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DIFFERENTIATING PAIN- AND INNOCUOUS TACTILE-RELATED ACTIVATION OF HUMAN PRIMARY SOMATOSENSORY CORTEX USING TEMPORAL ANALYSIS OF fMRI

by

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ABSTRACT

The role of primary somatosensory cortex (S1) in pain perception remains uncertain. Human imaging studies have had variable success in showing pain-related activation in S1, and single-unit recordings in primate S1 have revealed few nociceptors. This study assessed the fMRI time course of S1 activity in humans during noxious heat and innocuous tactile stimulation to determine if temporal differences in the perception of these stimuli would be reflected by temporal differences in S1 activation.

Four normal subjects participated in three fMRI sessions each. Thermal (painful heat 45-46°C; neutral heat 35-36°C) and tactile stimuli (brushing at 2Hz) were applied to the left leg on separate runs. Activation maps were generated comparing painful to neutral heat and tactile to rest. Directed searches were performed on identified S1 regions reliably activated by brush and noxious heat stimuli, from which regions of interest (ROI) were selected in each subject. Time course for each stimulus modality was extracted from these ROIs, and data were further averaged to examine the mean time course of activation per stimulus cycle.

Both brushing and noxious heat produced significant activation within contralateral S1 which could be differentiated by the time course of activation relative to the onset of stimulation. These data indicate that S1cortex is involved in the processing of nociceptive information. The data are consistent with other indications that this structure has a role in the perception of pain intensity.

RÉSUMÉ

Le rôle du cortex somatosensoriel (S1) dans la perception de la douleur demeure incertain. Les études d'imagerie effectuées chez l'humain ont eu un plus ou moins de succès à démontrer l'activation reliée à douler dans S1. Également, les enregistrements unitaires chez le singe ont révélé peu de "nocicepteurs" dans cette région. À l'aide de l'imagerie par résonance magnétique, la présente étude a pour but d'évaluer, chez l'humain, le décours temporel de l'activité de S1 pedant l'application de des stimulations douloureuses chaude et de stimulations tactiles non-douloureuses. Cette évaluation permettra de déterminer si les différences temporelles dans la perception des stimuli (douloureux et non-douloureux) se réflètent dans l'activité de S1.

Quatre sujets normaux ont participé à trois séances de IRMf chacun. Des stimulations thermiques (chaleur douloureuse: 45-46 °C et chaleur neutre: 35-36 °C) et tactiles (pinceau stimulant à 2Hz) ont été appliquées sur la jambe gauche au cours de différentes séances. Des cartes d'activation ont été générées en comparant la chaleur douloureuse et la chaleur neutre, et le pinceau au repos. Par la suite, des recherches dirigées ont été réalisées vers les régions de S1 activées par le pinceau ou la chaleur douloureuse. À partir de ces régions, des régions d'intérêt (RI) ont été sélectionnées pour chaque sujet. Le décours temporel pour chaque stimulus a été extrait de ces RIs. Ensuite, les moyennes ont été calculées pour examiner le décours temporel moyen de l'activation par cycle de stimulation.

La stimulation tactile et la chaleur douloureuse ont évoqué une activation significative dans le S1 controlatéral, différentiables par le décours temporel de l'activation comparativement à celui du début de la stimulation. Ces résultats nous indiquent que le cortex S1 est impliqué dans le traitement de l'information nociceptive, et suggèrent également que cette structure corticale jouerait un rôle dans la perception même de la douleur.

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And to my Lord and Saviour Jesus Christ,

Gloria in Excelsis Deo

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Chapter 1

INTRODUCTION

The general notion of pain is often associated with sensation. However, pain is a unique sensory experience that involves numerous complex aspects. For instance, when injury occurs, one can easily identify the source of pain (e.g. face or hand) and can vividly describe it in terms of certain qualities that are almost exclusively associated with pain (e.g. aching, burning, pricking, stinging, etc.). These qualities may differ in varying intensities. The human abilities to localize, and to distinguish the quality and intensity of the perceived painful sensation forms the so-called sensory-discriminative aspect of pain. However, the most striking evidence that pain is a complex subjective experience is that it also encompasses an unpleasant emotional component. This affective-motivational aspect of pain experience may vary in severity from unpleasant or annoying feelings to agonizing or excruciating distress, and it often provides a context for the experience itself. Certainly, this aspect of pain delineates the 'suffering' feature of the experience. However, this aspect of pain also evokes both the withdrawal reflexes and the highly organized avoidance and escape behaviour that are essential for our survival.

