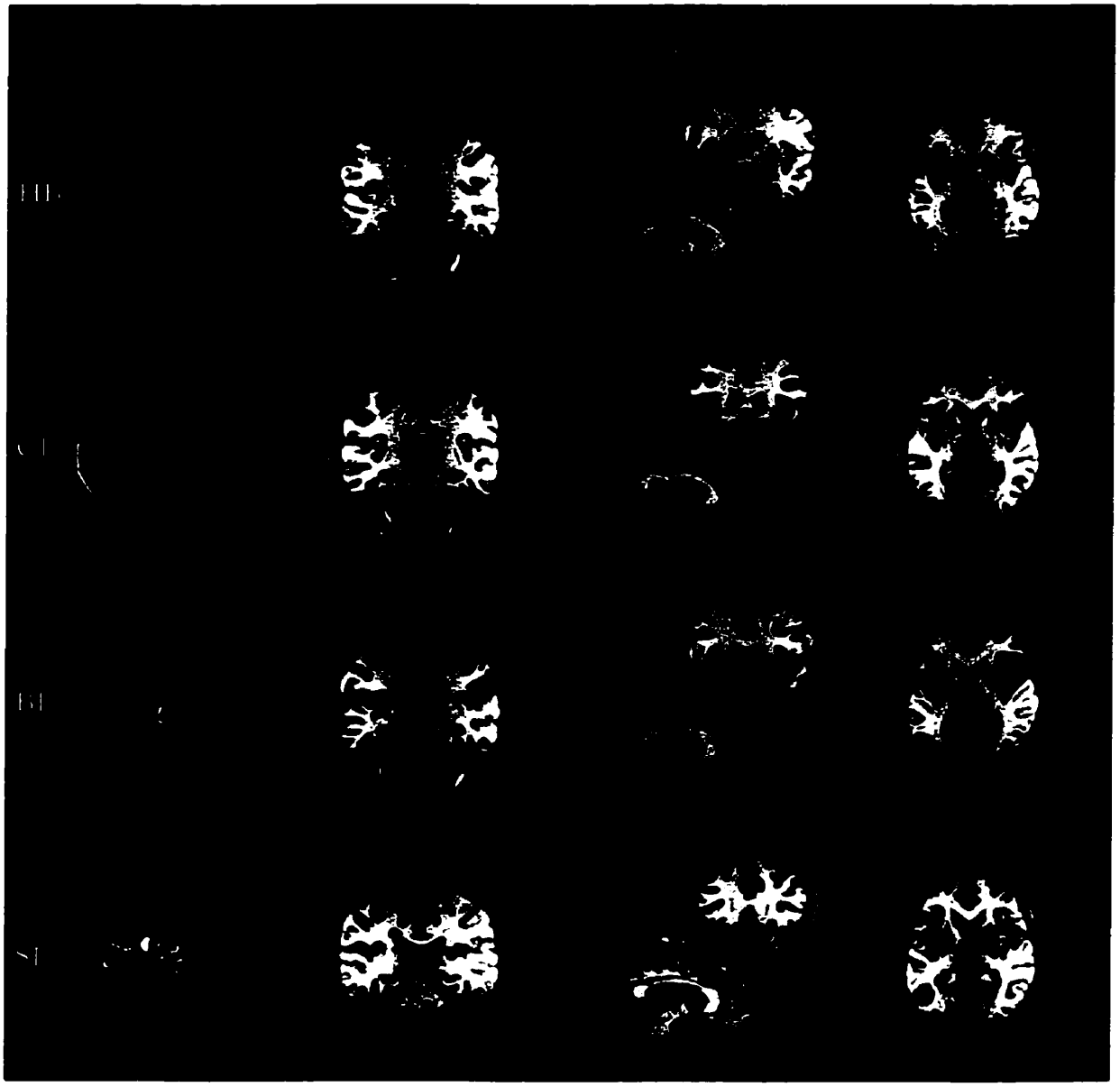

Figure 5. Single session analysis of pain runs revealed intensity related variability within subjects. Some pain related regions were present in one session but not the other (first session – red; second session - blue). However, when present, the spatial location of peaks were consistent within individual subjects.

Other regions of activation. Other regions were activated less consistently across subjects and scanning days. On different days, in individual subjects, areas of activation were observed in regions of the frontal gyri, parietal lobules, occipital cortex (table 11a).

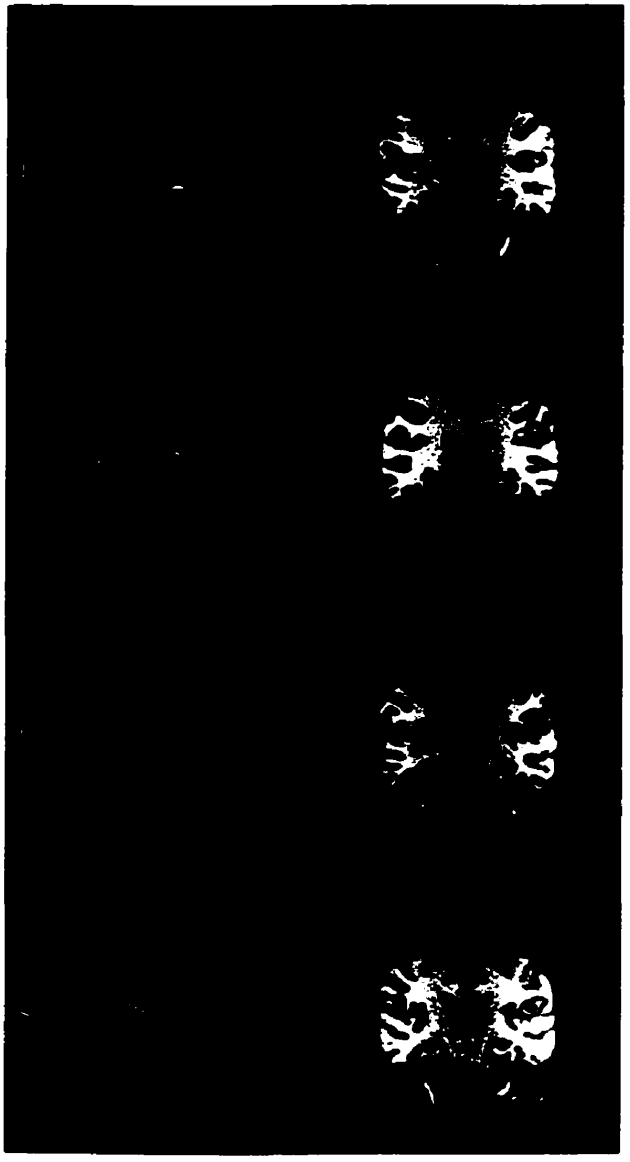

Figure 6. Single session analysis of brush stimuli revealed consistent activation across scanning days for all subjects (first session – orange; second session - blue). Only one subject (HB) did not show S1 activation during one session. Coordinates are expressed in millimeters.

Subcortical regions. Basal ganglia was activated during sessions of three subjects (sometimes bilateral, other times only contralateral – table 11a).

3.3.2 Brush-related activation

Tactile stimulation consistently produced significant activation in S1 across subjects and scanning days (figure 6, table 11b). With the exception of the one session (HB_1), all sessions showed significant activation of contralateral S1 in regions consistent with the anatomical position of each subject's post-central gyrus (table 11b). S2 was also activated bilaterally across all subjects and sessions (figure 6, table 11b). Other regions were less reliably activated in response to the brush stimuli (table 11b).

Subcortical. The response in the contralateral thalamus approached significance in only one session of one subject (table 11b).

Table 11. Comparison of activation sites across single sessions

Region	Subject$_{session}$							
	HB_1	HB_2	CJ_1	CJ_2	BJ_1	BJ_2	SJ_1	SJ_2
a. *Pain-related activation*								
S1	C		*C*		C			B
S2	*C*	*B*	B	*C*	C, *I*		B	B
i. parietal lobule		*C*	*C*		*C*		*C*	B
ACC	B	B	B	C	B	*C*	B	B
IC	B	C, *I*	B	B	B	*B*	B	B
operculum	B	*B*	C, *I*	C	B		C	B
SMA	B	C	C		M		*M*	B
frontal			B	C	B			
s. parietal lobule					B	*I*		B
occipital		C	M					
basal ganglia	B	*B*			B	*C*		C
thalamus					*C*			B
b. *Brush-related activation*								
S1		C	C	C	C	C	C	C
S2	B	B	B	B	B	*B*	B	B
SMA	*I*	I	I					
parietal	I	I	I				C	
precentral g.	I	I	B				C	
postcentral g.		I	I					
temporal	I		C	B				
occipital	I	C						
frontal							C	
posterior IC				C				
operculum		I					C	
thalamus				*C*				

C – contralateral activation relative to side of stimulation; I – ipsilateral activation relative to side of stimulation; B – bilateral activation relative to side of stimulation. Italics indicate that the activation is below the threshold of statistical significance.