Early theories of pain differed largely from the multidimensional view of pain experience. Scientists were mainly concerned with the physiological specialization of structures responsible for the painful sensation, proposing the idea of a "pain centre" in the brain. Thus pain processing was conceived as a direct channel functioning on the basis of a bell ringing mechanism (Descartes, 1664). Observations from the results of focal lesions and stimulation at the beginning of 1900s led to the view that pain is a phenomenon related only to the diencephalon and that telencephalic participation in pain perception is trivial (Head & Holmes, 1911; Penfield & Boldrey, 1937). These observations, however, did not examine the possible involvement of multiple brain regions in pain perception.

Modern theories of pain processing acknowledge the multidimensional nature of pain and suggest that various brain regions may be likely to play key roles in nociception (Melzack & Casey, 1968; Price, 1988). Accumulated data from anatomical and physiological studies have confirmed that a number of subcortical and cortical areas are involved in pain processing. More recently, brain imaging studies using PET or fMRI have provided further evidence of the role of cortex in this complex sensory experience (see Bushnell *et al.*, 1999 for review). These studies have revealed that cortical processing of pain is distributed and involves multiple regions of the brain that are functionally segregated into systems corresponding to the sensory-discriminative and the motivational-affective components of pain. Such areas comprise the primary and

secondary somatosensory cortices (S1 and S2), which are thought to contribute to the discriminative aspects of painful sensation, while the anterior cingulate cortex (ACC) and insula cortex (IC) are more likely to be involved in the affective aspects of nociception (Talbot *et al.*, 1991; Coghill *et al.*, 1994; Rainville *et al.*, 1997).

Despite extensive research efforts, the idea of the involvement of multiple cortical regions in pain processing remains controversial and is yet to be fully clarified. Specifically, the role of the S1 cortex in human pain processing has been the subject of massive debate. The next section will present an overview of pain pathways, after which the involvement of S1 in pain processing will be discussed in light of clinical, anatomical and physiological evidence, as well as the controversies raised by some of the brain imaging studies. A brief introduction to the technique of blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) will follow along with a discussion of the advantages of fMRI over PET in imaging cortical activity.

1.1 THE PAIN PATHWAY

Numerous research efforts in the field of neurophysiology of nociceptive processing at both peripheral and central levels have increased our knowledge and understanding of the multidimensional features of pain. Briefly, the pain pathway in normal human subjects involves the activation of special receptors in peripheral sensory

endings by means of a painful stimulus (e.g. mechanical, chemical or thermal) via membrane depolarization. This discriminative information is then transmitted via the nociceptive afferent fibres in the contralateral spinal dorsal horn to the ventrobasal thalamus and finally to the somatosensory cortex (Jones, 1985). Evidence has shown that pain sensation normally results from the activity of nociceptors and not from the overactivation of other types of receptors (Wall & McMahon, 1985; Torebjork *et al.*, 1988), and that different qualities of pain are likely subserved by distinct sensory channels (Willis & Coggeshall, 1991). However, painful sensation does not always involve activation of peripheral nociceptive afferents; pain can also result from the activation of central nociceptive pathways (Boivie *et al.*, 1989). Some clinical evidence also suggests that the motivational-affective state can mimic noxious sensations, most notably in patients suffering from anxiety, neurotic depression, or hysteria (Chatuverdi, 1987; Merskey, 1989). Overall, the findings support the view that many complex mechanisms underlie this unique sensory experience. The next section will present an overview of the peripheral structures involved in the processing of painful information.