Table 12. Comparison of fMRI studies of pain

Study	Pain Stimulus	Scanning parameters	Analysis	S1 scanned	Results
(Davis *et al.*, 1995)	noxious TENS (50Hz) – hand (median nerve), ~ 28 s	1.5 T, head coil, single 4 mm slice (axial for S1, sagittal for Cg), 6.8 s and 4.7 s per image, TR = 68 ms, TE = 40 ms, flip angle = 45°, FOV = 30 x 22 cm and 48 x 30 cm, matrix = 256 x 128	*t*-test, individual subject analysis (n = 6)	✓	S1 (C), ACC (C)
(Davis *et al.*, 1997)	noxious TENS (50Hz) – hand (median nerve), ~ 28 s	1.5 T, head coil, single 4 mm sagittal slice, ~ 4.7 s per image, TR = 68 ms, TE = 40 ms, flip angle = 45°, FOV = 48 x 24 cm, matrix = 256 x 128	*t*-test and correlation, individual subject analysis (n = 10)		ACC (C)
(Davis *et al.*, 1998a)	noxious thermal – hand, 2°C (40 s) and 47.5°C (5 s x 7, separated by 1s), Medoc thermode (9 cm^2)	1.5 T, head coil, six 4 mm axial slices, 1.92 s per volume, TR = 480 ms, TE = 40 ms, FOV = 22 x 22 cm	correlation, individual subject analysis (n = 12)		IC (B), S2 (C), basal ganglia, thalamus
(Davis *et al.*, 1998b)	noxious thermal – hand, 2°C (1 s) and 47.5°C (3 s), Medoc thermode (9 cm^2)	1.5 T, head coil, six 4 mm axial and four 4mm sagittal slices, 1.9 s and 1.3 s per volume, TR = 480 ms and 320 ms, TE = 40 ms, FOV = 22 x 22 cm; online ratings	correlation, individual subject analysis (n = 4)		S2 (B), ACC (B), IC (B), thalamus (B)
(Oshiro *et al.*, 1998)	noxious TENS (8Hz) – fingertip, 20 s	1.5 T, EPI, 8 mm multislice supratentorial (?), 2 s per volume, TE = 50ms, flip angle 60°, FOV = 20 x 40 cm, matrix = 64 x 128	correlation, (n = ?)	✓	S1 (C), S2 (B), IC (B), frontal (B), thalamus (C)
(Jones *et al.*, 1998)	noxious cold stones – hand (palm), ~ 45 s	1.0 T, head coil, FLASH, two 10 mm sagittal slices, TR = 91 ms, TE = 60 ms, flip angle = 40°, matrix = 128 x 128	correlation, individual subject analysis? (n = 10)		ACC (B), medial frontal gyrus, parieto-occipital cortex (I)
(Porro *et al.*, 1998)	subcutaneous ascorbic acid injection – foot	1.5 T, head coil, FLASH, two 5 mm sagittal slices, 21 s per volume, TR = 63 ms, TE = 40 ms, flip angle = 40°, FOV = 230-245 mm , matrix = 128 x 128	correlation, individual subject analysis (n = 24)	✓	S1, M1, ACC, SMA, PCC, medial parietal (precuneus),
(Disbrow *et al.*, 1998)	noxious TENS (2Hz) – finger, 32 s; noxious thermal – forearm, 32 s Peltier thermode (4 cm^2); noxious mechanical – hand, 32 s, Surgi-Clamp	1.5 T, head coil, EPI, sixteen 6 mm slices, TR = 2 s, TE = 40ms, FOV = 22 cm, matrix = 64 x 64	correlation, individual subject analysis (n = 12)	✓	TENS – S1 (C), cerebellum (I) thermal/mechanical – none
(Berman *et al.*, 1998)	noxious thermal – hand and foot, 0-2°C (2 s) and 55-57°C (2s), heated or cooled water packets	1.5 T, EPI, twenty-one 4.5 mm axial slices, 4 s per volume, TR = 4 s, TE = 60 ms, flip angle = 60°	?, individual subject analysis (n = 8)	✓	S1 (C)
(Becerra *et al.*, 1999)	noxious thermal – hand, 46°C (29 s), Medoc thermode (9 cm^2)	1.5 T, head coil, EPI, twenty 7mm coronal slices, TR = 2.5 s, TE = 70 ms, flip angle = 90°	Kolmogorov-Smirnov, individual and multisubject analysis (n = 6/group)	✓	S1 (C), S2 (B), ACC, IC (B), SMA, m. frontal (C), PCC, temporal lobe (B), cerebellum (I), thalamus (C)
(Gelnar *et al.*, 1999)	noxious thermal – finger, ?°C (35 s), thermode?	1.5 T, surface coil, EPI, eight 6 mm coronal slices, TR = 3.5 s, TE = 60 ms, flip angle = 90°, FOV = 40 x 20 cm, matrix = 256 x 128	*t*-test, individual and multisubject analysis (n = 9)	✓	S1, M1, ACC, S2, SMA, premotor, posterior parietal, IC (all contra)
(Baron *et al.*, 1999)	secondary mechanical allodynia – forearm, von Frey filament (34.7 g)	1.5 T, head coil, EPI, eight 5-6mm axial slices, TR = 2 s, TE = 69 ms, flip angle = 60°, FOV = 40 x 40 cm, matrix = 128 x 128	correlation, individual subject analysis (n = 9)	✓	middle frontal gyrus (C), inferior frontal gyrus (C)

✓ indicates that S1 was included in the scanned region. C – contralateral, I – ipsilateral, B – bilateral.

Chapter 4
DISCUSSION

The results of this study demonstrate that pain and touch evoke reliable patterns of cortical activation. All subjects produced activation patterns similar to those most commonly observed in imaging studies using PET (pain – S1, S2, ACC, IC; tactile –S1, S2). Whereas tactile stimulation produced very consistent patterns of activation both between and within subjects, greater variability was observed in response to painful stimuli. The variability between subjects was related to location of peaks, while variability within a subject was related to the extent and strength of activation. Spatial variability, due to anatomical and functional variability, contributed to between subject differences. In contrast, the location of peaks for an individual subject was very consistent, but significant activation not always present.

Individual subject analysis revealed a widespread network of activated sites, including regions such as sensory, motor, limbic and association areas. This idiosyncratic activation pattern for each subject may reflect cognitive state as well as

sensory perception. Upon group analysis, however, atypical peaks disappear leaving peaks common across all subjects. These peaks most likely represent the common regions involved in the sensory experience.

4.1 CORTICAL REGIONS

4.1.1 Primary somatosensory cortex

The role of S1 in pain processing has been subject to much debate. Although anatomical and physiological studies have confirmed the presence of nociceptive neurons within S1 (Casey & Morrow, 1983b), the debate continues due to discrepancies between brain imaging studies. Only about half of all PET studies of pain demonstrate S1 activation (Bushnell *et al.*, 1999). In contrast, the majority of fMRI studies of pain, assessing individual subjects, have shown S1 activation when it is included in the scanned region (table 12).

PET requires the averaging of multiple subjects and the use of a large blurring kernel in order to acquire good signal to noise ratio. It has been hypothesized that these processing steps may act to degrade an actual focal activation, thereby leading to negative results (Bushnell *et al.*, 1999). The present study has confirmed this hypothesis, demonstrating significant (real) sites of activation (particularly in S1) that disappear upon blurring and averaging.

Individual subjects showed focal S1 activity in at least one of their two sessions, while three of the four subjects showed S1 activity upon analysis of both sessions. In contrast, the grouped analysis failed to reveal significant S1 activity. Furthermore, blurring the fMRI data sets to a kernel analogous to PET (~14mm) caused the focal activity to be diluted such that two of the three subjects who showed significant activity upon individual subject analysis no longer showed significant S1 activation.