1.1.1 Peripheral Afferents

Nociceptive information is detected by the peripheral endings of primary nociceptive neurons or the *nociceptors* (Sherrington, 1906) located in different kinds of tissue such as the superficial layers of the skin, muscle, visceral organs, venous and arterial walls, and the spinal and cerebral meninges. These nociceptors are innervated

by several different types of primary nociceptive afferent fibres (Bishop, 1946). The most common type are the small-diameter, unmyelinated C-fibres that respond to relatively lowly (0.5-1.4 m/s) (Van Hees & Gybels, 1981) to a variety of high-intensity of mechanical, thermal and chemical stimuli (Bessou & Perl 1969; Burgess & Perl 1973). The sensation produced by these nociceptors is often described as dull or burning pain (Ochoa & Torebjörk, 1989). Another type of nociceptive afferent fibre is the thinly myelinated Aδ fibre that responds to both thermal and mechanical stimuli (Burgess & Perl, 1967; Perl 1968) with a conduction velocity of 5-30 m/s (Adriaensen *et al.*, 1983). They are often associated with sharp and pricking pain (Konietzny *et al.*, 1981). The large myelinated Aβ fibres are responsible for transmitting tactile information (Torebjörk & Ochoa, 1980; Vallbo, 1981; Ochoa & Torebjörk, 1983; Cervero, 1985).

1.1.2 Central Pathways

1.1.2.1 Spinal Organization

The central pathways for processing nociceptive information begin when painful information reaches the level of the spinal cord dorsal horn via both Aδ and C primary nociceptive afferent fibres. After segregating from the large myelinated Aβ fibres, the Aδ and C-fibres bifurcate into ascending and descending branches for a few segments of the spinal cord as part of the tract of Lissauer (Coggeshall *et al.*, 1981). Studies show that the Aδ and C-afferents terminate primarily in the most superficial

layers of the spinal cord, namely the marginal zone (lamina I) and the substantia gelatinosa (lamina II)(Heimer & Wall, 1968; LaMotte, 1977; Ralston, III & Ralston, 1979; Perl, 1980), but some fibres also terminate in a deeper layer such as lamina V(Light & Perl, 1979). These nociceptive fibres form direct or indirect connections with three major classes of neurons in the dorsal horn: 1) projection neurons; 2) local excitatory interneurons; and 3) inhibitory interneurons. In general, projection neurons in lamina I that are exclusively activated by nociceptive stimuli (i.e. the nociceptive specific or NS neurons) receive input directly from terminations of Aδ fibres and indirectly from C fibres through interneurons in layer II (Christensen & Perl, 1970; Cervero & Iggo, 1980). These neurons have discrete receptive fields and response characteristics that enable them to distinguish the location and quality of noxious stimuli (Price & Mayer, 1974; Willis *et al.*, 1974; Price & Dubner, 1977). Other projection neurons in lamina I receive input from low-threshold mechanoreceptors, and are termed wide dynamic range (WDR) neurons (Cervero *et al.*, 1976; Ralston, III & Ralston, 1979; Woolf & Fitzgerald, 1983). The response characteristics of these neurons depend on the intensity of the stimulation from a variety of stimuli, including noxious, to which they respond with increase frequency discharge (Handwerker *et al.*, 1975; Price & Brown, 1975; Kenshalo, Jr. *et al.*, 1979). NS projection neurons are also present in deeper layers of lamina V, thus they receive both direct and indirect convergent input from the nociceptive afferents (Willis *et al.*, 1974; Menétrey *et al.*, 1977). The second major population of WDR projection neurons is also found in this

spinal laminae, and they receive input from large myelinated Aβ fibers (Wall, 1960; Willis & Coggeshall, 1991).

1.1.2.2 Ascending Nociceptive Pathways

Peripheral nociceptive input to the dorsal horn is conveyed to higher subcortical and cortical structures by the projection neurons via several ascending fibre tracts that terminate at different levels. Studies done in primates have found five major ascending pathways originating from different laminae of the spinal dorsal horn (Willis, 1985): the spinothalamic tract, the spinoreticular tract, the spinomesencephalic tract, the spinocervical tract, and the postsynaptic dorsal column pathway. Of these five, the first three ascend in the anterolateral ascending system, which plays a dominant role in conveying pain and temperature. Axons forming the anterolateral system originate predominantly from projection neurons in lamina I and in the deep laminae of the contralateral spinal cord, although some of the axons project ipsilaterally. On the other hand, the spinocervical and the postsynaptic dorsal column pathways ascend in the dorsal quadrant of the spinal cord.