Individual subject activation maps reveal small differences in the location of S1 activation, which seem to be related to intersubject variability in sulcal anatomy (figure 4). The post-central gyrus may be susceptible to anatomical variability and since pain perception is somatotopically organized in S1 (Lamour *et al.*, 1983), differences may also be introduced by functional variability in somatotopic organization. Furthermore, because of the relative paucity of S1 nociceptive neurons (Kenshalo, Jr. & Isensee, 1983; Kenshalo, Jr. *et al.*, 1988), the region of pain-related activation is very small and vulnerable to dilution upon averaging and blurring. Therefore, the observed signal degradation of S1 may occur as a result of small differences in the location of finite pain-related activity and this may explain, in part, the inconsistencies found among PET studies.

There is also some indication that S1 is highly influenced by cognitive factors. Recent PET studies showed that S1 activity is modulated by cognitive

manipulations, such as attention and hypnosis. Directing attention towards or away from a painful heat stimulus not only modifies the subjective intensity of pain, but also modulates activity within S1 (Carrier *et al.*, 1998; Bushnell *et al.*, 1999; Peyron *et al.*, 1999). Hypnotic suggestions that specifically alter perceived pain intensity also modulate pain-related activity within S1 (Hofbauer *et al.*, 1998; Bushnell *et al.*, 1999), whereas suggestions that specifically alter perceived unpleasantness have no significant effect (Rainville *et al.*, 1997). Therefore, failure to give subjects instructions to attend to the painful stimuli may result in the failure of S1 to show significant pain-related activation. Differences in experimental paradigm may result in varying cognitive states that differentially influence S1, and thus contribute to the discrepant results across studies.

Although a major proportion of human brain imaging studies show S1 activity in response to painful stimuli, it remains to be the most disputed region of activation. However, this is not surprising given the high degree of anatomical and functional variability in S1, its susceptibility to cognitive manipulations, as well as its function in processing sensory-discriminative aspects of pain. Furthermore, studies have employed a variety of noxious stimulation, including phasic or tonic, stationary or moving, thermal, chemical and electrical stimuli, to induce experimental pain. Thus, the variability among brain imaging results may actually reflect the sensitivity

of S1 to differences in the quality, intensity, location, spatial extent and timing of these myriad painful stimuli.

4.1.2 Secondary somatosensory cortex (S2)

Brain imaging studies have consistently demonstrated tactile- and pain-related activation within S2. Studies of innocuous stimulation reliably evoke bilateral activation (Burton *et al.*, 1993; Coghill *et al.*, 1994; Polonara *et al.*, 1999), while noxious stimulation has been observed to elicit contralateral (Talbot *et al.*, 1991; Coghill *et al.*, 1994) or bilateral (Davis *et al.*, 1998b) peaks of activation. Furthermore, primate electrophysiological recording studies have demonstrated that approximately half of all cells identified within the S2 region have bilateral receptive fields (Robinson & Burton, 1980; Dong *et al.*, 1989; Dong *et al.*, 1994). These findings are confirmed in the present study. All subjects showed significant activity along the upper bank of the lateral sulcus (parietal operculum) – a region consistent with S2 in human and monkey – in response to both tactile and noxious heat stimulation. Activation was consistently bilateral for tactile stimulus, while heat pain elicited bilateral, contralateral or ipsilateral peaks.

Clinical evidence further points to the integral role of S2 in the processing of innocuous and noxious stimuli. Patients with damage involving the parietal operculum exhibit contralateral deficits in tactile discrimination (Greenspan &

Winfield, 1992), as well as deficits in pain sensitivity, requiring higher intensities of heat, cold or mechanical stimulation to elicit painful sensations (Greenspan & Winfield, 1992; Greenspan *et al.*, 1999). Furthermore, pain sensibility was considerably diminished in monkeys with damage to the S2 region (Dong *et al.*, 1996). These findings strongly suggest that S2 is essential for the preservation of normal pain thresholds.

Other evidence further supports a role of S2 in the sensory-discriminative processing of pain. Primate electrophysiological recordings have identified neurons within the S2 region capable of accurately encoding the duration of painful stimulation (Dong *et al.*, 1989). Similarly, neurons within the lateral sulcus have been isolated, which reliably encode the magnitude of pain intensity (Dong *et al.*, 1994; Robinson & Burton, 1980). However, S2 encodes stimulus intensity with less precision than S1 and may not be able to process the more complex discriminative functions characteristic of S1 (Robinson & Burton, 1980; Dong *et al.*, 1994). Rather, S2 seems to play a key role in the detection of pain, as well as several other pain-related functions including multimodal sensory integration (touch, pain, visual), tactile learning, and spatially directed attention (Robinson & Burton, 1980; Dong *et al.*, 1994; Kenshalo, Jr. & Douglass, 1995).

Primate electrophysiological studies have revealed that S2 contains a relatively small number of neurons that respond to noxious stimuli (Robinson & Burton, 1980; Dong *et al.*, 1994). Furthermore, a number of neighboring brain regions, including area 7b in monkeys or inferior parietal lobule in human, and posterior insular areas (Dong *et al.*, 1996), have also been found to respond to noxious stimuli. Thus, the possibility arises for multiple sites to be activated, within close proximity, in response to painful stimulation. Any variability or negative findings may be related to these multiple pain regions, since averaging or blurring may degrade focal signals.

4.1.3 Anterior cingulate cortex

Painful stimuli have been found to activate two distinct regions of the anterior cingulate cortex (ACC) (Vogt *et al.*, 1996). The mid-ACC region (area 24') is the most commonly reported site of activation across all brain imaging studies (Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994; Craig *et al.*, 1996; Andersson *et al.*, 1997; Davis *et al.*, 1997) (Porro *et al.*, 1998; Iadarola *et al.*, 1998; Derbyshire SWG & Jones AKP, 1998). A less frequently observed area is found in the anterior portion of the ACC (perigenual cingulate cortex). Both regions respond to noxious stimuli (Sikes & Vogt, 1992) and appear to have different functional roles. Evidence suggests that the midcingulate cortex may be involved in response selection, pre-motor, and affect, while the perigenual cortex may take part in

anticipation, attention, emotional response or affect (Vogt *et al.*, 1996; Davis *et al.*, 1997; Rainville *et al.*, 1997; Ploghaus *et al.*, 1999).

A PET study examining individual differences in ACC pain activation (Vogt *et al.*, 1996) found multiple regions of activation that varied between subjects. Sites of activation were bilateral and lay within two general regions – the midcingulate and perigenual cortices. Individual subjects showed diverse patterns of activation, with differences in the number and location of peaks. The present study parallels these findings, as well as the results across brain imaging studies. The mid-ACC was the most commonly observed region of activation, while only one session of one subject showed activation in the perigenual cortex. Individual subject t-maps showed a number of distinct foci, while group analysis revealed a more confined region of activation.

Considerable anatomical variability exists between subjects in the cingulate sulcus (Vogt *et al.*, 1995; Vogt *et al.*, 1996; Paus *et al.*, 1996). This variability, along with functional differences, may contribute to the variability between individual subject activation maps. Non-overlapping regions of activation may be overlooked upon group analysis (Schlaug *et al.*, 1994), and may explain why PET results generally do not show multiple foci of activation within the ACC.

4.1.4 Insular Cortex

Brain imaging studies of pain have consistently reported activation within the anterior insular cortex. The insula was the most consistent pain-related peak of activation observed in the present study. All subjects showed bilateral activation in the anterior portion of the insular cortex for all sessions. Insula was also the strongest region of activation revealed by group analysis. This robust activation highlights the significant role of IC in pain processing, and confirms previous results that showed it to be the only significant pain-related activation when compared to vibrotactile stimulus (Coghill *et al.*, 1994).

The strong pain-related activation observed across the majority of brain imaging studies reflects the critical integrative role of the insula in pain processing. Anatomical evidence reveals reciprocal connections of the insula with multiple regions of the pain processing system, including S1, S2, and ACC (Augustine, 1985), as well as the posterior portion of the ventral medial thalamic nuclei – a region containing nociceptive neurons (Mufson & Mesulam, 1982; Friedman & Murray, 1986; Friedman *et al.*, 1986; Craig *et al.*, 1994; Augustine, 1996). The distributed circuitry of the insula makes this region well-suited to take part in the integration of pain, memory and motivational-affective processes (Friedman *et al.*, 1986; Coghill *et al.*, 1994).

Assessments of patients with lesions of the insular cortex lend further support to the role of IC in the motivational-affective component of pain perception. Lesions of the insula can result in increased pain tolerance, lack of withdrawal, and absent or inappropriate emotional responses to painful stimuli (Berthier *et al.*, 1988).

4.2 CONCLUSION

It is now clear that the cerebral cortex plays a crucial role in the pain experience. S1, S2, IC and ACC make up part of a distributed pain processing network that reflects the complex, multidimensional nature of pain perception. These cortical regions interactively process the sensory-discriminative and motivational-affective components of pain.

Functional MRI has allowed researchers to take a closer look at pain processing in the brain by enabling the examination of individual subjects and eliminating the need to average across multiple subjects. The present study illustrates that there is considerable variability both between and within subjects. The between-subject variability was associated with the precise location of activation, largely due to anatomical variability. Conversely, the variability within an individual subject was associated with the presence or absence of activation, which may be related to the cognitive state at the time of scanning. Either variability can result in

the degradation of a real signal and this was demonstrated in the results of the grouped analysis. Therefore, the discrepancies between brain imaging studies of pain may simply be the consequence of between and within subject variability.

In order to further characterize pain perception in the brain, it is imperative to carry out studies that precisely control for the manifold variables that influence the pain experience. These include stimulus quality, intensity, duration and spatial extent, as well as possible cognitive factors, such as subject instructions and attention. Standardized analytical techniques would clarify the results across research groups and imaging modalities.

4.3 LIMITATIONS

One disadvantage of this study was the lack of sensitive psychophysical measurements for subject perception. Without a reliable measure of pain perception, it is not possible to verify the specific sources of variability. Future studies employing online rating methods will help clarify the effects of perceptual differences on neuronal activation. Furthermore, the cognitive state of the subject was not well controlled for, as subject instructions were not scripted until the latter part of the study. This may have resulted in variable cognitive states across different sessions and may have contributed to within subject differences.

Another limitation of this study was the stimulus equipment. Non-Peltier MR-compatible thermodes were used to administer thermal stimulus. Temperature adjustments were made only between runs, as it was not possible to fine-control them during scans. Two thermodes were used, at fixed temperatures, and were applied manually to the leg region. Therefore, since the thermodes were applied manually by the experimenter, the timing and duration of the stimulation were imprecise. Additional variability in the duration of stimulation may have also been introduced by slight variations in scanning parameters, made early in the study. These potential inconsistencies may have contributed to perceptual differences, as a closer examination of the psychophysical response revealed that peak pain perception occurred in the last 3 seconds of stimulation (Chen *et al.*, 1999). Future studies employing a fMRI compatible, computer-controlled Peltier thermode will eliminate much of the variability in the timing and duration of thermal stimulation.

4.4 FUTURE WORK

fMRI provides sufficient sensitivity for assessing cerebral pain mechanisms in individual subjects and, in contrast to PET techniques, its non-invasive nature allows for repeated evaluations and longitudinal studies of rare disorders involving non-uniform patient populations. This is of particular significance in elucidating the neural mechanisms of pain in patients suffering from rare neuropathic pain

conditions. These patients experience chronic intractable pain due to peripheral and/or central nervous system damage (e.g. amputation, hemispherectomy (Marchand *et al.*, 1999; Morin *et al.*, 1999; Olausson *et al.*, 1999), diabetic neuropathy, trigeminal neuralgia, etc.). Many of them have already participated in imaging studies using PET and thus, cannot be exposed to further radioactivity.

Appendix A

Tables for Individual Session Analysis

Pain-related activation sites - Subject HB, Session # 1
average pain rating ~ 4.2

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	8	-46	74	6.0
S2 (contra)	*52*	*-26*	*22*	*4.6*
ACC (contra)	8	-6	38	7.2
	8	14	34	5.6
ACC (ipsi)	-4	6	42	6.5
	-2	-4	44	6.2
IC (contra)	36	10	6	6.3
IC (ipsi)	-34	8	10	6.1
operculum (contra)	54	8	2	5.1
operculum (ipsi)	-58	2	2	6.2
SMA	4	-10	68	8.5
	-2	-12	68	6.5
basal ganglia (contra)	24	10	-2	5.9
basal ganglia (ipsi)	-24	8	-4	5.9

4 runs, df = 318, global threshold t-value = 4.67, p = 0.05

Pain-related activation sites - Subject HB, Session #2
average pain rating ~ 2.5

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S2 (contra)	*40*	*-28*	*24*	*3.7*
S2 (ipsi)	*-44*	*-34*	*22*	*3.6*
	-44	*-20*	*14*	*4.1*
i. parietal lobule	*56*	*-36*	*26*	*3.9*
ACC (contra)	8	16	32	5.4
	6	0	42	5.3
ACC (ipsi)	-4	8	40	5.2
	-2	0	48	5.4
IC (contra)	34	24	-6	5.1
IC (ipsi)	*-40*	*8*	*2*	*4.2*
operculum (contra)	*56*	*8*	*4*	*4.1*
operculum (ipsi)	*-50*	*-2*	*4*	*4.6*
SMA	4	-6	72	4.9
parieto-occipital	-6	-78	24	6.2
basal ganglia (contra)	*16*	*10*	*-4*	*4.5*
basal ganglia (ipsi)	*-8*	*6*	*-4*	*4.6*

2 runs, df = 139, global threshold t-value = 4.78, p = 0.05

Brush-related activation sites – Subject HB, Session #2
average intensity rating ~ 2.2

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S2 (contra)	54	-26	18	5.9
S2 (ipsi)	-48	-38	24	6.3
	-62	-24	28	5.5
SMA	*-8*	*-10*	*64*	*4.5*
i. parietal lobule	-54	-30	52	5.6
m. temporal gyrus	-48	-58	4	5.1
precentral gyrus	-54	-4	48	4.9
occipital	-48	-74	8	5.8

3 runs, df = 231, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites – Subject HB, Session #3
average intensity rating ~ 0.9

Region		Stereotaxic coordinates (mm)			t
		M-L	A-P	S-I	
S1		14	-40	74	9.6
S2 (contra)	band of activation	42	-26	22	7.8
		64	-16	20	7.7
S2 (ipsi)		-52	-32	12	9.3
SMA		-6	-4	60	8.0
operculum		-62	-8	8	7.2
i. parietal lobule		-54	-26	48	6.8
s. parietal lobule		-20	-62	56	4.8
postcentral gyrus		-60	-20	32	7.1
precentral gyrus		-56	-4	44	6.6
occipital		30	-84	24	5.0

4 runs, df = 320, global threshold t-value = 4.67, p = 0.05

Pain-related activation sites - Subject CJ, Session # 1
average pain rating ~ 4.1

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	*24*	*-38*	*68*	*4.5*
S2 (contra)	36	-20	18	7.1
S2 (ipsi)	-38	-20	16	6.9
i. parietal lobule	*60*	*-36*	*28*	*4.3*
ACC (bilateral)	2	20	42	6.3
IC (contra)	34	14	4	6.8
IC (ipsi)	-38	10	4	4.8
operculum (contra)	54	16	4	6.5
operculum (ipsi)	*-56*	*0*	*12*	*4.4*
SMA	6	-4	62	4.9
m. frontal gyrus	30	38	8	6.5
	-36	44	22	5.0
i. frontal gyrus	56	18	18	6.0
occipital	0	-84	20	6.0

5 runs, df = 405, global threshold t-value = 4.65, p = 0.05

Pain-related activation sites - Subject CJ, Session #2
average pain rating ~ 3.0

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S2 (contra)	*34*	*-22*	*22*	*3.5*
ACC (contra)	4	22	42	5.3
IC (contra)	42	10	-6	6.0
IC (ipsi)	-42	14	-2	5.5
operculum (contra)	48	14	0	5.8
m. frontal gyrus	32	40	4	4.7

3 runs, df = 230, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites - Subject CJ, Session #2
average intensity rating ~ 2.0

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	20	-38	76	7.4
S2 (contra) band of activation	50	-38	26	9.1
	56	-32	24	8.5
S2 (ipsi)	-54	-36	30	6.0
	-50	-26	22	5.5
SMA	-2	4	62	5.4
i. parietal lobule	-54	-18	36	5.9
m. temporal gyrus	56	-58	12	7.2
postcentral gyrus	-60	-10	42	5.7
precentral gyrus	52	6	34	6.2
	-58	6	40	5.9

3 runs, df = 231, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites - Subject CJ, Session #3
average intensity rating ~ 1.3

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	16	-28	78	11.0
	22	-36	72	9.5
S2 (contra)	50	-28	30	10.6
S2 (ipsi)	-54	-36	24	6.3
m. temporal gyrus	62	-48	10	7.0
	-48	-48	10	5.4
s. temporal gyrus	50	-30	6	5.0
posterior insula	36	-16	20	5.9
thalamus (pulvinar)	*14*	*-30*	*6*	*4.5*