1.1.2.2.1 Spinothalamic Tract

The widely studied spinothalamic tract (STT) is the main spinal cord pathway that conveys sensory information related to pain and temperature (Vierck & Luck, 1979). STT neurons originate primarily from laminae I, IV and V of the spinal

cord (Willis *et al.*, 1979; Apkarian & Hodge, 1989a). After decussating to the contralateral site of the spinal cord, their axons ascend in the contralateral anterolateral quadrant and terminate somatotopically in different regions of thalamus (Willis, 1985; Willis & Coggeshall, 1991). The particular nuclei of termination include the lateral thalamus, in which spinal projection terminates in the ventral posterior lateral nucleus (VPL), the ventral posterior medial (VPM) (Mehler *et al.*, 1960; Applebaum *et al.*, 1979; Boivie, 1979; Berkley, 1980), the ventral posterior inferior nucleus (VPI) (Apkarian & Hodge, 1989b; Stevens *et al.*, 1993) and the medial part of the posterior complex nuclei (POm) in the lateral thalamus (Mehler, 1974; Kerr, 1975; Ralston, III & Ralston, 1992). In general, STT neurons that project to the lateral thalamus have small, contralateral cutaneous receptive fields and are therefore suitable for encoding the sensory-discriminative aspects of pain (Willis *et al.*, 1974). Neurons in these regions (both nociceptive specific and wide-dynamic-range) then send projections to cortical regions such as the primary and secondary somatosensory cortex.

Regions of termination in the medial thalamus include the central lateral nucleus (CL) and other intralaminar nuclei (Mehler *et al.*, 1960; Applebaum *et al.*, 1979; Boivie, 1979; Berkley, 1980; Apkarian & Hodge, 1989b). STT cells that project to this region of the thalamus have response properties identical to those of STT cells that project just to the lateral thalamus (Giesler JR *et al.*, 1981). However, STT cells that just project to the CL nucleus have very large receptive fields, suggesting that these

neurons would be more suited to a role in the motivational-affective aspects of pain (Giesler JR *et al.*, 1981; Willis, 1985; Willis & Westlund, 1997). These medial thalamic regions then project to a diversity of cortical and subcortical structures including the limbic and motor regions. Craig *et al.* (1994) have recently described another STT projection using anterograde tracing and single unit recording. They found that the posterior part of the ventral medial thalamus (VMpo) also receives input from STT lamina I neurons that are specifically responsive to noxious and thermal information. Neurons in the VMpo subsequently send projections to the insular cortex (Friedman *et al.*, 1986).

1.1.2.2.2 Spinoreticular Tract

Nociceptive information also reaches the subcortical structures via the spinoreticular tract (SRT) that sends fibres from the laminae VII and VIII of the spinal cord to the reticular formation in the brainstem (Willis & Coggeshall, 1991). The majority of axons of these cells ascend in the anterolateral quadrant after crossing the spinal midline, but some spinoreticular fibres also form uncrossed projections (Kevetter *et al.*, 1982). Some spinoreticular neurons terminate on cells within the reticular formation involved in descending pain modulation pathways (Casey, 1971; Willis & Westlund, 1997). Others make up the spino-reticulo-thalamic tract that projects to medial thalamic areas, especially to the intralaminar nuclei, along with the spinothalamic tract (Mehler *et al.*, 1960). Both physiological (Haber *et al.*, 1982; Giesler *et al.*, 1981)

and anatomical studies (Kevetter *et al.*, 1982) have shown that some SRT neurons are colateral branches of STT cells. There is no obvious somatotopic organization of the spinoreticular tracts (Willis & Westlund, 1997). Many reticular neurons respond preferentially to noxious stimuli (Wolstencroft, 1964; Fields *et al.*, 1977).