4 runs, df = 320, global threshold t-value = 4.67, p = 0.05

Pain-related activation sites - Subject BJ, Session # 1
average pain rating ~ 4.1

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	12	-32	66	7.7
S2 (contra)	46	-24	16	6.1
S2 (ipsi)	*-62*	*-24*	*20*	*4.2*
i. parietal lobule	*56*	*-28*	*32*	*4.1*
ACC (contra)	4	-6	46	8.0
	6	16	36	5.2
ACC (ipsi)	-12	-8	48	5.7
	-6	8	46	5.4
IC (contra)	32	26	2	5.5
IC (ipsi)	-44	0	8	5.5
operculum (contra)	54	10	4	5.5
operculum (ipsi)	-48	-6	8	5.7
SMA	0	-20	64	9.1
m. frontal gyrus	26	46	32	5.4
	-30	38	34	5.2
s. frontal gyrus (med.)	14	-2	62	5.2
s. parietal lobule	16	-46	66	7.4
	-16	-48	68	6.1
c. parietal lobule	6	-42	60	7.2
precuneus	8	-72	40	5.8
	-6	-76	40	6.2
cuneus	10	-92	10	6.7
	14	-68	8	6.0
basal ganglia (contra)	26	0	14	5.1
	28	*10*	*4*	*4.6*
basal ganglia (ipsi)	-24	4	0	4.7
thalamus	*20*	*-18*	*0*	*4.4*

3 runs, df = 230, global threshold t-value = 4.70, p = 0.05

Pain-related activation sites - Subject BJ, Session #2
average pain rating ~ 3.8

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
ACC (contra)	*12*	*14*	*34*	*4.6*
IC (contra)	*42*	*6*	*10*	*4.3*
IC (ipsi)	*-36*	*0*	*14*	*3.6*
s. parietal lobule	*-20*	*-46*	*66*	*4.5*
basal ganglia (contra)	*28*	*6*	*2*	*4.0*

3 runs, df = 230, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites – Subject BJ, Session #2
average intensity rating ~ 2.5

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	12	-30	80	5.2
	22	-36	72	4.8
S2 (contra)	42	-24	14	4.7
S2 (ipsi)	-50	-24	18	5.1

3 runs, df = 231, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites – Subject BJ, Session #3
average intensity rating ~ 1.0

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	22	-34	74	5.9
S2 (contra)	*42*	*-22*	*18*	*3.8*
S2 (ipsi)	*-48*	*-26*	*16*	*3.6*

3 runs, df = 231, global threshold t-value = 4.70, p = 0.05

Pain-related activation sites – Subject SJ, Session # 1
average pain rating ~ 4.4

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S2 (contra)	48	-22	14	5.1
S2 (ipsi)	-38	-20	14	7.5
i. parietal lobule	*52*	*-34*	*32*	*3.7*
ACC (contra)	10	30	24	5.7
	2	*26*	*32*	*4.7*
	4	*-2*	*44*	*4.6*
ACC (bilateral)	2	32	24	5.4
IC (contra)	36	24	2	8.7
IC (ipsi)	-40	16	2	6.7
	-34	22	10	4.9
operculum (contra)	48	8	4	8.0
SMA	0	-6	60	*4.2*

2 runs, df = 139, global threshold t-value = 4.78, p = 0.05

Pain-related activation sites - Subject SJ, Session #3

average pain rating ~ 4.1

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1 (contra)	20	-24	62	9.5
	18	-26	56	9.7
	12	-28	64	7.7
S1 (ipsi)	-16	-30	64	8.4
S2 (contra)	36	-26	16	6.0
S2 (ipsi)	-46	-30	16	7.7
i. parietal lobule (contra)	56	-38	34	7.1
i. parietal lobule (ipsi)	-58	-38	32	5.6
ACC (contra)	2	-8	46	11.3
	10	6	36	9.7
	10	22	26	8.9
ACC (ipsi)	-10	10	36	8.2
IC (contra) band of activation	42	8	4	8.2
	40	10	-2	8.2
IC (ipsi)	-44	8	-4	8.5
operculum (contra)	54	4	6	6.3
operculum (ipsi)	-48	2	4	7.1
SMA	0	-8	60	11.7
	8	-16	70	10.0
	8	0	68	8.9
	-10	-4	60	7.4
s. parietal lobule	6	-52	74	9.7
	-20	-46	72	6.8
basal ganglia (contra)	16	6	4	7.6
thalamus	14	-10	14	7.4
	-14	-10	14	8.0

3 runs, df = 230, global threshold t-value = 4.70, p = 0.05

Brush-related activation sites - Subject SJ, Session #1
average intensity rating ~ 1.8

Region	Stereotaxic coordinates (mm)			t
	M-L	A-P	S-I	
S1	22	-36	56	5.3
	20	-40	62	5.1
S2 (contra)	50	-22	14	9.7
S2 (ipsi)	-60	-18	22	8.0
operculum	52	-2	4	5.1
i. parietal lobule	42	-36	62	5.3
precentral gyrus	32	-6	52	5.1
m. frontal gyrus	34	66	-2	5.1

2 runs, df = 139, global threshold t-value = 4.78, p = 0.05

Brush-related activation sites - Subject SJ, Session #1
average intensity rating ~ 1.8

Region		Stereotaxic coordinates (mm)			t
		M-L	A-P	S-I	
S1		24	-38	72	6.7
		20	-36	64	5.5
S2 (contra)	band of activation	52	-20	16	6.9
		44	-32	24	6.8
S2 (ipsi)		-50	-22	22	6.5

4 runs, df = 320, global threshold t-value = 4.67, p = 0.05

Appendix B

SUBJECT CONSENT FORM

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)
CONSENT FORM

MONTREAL NEUROLOGICAL INSTITUTE AND HOSPITAL
McConnell Brain Imaging Centre

Title of the project: **Replication of the Functional Brain Imaging of Pain using fMRI**

Investigators: B. Ha, J. Chen, M.C. Bushnell, G. Duncan

Reason for the study

Functional brain imaging allows for the identification of specific regions of the brain that are activated in response to an external stimuli. In previous studies, we identified areas of the brain that are activated by the pain experience using an invasive functional brain imaging technique called positron emission tomography (PET). The purpose of this study is to replicate these studies using a new non-invasive magnetic resonance imaging technique (MRI), called functional MRI (fMRI). PET makes use of injections of radioactive ions whereas magnetic resonance uses no ionizing radiation at all. Furthermore, there are no known health risks associated with exposure to the static or variable magnetic fields used in MRI.

Procedures

Your participation in this study will involve one 90 minute session. During this session, you will undergo magnetic resonance imaging (MRI), a non-invasive test that uses a magnetic field and radiofrequency waves to visualize certain types of tissue. This allows us to examine internal organs such as the brain and monitor physiological parameters such as blood flow and oxygenation.

You will be asked to lie on a couch that will be moved into a cylindrical opening where pictures of your head will be taken during a period of 90 minutes. The machine will be quite noisy during the scan. To reduce the noise, you will be given earplugs.

During this experiment, you will be subjected to varying levels of thermal stimuli presented on the skin by a contact thermode. The stimuli range from 0 to 50□C; due to the short duration (less than 30 seconds) of these stimuli, they will not damage the skin. Following each stimulus you will be asked to evaluate the intensity and unpleasantness of the stimulation on a scale of 0-100.

Contraindications

The following are contraindications for this study:

- Pacemaker
- Aneurysm Clip
- Heart/Vascular Clip
- Prosthetic Valve
- Metal Prosthesis
- Pregnancy
- Current use of narcotic or other analgesic medication
- Cardiovascular or neurological disease

Advantages of the proposed study
MRI is a test, not a treatment. There is no immediate advantage to participate in this study. However, it is hoped that the information obtained in this study will help researchers in understanding the mechanisms of pain.

Disadvantages of the proposed study
During this study, you will be exposed to a strong magnetic field and radio waves. However, no long-term negative side-effects have been observed from this type of examination. As mentioned above, the MR machine is very noisy and you will be given earplugs to reduce this effect. Metallic objects can be attracted with great force by the magnetic field. You will be asked to remove all such objects from your person and clothing prior to the experiment. The thermal stimuli may cause some pain and/or discomfort and/or temporary reddening of the skin. These stimuli will not damage or burn your skin.

Effects of participation in this study on your treatment
Magnetic resonance imaging does not interfere with any treatment or other diagnostic tests.

Confidential nature of this study
Your participation is strictly confidential. The investigators will take all reasonable measures to protect the confidentiality of your records. Your identity will not be revealed in any presentation or publication that results from this project.

Incidental findings
Any incidental findings regarding your own health will be communicated to you and , upon your request, to your physician.

Discontinuation of the study by the investigator
At any time during the testing, the investigators have the right to terminate the study for purely scientific reasons.

Subject's statement concerning withdrawal from the study
Your participation in this research study is voluntary and you may withdraw at any time, including during the procedure.

Compensation
After you have completed the study, you will receive a sum of 50 dollars as compensation for your time and inconvenience.

Inquiries
If you have any further questions, you may always contact us (398-6385).

QUESTIONNAIRE AND DECLARATION OF CONSENT

Previous surgery (type and date) _____.

Does the subject have any of the following ?

	YES	NO
Cardiac pacemaker	☐	☐
Surgical clip on an aneurysm or other vessel	☐	☐
Surgical clip or valve on the heart	☐	☐
Prostheses (specify type and location) _____	☐	☐
Implants (specify type and location) _____	☐	☐
Metal or metallic fragments in any other part of the body (specify) _____	☐	☐
Is the subject pregnant?	☐	☐
Is the subject currently taking any prescription medication? (specify) _____	☐	☐

SUBJECTS DECLARATION OF CONSENT

I, _____, have read the above description with one of the above investigators, _____.

I fully understand the procedures, advantages and disadvantages of the study which has been explained to me. I freely and voluntarily consent to participate in this study.

Further, I understand that I may seek information about each test either before or after it is given, that I am free to withdraw from the testing at any time if I desire, and that my personal information will be kept confidential.

Subject

Name	Signature	Date	Contact No.

Investigator

Name	Signature	Date	Contact No.

Physician

Name	Signature	Date	Contact No.

Reference List

Al-Chaer, E. D., Lawand, N. B., Westlund, K. N., & Willis, W. D. (1996). Visceral nociceptive input into the ventral posterolateral nucleus of the thalamus: a new function of the dorsal column pathway. *Journal of Neurophysiology* **76**, 2661-2674.

Albe-Fessard, D., Berkley, K. J., Kruger, L., Ralston, H. J., & Willis, W. D. (1985). Diencephalic mechanisms of pain sensation. *Brain Research Reviews* **9**, 217-296.

Andersson, J. L. R., Lilja, A., Hartvig, P., Långström, B., Gordh, T., Handwerker, H., & Torebjörk, E. (1997). Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. *Experimental Brain Research* **117**, 192-199.

Apkarian, A. V. & Hodge, C. J. (1989). Primate spinothalamic pathways: I. A quantitative study of the cells of origin of the spinothalamic pathway. *J.Comp.Neurol.* **288**, 447-473.

Augustine, J. R. (1985). The insular lobe in primates including humans. *Neurological Research* **7**, 2-10.

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews* **22**, 229-244.

Baron, R., Baron, Y., Disbrow, E., & Roberts, T. P. (1999). Brain processing of capsaicin-induced secondary hyperalgesia: a functional MRI study. *Neurology* **53**, 548-557.

Basbaum, A. I. & Fields, H. L. (1984). Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience* 7, 309-338.

Becerra, L. R., Breiter, H. C., Stojanovic, M., Fishman, S., Edwards, A., Comite, A. R., Gonzalez, R. G., & Borsook, D. (1999). Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. *Magn Reson.Med.* **41**, 1044-1057.

Berkley, K. J. (1980). Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cat and monkeys I. Ascending somatic sensory inputs to lateral diencephalon. *Journal of Comparative Neurology* **193**, 283-317.

Berman, H. H., Kim, K. H., Talati, A., & Hirsch, J. (1998). Representation of nociceptive stimuli in primary sensory cortex. *Neuroreport* **9**, 4179-4187.

Berthier, M., Starkstein, S., & Leiguarda, R. (1988). Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann.Neurol.* **24**, 41-49.

Bishop, G. H. (1946). Neural mechanisms of cutaneous sense. *Physiol.Rev.* **26**, 77-102.

Brodal, A. & Rexed, B. (1953). Spinal afferents to the lateral cervical nucleus in the cat. *J.Comp Neurol.* **98**, 179-211.

Bullmore, E., Brammer, M., Williams, S. C., Rabe-Hesketh, S., Janot, N., David, A., Mellers, J., Howard, R., & Sham, P. (1996). Statistical methods of estimation and inference for functional MR image analysis. *Magn Reson.Med.* **35**, 261-277.

Burgess, P. R. & Perl, E. R. (1973). Cutaneous mechanoreceptors and nociceptors. In *Handbook of sensory physiology: somatosensory system*, ed. A. Iggo, pp. 29-78. Springer, Heidelberg.

Burton, H., Videen, T. O., & Raichle, M. E. (1993). Tactile-vibration-activated foci in insular and parietal- opercular cortex studied with positron emission tomography:

Mapping the second somatosensory area in humans. *Somatosens.Mot.Res.* **10**, 297-308.

Bushnell, M. C. & Duncan, G. H. (1987). Mechanical response properties of ventroposterior medial thalamic neurons in the alert monkey. *Experimental Brain Research* **67**, 603-614.

Bushnell, M. C. & Duncan, G. H. (1989). Sensory and affective aspects of pain perception: Is medial thalamus restricted to emotional issues? *Experimental Brain Research* **78**, 415-418.

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J.-I., & Carrier, B. (1999). Pain perception: Is there a role for primary somatosensory cortex? *Proc.Natl.Acad.Sci.USA* **96**, 7705-7709.

Bushnell, M. C., Duncan, G. H., & Tremblay, N. (1993). Thalamic VPM nucleus in the behaving monkey. I. Multimodal and discriminative properties of thermosensitive neurons. *Journal of Neurophysiology* **69**, 739-752.

Carrier, B., Rainville, P., Paus, T., Duncan, G. H., & Bushnell, M. C. (1998). Attentional modulation of pain-related activity in human cerebral cortex. Soc.Neurosci.Abst. 24[1], 1135-#447.6.

Casey, K. L., Minoshima, S., Berger, K. L., Koeppe, R. A., Morrow, T. J., & Frey, K. A. (1994). Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *Journal of Neurophysiology* **71**, 802-807.

Casey, K. L., Minoshima, S., Morrow, T. J., & Koeppe, R. A. (1996). Comparison of human cerebral activation patterns during cutaneous warmth, heat pain, and deep cold pain. *Journal of Neurophysiology* **76**, 571-581.

Casey, K. L. & Morrow, T. J. (1983b). Nocifensive responses to cutaneous thermal stimuli in the cat: Stimulus-response profiles, latencies, and afferent activity. *Journal of Neurophysiology* **50**, 1497-1515.

Casey, K. L. & Morrow, T. J. (1983a). Ventral posterior thalamic neurons differentially responsive to noxious stimulation of the awake monkey. *Science* **221**, 675-677.

Cervero, F. & Iggo, A. (1980). The substantia gelatinosa of the spinal cord. *Brain* **103**, 717-772.

Chen, J.-I., Ha, B., Petre, V., Bushnell, M. C., & Duncan, G. H. (1999). Evidence for temporal summation of heat pain observed in S1 cortex using fMRI. *Society for Neuroscience* **25**.

Christensen, B. N. & Perl, E. R. (1970). Spinal neurons specifically excited by noxious or thermal stimuli: marginal zone of the spinal cord. *Journal of Neurophysiology* **33**, 293-307.

Chudler, E. H., Anton, F., Dubner, R., & Kenshalo, D. R., Jr. (1990). Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: Effect of interstimulus interval. *Journal of Neurophysiology* **63**, 559-569.

Coggeshall, R. E., Chung, K., Chung, J. M., & Langford, L. A. (1981). Primary afferent axons in the tract of Lissauer in the monkey. *J.Comp.Neurol.* **196**, 431-442.

Coghill, R. C., Talbot, J. D., Evans, A. C., Meyer, E., Gjedde, A., Bushnell, M. C., & Duncan, G. H. (1994). Distributed processing of pain and vibration by the human brain. *J.Neurosci.* **14**, 4095-4108.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric date in standardized Talairach space. *Journal of Computer Assisted Tomography* **18**, 192-205.

Craig, A. D., Broman, J., & Blomqvist, A. (1992). Lamina I spinocervical tract terminations in the medial part of the lateral cervical nucleus in the cat. *J.Comp.Neurol.* **322**, 99-110.