1.1.2.2.3 Spinomesencephalic Tract

The spinomesencephalic tract (SMT) originates from the axons whose cells are located in the contralateral laminae I and V of the spinal cord (Willis *et al.*, 1979; Willis & Coggeshall, 1991). SMT neurons are nociceptive, responding either to noxious stimuli only or best to noxious but also to innocuous stimuli (Willis & Coggeshall, 1991). The receptive fields of these cells that project to the thalamus as well as to the midbrain tend to be restricted and small, whereas those projecting only to the midbrain tend to be complex, having excitatory and inhibitory fields (Yezierski *et al.*, 1987). The SMT tract terminates in different parts of the midbrain, primarily in the superior colliculus and the periaqueductal gray matter (PAG) (Mehler *et al.*, 1960; Kerr, 1975; Wiberg *et al.*, 1987). Projections to PAG terminate in an endogenous pain-modulating system (Reynolds, 1969), whose activation produces analgesia and endogenous opiate-like substances (Basbaum & Fields, 1984). On the other hand, inputs to the superior colliculus are likely to play a role in multisensory integration and behavioural reactions involved in the process of orienting toward painful stimuli (McHaffie *et al.*, 1989).

1.1.2.2.4 Spinocervical Tract

The existence of a significant spinocervical tract (SCT) in humans is still uncertain. However, in primates and cats, the axons that form the spinocervical tract (SCT) have their cells of origin located in the contralateral spinal laminae III, IV and V (Wall, 1960; Bryan *et al.*, 1974; Willis, 1985; Downie *et al.*, 1988). Most of these neurons respond solely to tactile stimuli, but some are also activated by noxious stimuli (Brown & Franz, 1969; Cervero *et al.*, 1977; Bryan *et al.*, 1974; Downie *et al.*, 1988). Unlike the pathways in the aforementioned anterolateral ascending system, the spinocervical tract travels in the dorsolateral quadrant of the spinal cord to the lateral cervical nucleus (Brodal & Rexed, 1953). The axons of neurons of the lateral cervical nucleus then decussate and ascend in the medial lemniscus in the brain stem to midbrain nuclei and to the thalamus, particularly the VPL and POm (Berkley, 1980; Boivie, 1980). Neurons in these thalamic regions then project to cortical regions such as S1. In monkeys, it was shown that the POm projects to the retroinsular cortex (Albe-Fessard *et al.*, 1985). Nociceptive transmission via the SCT tract may potentially account for the frequent recurrence of pain after anterolateral cordotomy.

1.1.2.2.5 Postsynaptic Dorsal Column

The postsynaptic dorsal column is another pain pathway that does not ascend in the anterolateral quadrant of the spinal cord. This pathway is formed by the axons of some nociceptive neurons in spinal laminae III and IV along with the axon

collaterals of large diameter primary afferents. These fibres synapse in the dorsal column nuclei in the medulla (Rustioni, 1973; Rustioni, 1974; Rustioni *et al.*, 1979; Bennett *et al.*, 1983; Giesler *et al.*, 1984). From there, projections are sent to the contralateral VPL thalamic nuclei via the medial lemniscus, then to the S1 cortex. Studies show that the trajectories of postsynaptic dorsal column fibres are somatotopically organized in the dorsal column (Cliffer & Giesler, Jr., 1989; Hirshberg *et al.*, 1996). Recent evidence suggests that the postsynaptic dorsal column cells and the cells of the gracile nucleus in the midbrain dorsal column nuclei may be particularly important for the transmission of visceral pain (Al-Chaer *et al.*, 1996).

It has been suggested that another pain pathway, the spino-ponto-amygdaloid system, conveys nociceptive input to subcortical and cortical structures subserving avoidance learning and/or the affective-motivational aspect of pain (Bernard & Besson, 1990). This pathway consists primarily of neurons in lamina I and V that ascend in the dorsolateral funiculus and synapse in the parabrachial area of the pons before reaching the amygdaloid complex in the brain.