Craig, A. D., Bushnell, M. C., Zhang, E.-T., & Blomqvist, A. (1994). A thalamic nucleus specific for pain and temperature sensation. *Nature* **372**, 770-773.

Craig, A. D., Reiman, E. M., Evans, A. C., & Bushnell, M. C. (1996). Functional imaging of an illusion of pain. *Nature* **384**, 258-260.

Davis, K. D., Kwan, C. L., Crawley, A. P., & Mikulis, D. J. (1998b). Event-related fMRI of pain: entering a new era in imaging pain. *Neuroreport* **9**, 3019-3023.

Davis, K. D., Kwan, C. L., Crawley, A. P., & Mikulis, D. J. (1998a). Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *Journal of Neurophysiology* **80**, 1533-1546.

Davis, K. D., Taylor, S. J., Crawley, A. P., Wood, M. L., & Mikulis, D. J. (1997). Functional MRI of pain- and attention- related activations in the human cingulate cortex. *Journal of Neurophysiology* **77**, 3370-3380.

Davis, K. D., Wood, M. L., Crawley, A. P., & Mikulis, D. J. (1995). fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *NeuroReport* **7**, 321-325.

Derbyshire SWG & Jones AKP (1998). Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. *Pain* **76**, 127-135.

Derbyshire, S. W. G., Jones, A. K. P., Gyulai, F., Clark, S., Townsend, D., & Firestone, L. L. (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* **73**, 431-445.

Descartes, R. (1901). *De Homine Liber (1662);* translated by M.Foster, *Lectures on the History of Physiology during the 16th, 17th and 18th Centuries* Cambridge University Press, Cambridge.

Disbrow, E., Buonocore, M., Antognini, J., Carstens, E., & Rowley, H. A. (1998). Somatosensory cortex: a comparison of the response to noxious thermal, mechanical, and electrical stimuli using functional magnetic resonance imaging. *Hum.Brain Mapp.* **6**, 150-159.

Dong, W. K., Chudler, E. H., Sugiyama, K., Roberts, V. J., & Hayashi, T. (1994). Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *Journal of Neurophysiology* **72**, 542-564.

Dong, W. K., Hayashi, T., Roberts, V. J., Fusco, B. M., & Chudler, E. H. (1996). Behavioral outcome of posterior parietal cortex injury in the monkey. *Pain* **64**, 579-587.

Dong, W. K., Ryu, H., & Wagman, I. H. (1978). Nociceptive responses of neurons in the medial thalamus and their relationship to spinothalamic pathways. *Journal of Neurophysiology* **41**, 1592-1613.

Dong, W. K., Salonen, L. D., Kawakami, Y., Shiwaku, T., Kaukoranta, E. M., & Martin, R. F. (1989). Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. *Brain Res.* **484**, 314-324.

Foltz, E. L. & Lowell, E. W. (1962). Pain "relief" by frontal cingulumotomy. *J.Neurosurg.* **19**, 89-100.

Fox, P. T., Burton, H., & Raichle, M. E. (1987). Mapping human somatosensory cortex with positron emission tomography. *Journal of Neurosurgery* **67**, 34-43.

Friedman, D. P. & Murray, E. A. (1986). Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *Comparative Neurology* **252**, 348-374.

Friedman, D. P., Murray, E. A., O'Neill, J. B., & Mishkin, M. (1986). Cortical connections of the somatosensory fields of the lateral sulcus of macaques: Evidence for a corticolimbic pathway for touch. *J.Comp.Neurol.* **252**, 323-347.

Gelnar, P. A., Krauss, B. R., Sheehe, P. R., Szeverenyi, N. M., & Apkarian, A. V. (1999). A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. *Neuroimage.* **10**, 460-482.

Giesler, G. J., Yezierski, R. P., Gerhart, K. D., & Willis, W. D. (1981). Spinothalamic tract neurons that project to medial and/or lateral thalamic nuclei:

evidence for a physiologically novel population of spinal cord neurons. *Journal of Neurophysiology* **46** , 1285-1308.

Gingold, S. I., Greenspan, J. D., & Apkarian, A. V. (1991). Anatomic evidence of nociceptive inputs to primary somatosensory cortex: Relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys. *J.Comp.Neurol.* **308**, 467-490.

Greenspan, J. D., Lee, R. R., & Lenz, F. A. (1999). Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. *Pain* **81**, 273-282.

Greenspan, J. D. & Winfield, J. A. (1992). Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* **50**, 29-39.

Head, H. & Holmes, G. (1911). Sensory disturbances from cerebral lesions. *Brain* **34**, 102-254.

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (1998). Cognitive modulation of pain sensation alters activity in human cerebral cortex. *Soc.Neurosci.Abst.* **24**, 1135-1135.

Hurt, R. W. & Ballantine, H. T., Jr. (1973). Stereotactic anterior cingulate lesions for persistent pain: A report on 68 cases. *Clinical Neurosurgery* **21**, 334-351.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R., & Dostrovsky, J. O. (1999). Pain-related neurons in the human cingulate cortex. *Nat.Neurosci.* **2**, 403-405.

Hutchison, W. D., Dostrovsky, J. O., Davis, K. D., & Lozano, A. M. (1993). Single unit responses and microstimulation effects in cingulate cortex of an awake patient. *7th World Congress on Pain Abstracts* **1**, 461-462.

Iadarola, M. J., Berman, K. F., Zeffiro, T. A., Byas-Smith, M. G., Gracely RH, Max, M. B., & Bennett, G. J. (1998). Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain* **121**, 931-947.

Jones, A. K. P., Qi, L. Y., Fujirawa, T., Luthra, S. K., Ashburner, J., Bloomfield, P., Cunningham, V. J., Itoh, M., Fukuda, H., & Jones, T. (1991). In vivo distribution of opioid receptors in man in relation to the cortical projections of the medial and lateral pain systems measured with positron emission tomography. *Neurosci.Lett.* **126** , 25-28.

Jones, A. P., Hughes, D. G., Brettle, D. S., Robinson, L., Sykes, J. R., Aziz, Q., Hamdy, S., Thompson, D. G., Derbyshire, S. W. G., Chen, A. C. N., & Jones, A. K. P. (1998). Experiences with functional magnetic resonance imaging at 1 tesla. *British Journal of Radiology* **71**, 160-166.

Jorum, E., Lundberg, L. E. R., & Torebjörk, H. E. (1989). Peripheral projections of nociceptive unmyelinated axons in the human peroneal nerve. *J.Physiol.(Lond)* **416**, 291-301.

Kenshalo, D. R., Jr., Chudler, E. H., Anton, F., & Dubner, R. (1988). SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res.* **454**, 378-382.

Kenshalo, D. R., Jr. & Douglass, D. K. (1995). The role of the cerebral cortex in the experience of pain. In *Pain and the Brain: From Nociception to Cognition*, eds. Bromm, B. & Desmedt, J. E., pp. 21-34. Raven, New York.

Kenshalo, D. R., Jr., Giesler, G. J., Leonard, R. B., & Willis, W. D. (1980). Responses of neurons in primate ventral posterior lateral nucleus to noxious stimuli. *Journal of Neurophysiology* **43**, 1594-1614.

Kenshalo, D. R., Jr. & Isensee, O. (1983). Responses of primate SI cortical neurons to noxious stimuli. *Journal of Neurophysiology* **50**, 1479-1496.

Kenshalo, D. R., Jr., Thomas, D. A., & Dubner, R. (1991). Primary somatosensory cortical lesions reduce the monkey's ability to discriminate and detect noxious thermal stimulation. *Soc.Neurosci.Abstr.* **17**, 1206-1206.

Kido, D. K., LeMay, M., Levinson, A. W., & Benson, W. E. (1980). Computed tomographic localization of the precentral gyrus. *Radiology* **135**, 373-377.

Koltzenburg, M., Handwerker, H. O., & Torebjörk, H. E. (1993). The ability of humans to localise noxious stimuli. *Neurosci.Lett.* **150**, 219-222.

Konietzny, F., Perl, E. R., Trevino, D., Light, A., & Hensel, H. (1981). Sensory experiences in man evoked by intraneural electrical stimulation of intact cutaneous afferent fibers. *Experimental Brain Research* **42**, 219-222.

Lamour, Y., Willer, J. C., & Guilbaud, G. (1983). Rat somatosensory (SmI) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation. *Experimental Brain Research* **49**, 35-45.

Lange, N. & Zeger, S. L. (1997). Non-linear Fourier time series analysis for human brain mapping by functional magnetic resonance imaging. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* **46**, 1-29.

Lewin, W. & Phillips, C. G. (1952). Observations on the partial removal of the post-central gyrus for pain. *Journal of Neurology, Neurosurgery and Psychiatry* **15**, 143-147.

Marchand, S., Ha, B., Olausson, H., Morin, C., Ptito, A., Pike, B., & Bushnell, M. C. (1999) Cortical activation by tactile stimulation in hemispherectomized patients: An fMRI study. *Society for Neuroscience* **25**.

Marshall, J. (1951). Sensory disturbances in cortical wounds with special reference to pain. *Journal of Neurology Neurosurgery and Psychiatry* **14**, 187-204.

McHaffie, J. G., Kao, C.-Q., & Stein, B. E. (1989). Nociceptive neurons in rat superior colliculus: Response properties, topography, and functional implications. *Journal of Neurophysiology* **62**, 510-525.

Melzack, R. & Casey, K. L. (1968). Sensory, motivational and central control determinants of pain: A new conceptual model. In *The Skin Senses*, ed. Kenshalo, D. R., pp. 423-443. Thomas, Springfield, Ill.

Morin, C., Ha, B., Olausson, H., Marchand, S., Ptito, A., Pike, B., & Bushnell, M. C. (1999). Cortical Representation of Heat Pain in Hemispherectomized Patients: An fMRI Study. *Society for Neuroscience* **25**.

Mufson, E. J. & Mesulam, M.-M. (1982). Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *J.Comp.Neurol.* **212**, 23-37.

Musil, S. Y. & Olson, C. R. (1988). Organization of cortical and subcortical projections to anterior cingulate cortex in the cat. *J.Comp.Neurol.* **272**, 203-218.

Ochoa, J. & Torebjork, E. (1989). Sensations evoked by intraneural microstimulation of C nociceptor fibres in human skin nerves. *J.Physiol (Lond)* **415**, 583-599.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc.Natl.Acad.Sci.U.S.A* **87**, 9868-9872.

Olausson, H., Morin, C., Ha, B., Marchand, S., Ptito, A., & Bushnell, M. C. (1999). Tactile directional sensibility in hemispherectomized patients. *Society for Neuroscience* **25**.

Oshiro, Y., Fuijita, N., Tanaka, H., Hirabuki, N., Nakamura, H., & Yoshiya, I. (1998). Functional mapping of pain-related activation with echo-planar MRI: Significance of the SII-insular region. *NeuroReport* **9**, 2285-2289.

Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R., & Evans, A. C. (1996). Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cereb.Cortex* **6**, 207-214.

Penfield, W. & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* **60**, 389-443.

Penfield, W. & Jasper, H. (1954). *Epilepsy and the Functional Anatomy of the Human Brain* Little, Brown and Company, Boston.

Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Costes, N., Convers, P., Lavenne, F., Mauguiere, F., Michel, D., & Laurent, B. (1999). Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. ***Brain*** **122 (Pt 9)**, 1765-1780.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., & Rawlins, J. N. (1999). Dissociating pain from its anticipation in the human brain. *Science* **284**, 1979-1981.

Ploner, M., Schmitz, F., Freund, H. J., & Schnitzler, A. (1999). Parallel Activation of Primary and Secondary Somatosensory Cortices in Human Pain Processing. *Journal of Neurophysiology* **81**, 3100-3104.

Polonara, G., Fabri, M., Manzoni, T., & Salvolini, U. (1999). Localization of the first and second somatosensory areas in the human cerebral cortex with functional MR imaging. *AJNR Am.J.Neuroradiol.* **20**, 199-205.

Porro, C. A., Cettolo, V., Francescato, M. P., & Baraldi, P. (1998). Temporal and intensity coding of pain in human cortex. *Journal of Neurophysiology* **80**, 3312-3320.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* **277**, 968-971.

Rausell, E. & Jones, E. G. (1991). Chemically distinct compartments of the thalamic VPM nucleus in monkeys relay principal and spinal trigeminal pathways to different layers of the somatosensory cortex. *J.Neurosci.* **11**, 226-237.

Reynolds, D. V. (1969). Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* **164**, 444-445.

Robinson, C. J. & Burton, H. (1980). Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. *Journal of Comparative Neurology* **192**, 93-108.

Roy, C. S. & Sherrington, C. S. (1890). On the regulation of the blood-supply of the brian. *J.Physiol (Lond)* **11**, 85-108.

Schlaug, G., Knorr, U., & Seitz, R. (1994). Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. *Exp.Brain Res.* **98**, 523-534.

Sikes, R. W. & Vogt, B. A. (1992). Nociceptive neurons in area 24 of rabbit cingulate cortex. *Journal of Neurophysiology* **68**, 1720-1732.

Simoes, C. & Hari, R. (1999). Relationship between responses to co. *Neuroimage.* **10**, 408-416.

Sobel, D. F., Gallen, C. C., Schwartz, B. J., Waltz, T. A., Copeland, B., Yamada, S., Hirschkoff, E. C., & Bloom, F. E. (1993). Locating the central sulcus: comparison of MR anatomic and magnetoencephalographic functional methods. *AJNR Am.J.Neuroradiol.* **14**, 915-925.

Talbot, J. D., Marrett, S., Evans, A. C., Meyer, E., Bushnell, M. C., & Duncan, G. H. (1991). Multiple representations of pain in human cerebral cortex. *Science* **251**, 1355-1358.

Vierck, C. J. & Luck, M. M. (1979). Loss and recovery of reactivity to noxious stimuli in monkeys with primary spinothalamic cordotomies, followed by secondary and tertiary lesions of other cord sectors. *Brain* **102**, 233-248.

Vogt, B. A., Derbyshire, S., & Jones, A. K. (1996). Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *European Journal of Neuroscience* **8**, 1461-1473.

Vogt, B. A., Derbyshire, S., & Jones, A. K. (1996). Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *European Journal of Neuroscience* **8**, 1461-1473.

Vogt, B. A., Nimchinsky, E. A., Vogt, L. J., & Hof, P. R. (1995). Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *J.Comp.Neurol.* **359**, 490-506.

Vogt, B. A., Pandya, D. N., & Rosene, D. L. (1987). Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *The Journal of Comparative Neurology* **262**, 256-270.

Walker, A. E. (1940). The spinothalamic tract in man. *Archives of Neurology-Psychiatry* **43**, 284-298.

White, J. C. & Sweet, W. H. (1969). *Pain and the Neurosurgeon: A Forty-Year Experience* Thomas, Springfield, Ill.

Willis, W. D. (1985). *The Pain System: the neural basis of nociceptive transmission in the mammalian nervous system* Karger, New York.

Willis, W. D., Kenshalo, D. R., Jr., & Leonard, R. B. (1979). The cells of origin of the primate spinothalamic tract. *Journal of Comparative Neurology* **188**, 543-574.

Willis, W. D., Trevino, D. L., Coulter, J. D., & Maunz, R. A. (1974). Responses of primate spinothalamic tract neurons to natural stimulation of hindlimb. *Journal of Neurophysiology* **37**, 358-372.

Willis, W. D. & Westlund, K. N. (1997). Neuroanatomy of the pain system and of the pathways that modulate pain. *Journal of Clinical Neurophysiology* **14**, 2-31.

Willis, W. D. & Coggeshall, R. E. (1991). *Sensory mechanisms of the spinal cord*, 2nd ed. -- ed. Plenum Press, New York.

Worsley, K. J., Andermann, M., Koulis, T., MacDonald, D., & Evans, A. C. (1999). Detecting changes in nonisotropic images. *Hum.Brain Mapp.* **8**, 98-101.

Worsley, K. J., Liao, C., Grabove, M., Petre, V., Ha, B., & Evans, A. C. (2000). A general statistical analysis for fMRI data. *HBM 2000* **submitted**.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Hum.Brain Mapp.* **4**, 58-73.

Xu, X., Fukuyama, H., Yazawa, S., Mima, T., Hanakawa, T., Megata.Y., Kanda, M., Fujiwara, N., Shindo, K., Nagamine, T., & Shibasaki, H. (1997). Functional localization of pain perception in the human brain studied by PET. *NeuroReport* **8**, 555-559.

Yasui, Y., Itoh, K., Kamiya, H., Ino, T., & Mizuno, N. (1988). Cingulate gyrus of the cat receives projection fibers from the thalamic region ventral to the ventral border of the ventrobasal complex. *J.Comp.Neurol.* **274**, 91-100.

Young, G. B. & Blume, W. T. (1983). Painful epileptic seizures. *Brain* **106**, 537-554.