1.1.2.3 Thalamus

As reviewed previously, nociceptive information is conveyed both directly and indirectly to the thalamus by the various ascending pathways. Traditionally, the thalamus is functionally divided into lateral and medial components that are thought to

correspond to the sensory-discriminative and affective-motivational components of pain, respectively (Albe-Fessard *et al.*, 1985). Thalamic nuclei in these subdivisions receive dense nociceptive input from spinal nociceptive projection neurons. Such thalamic nuclei include the ventroposterior lateral and medial nuclei (VPL and VPM) (Bushnell & Duncan, 1987; Bushnell *et al.*, 1993; Casey & Morrow, 1983; 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 project to a number of different cortical areas, including S1, S2, ACC and IC.

1.1.2.4 Cortical Structures

Early last century, scientists cast doubt on the role of the cerebral cortex in pain (Head & Holmes, 1911; Penfield & Boldrey, 1937). However, more recent evidence from electrophysiological recordings in animals and imaging studies in humans strongly suggests the involvement of the cerebral cortex in pain (e.g. Kenshalo, Willis, 1991 for review; Talbot *et al.*, 1991). Results from these studies indicate that the cortical areas most prominently involved include the S1 and S2 cortex, ACC and IC. Among these regions, S1 remains the most disputable structure. The next section will present a brief overview of the role of the S1 cortex in pain processing in light of anatomical, physiological, and clinical studies, followed by a discussion of the

controversies raised by different study groups using imaging techniques.

1.1.2.4.1 S1 Cortex: Anatomical, Physiological and Clinical Evidence

Although considerable knowledge exists concerning the cortical processing of tactile, auditory, and visual information, there is still uncertainty about how the cortex processes noxious information. Early human lesion and stimulation data had suggested that S1 cortex plays a minimal role in pain processing (e.g. Head & Holmes, 1911; Penfield & Boldrey, 1937). Nevertheless, large anatomical studies have provided evidence that S1 receives input from thalamic neurons with nociceptive properties, including the ventral posterior lateral (VPL), ventral posterior medial nucleus (VPM) (Jones & Seavitt, 1974; Jones & Burton, 1976; Jones, 1979; Jones & Friedman, 1982; Pons & Kaas, 1985; Rausell & Jones, 1991; Rausell *et al.*, 1992) as well as the ventral posterior inferior (VPI) and central lateral nucleus (CL) (Gingold *et al.*, 1991). In addition, single-unit recordings have found small numbers of nociceptive neurons in the S1 cortex of monkeys (Kenshalo DR & Isenesee, 1983; Kenshalo, Jr. *et al.*, 1988). In addition, some single neurons within S1, in both anesthetized (Kenshalo DR & Isenesee, 1983; Kenshaolo *et al.*, 2000) and awake (Kenshalo, Jr. *et al.*, 1988) primates, encode the intensity of noxious heat stimuli.

Clinical evidence also implicates the involvement of S1 in pain perception. Focal lesion studies reported transient deficits in pain perception in patients with severe

cortical injury (Head & Holmes, 1911; Marshall, 1951; Boivie *et al.*, 1989), and epileptic patients with foci involving S1 experience painful seizures (Young & Blume, 1983). In addition, removal of S1 has been observed to impair localization while leaving the ability to perceive pain intact (Penfield & Jasper, 1954).

Since the majority of these S1 neurons have WDR response properties, it is likely that a significant proportion of neurons will also respond to innocuous vibrotactile stimuli. In conjunction with evidence from primate studies showing that bilateral ablation of S1 disrupts the ability to discriminate intensities of noxious heat (Kenshalo, Jr. *et al.*, 1991), the findings cited above suggest that this region is involved in the sensory-discriminative aspect of pain perception.

1.1.2.4.1 Discrepancies Among Studies

To this day, S1 remains the most disputed cortical structure in regard to human pain processing. Historically, clinical observations of focal brain lesions and electrical stimulation of the cortex have suggested that cortical involvement in pain perception is minimal or absent. Instead, they have suggested that the thalamic and subcortical structures make the predominant contribution to the experience of pain (Head & Holmes, 1911; Penfield & Boldrey, 1937). Although numerous anatomical and neurophysiological data have shown nociceptive projections from thalamus and the existence of nociceptive neurons in S1 cortex, the scarcity of these S1 nociceptive

neurons has led to questions concerning their functional significance in pain perception.

The inconsistent results observed in different human brain imaging experiments have added fuel to this controversy. In an initial study using positron emission tomography (PET) techniques, Talbot *et al.* (1991) reported that noxious stimulation of the forearm evoked pain-related activation within contralateral SI, as well as in secondary somatosensory cortex (S2) and anterior cingulate cortex (ACC). Although Jones and colleagues (Jones *et al.*, 1991) soon confirmed the pain-related activation within ACC, using similar PET techniques but presented to a fixed location on the dorsal hand, their failure to find activation in S1 sparked an ongoing debate (Jones *et al.*, 1992; Duncan *et al.*, 1992; Roland, 1992).

The discrepancies were attributed to inadequate subtraction of the tactile components of the stimuli. Jones and colleagues argued that their experimental paradigm successfully controlled for the non-nociceptive sensory component of the stimulus by placing the pain stimulus in the same location as the heat stimulus and then subtracting the cortical activity evoked by the heat stimulus from that evoked by the pain stimulus. Furthermore, Jones argued that in the case of the Talbot experiment, S1 activities observed according to their paradigm (multiple stimulus location) were rather the by-product of either an attention-related modulation of S1 activities or the effect of skin contact with the thermode (Jones *et al.*, 1992; Jones & Derbyshire, 1996).

To complicate the issue further, another group, using single photon-emission computed tomography (SPECT), has reported a significant decrease in blood flow in S1 when subjects submerged their fingers in hot water for 3 minutes (Apkarian *et al.*, 1992). A possible explanation for this observation could be offered by electroencephalographic findings indicating that S1 is initially activated by pain, but in a short time (seconds) the activation is replaced by inhibition or the return to baseline idling state (Backonja *et al.*, 1991). Since the publication of these first imaging studies, subsequent investigations have confirmed, at most, that S1 activation is a variable finding when human subjects receive painful stimuli (Bushnell *et al.*, 1999).

Although more recent brain imaging studies pointed towards an activation of S1 under painful conditions, some studies have also reported a substantial overlap in the cerebral processing of cutaneous noxious and innocuous stimuli (Coghill *et al.*, 1994; Gelnar.P.A. *et al.*, 1999). The spatial proximity of S1 activation under these two conditions further contributes to the present confusion about the role of S1 in pain processing.

1.2 FUNCTIONAL BRAIN IMAGING

The basis for modern functional brain imaging techniques came from an idea originally proposed by Roy & Sherrington in 1890 (Roy & Sherrington, 1890). The pair suggested that brain activity could increase cerebral blood flow (CBF) through a metabolic mediator, a proposition confirmed by numerous subsequent studies demonstrating that local changes in CBF are coupled with regional brain activity. Modern functional brain imaging tools have taken advantage of this "activation-dependent coupling" in order to map neuronal activity.

Since the 1970s, when Lassen and colleagues did the first pain imaging study using the radioisotope Xenon^{133} (Lassen *et al.*, 1978), a large number of pain imaging studies have been performed using positron emission tomography (PET). This imaging methodology rests on the intravenous injection of a radioactive tracer, usually radioactive water ($H_2{}^{15}O$), that is distributed in proportion to the blood flow. This method allows the CBF to be measured at a defined point in time, but does not allow the investigator to follow changes over time.

Functional magnetic resonance imaging (fMRI) has recently become a powerful noninvasive brain imaging technique for localizing functional neural activities and changes in cortical areas during a variety of sensory, motor, or cognitive tasks (Bandettini *et al.*, 1992; Ogawa *et al.*, 1992). In this respect, fMRI is potentially

revolutionary for imaging brain activity. In the near future it is likely to become the method of choice in brain imaging studies.

1.2.1 Advantages of fMRI

In many respects, fMRI offers several advantages over the conventional PET imaging technique. First, unlike PET, fMRI is based on a non-invasive approach to providing image contrast. It does not require the injection of radioactive tracer, therefore there are no associated health risks for subjects, and specific individuals may be specifically evaluated. Second, the superior temporal (less than 1 second) and spatial resolution ($\sim$1 mm) of fMRI (as opposed to PET's 10 minutes and 4-6 mm temporal and spatial sensitivity) allows a large amount of data to be collected from an individual subject during a two-hour scanning session (approximately hundreds of scans as opposed to the limited 10 to 12 scans per subject in PET). In this way, the length of the scanning period is reduced without compromising the sensitivity and accuracy of data interpretation. By contrast, the small number of scans available per session using the PET method requires the data from multiple subjects to be averaged in order to make reliable interpretations. Finally, the availability and the low cost of MRI technology for research also constitute significant advantages over PET.

1.2.2 Principles of the fMRI Signal

MRI is based on the detection of electromagnetic signals emanating from spinning hydrogen protons in the tissues when they are excited by a radio frequency (RF) pulse applied in the presence of an externally generated static magnetic field. The RF pulse excites the spinning protons and synchronizes their spins thereby creating a strong collective signal. Along with other factors, the presence of local variations in magnetic-field strength caused by tissues with differing magnetic susceptibility induces minute shifts in the RFs of nearby protons within each voxel, causing them to fall out of synchronization (dephasing) which leads to RF signal decay. Thus, differences in the rate of dephasing (termed T2*) are closely coupled with local hemodynamic changes which reflect neuronal activity and metabolic changes (Cohen & Bookheimer, 1994; DeYoe *et al.*, 1994).

1.2.3 Blood-Oxygenation-Level-Dependent (BOLD) fMRI

Early fMRI experiments used the administration of an exogenous contrast agent in order to measure changes in CBF. This method, however, was rapidly replaced by the discovery of an endogenous contrast agent, the deoxygenated hemoglobin inherent to blood. In 1936, Pauling first noted that the magnetic susceptibility of oxyhemoglobin and deoxyhemoglobin differed slightly (Pauling & Coryell, 1936). Thulborn and colleagues predicted and later demonstrated *in vitro* that the signal decay rate of deoxyhemoglobin is more rapid than that of oxyhemoglobin, implying that

changes in blood oxygenation can induce changes in blood MR signal intensity, thus creating image contrast (Thulborn *et al.* 1982). Since then the blood-oxygenation-level-dependent (BOLD) contrast method has become the most prevalent approach in fMRI experiments.

Ogawa and colleagues first reported the effects of blood oxygen on $T2^*$ in MR images, and labelled it as the "blood-oxygen-level-dependent" or BOLD method (Ogawa *et al.*, 1990). This approach takes advantage of the inherent paramagnetic qualities of deoxyhemoglobin for use as an endogenous contrast agent. The underlying concept is that a localized increase in neural activity produced by a sensory, motor or cognitive task results in an increase in regional cerebral blood flow (rCBF). Consequently, oxygen delivery is 2-4 times greater than the corresponding increase in blood volume (Grubb *et al.*, 1974). The excess oxygen supply causes an increase in the oxygenated hemoglobin concentration in the activated region, accompanied by a decrease in deoxyhemoglobin in the cerebral capillaries and veins (Fox & Raichle, 1986; Bandettini *et al.*, 1992; Kwong *et al.*, 1992). Due to the differential magnetic susceptibility of oxygenated (diamagnetic) and deoxygenated hemoglobin (paramagnetic), the presence of deoxyhemoglobin in a capillary degrades the homogeneity of the magnetic field, which in turn increases the dephasing (RF signal decay) of spinning hydrogen protons. As the amount of deoxyhemoglobin in the blood is washed out and diluted by the rising blood flow, less rapid dephasing occurs, and the

MR signal decays more slowly, thus effectively increasing the MR signal. The RF detector in the scanner picks up the changes, and ultimately regions of the brain that have enhanced activity appear as brighter regions on the functional MR image. These changes in the intensity of the signal can then be used indirectly to measure changes in rCBF secondary to neuronal activity. In other words, increases in neuronal activity are detected as an increase in the MR signal.

1.2.4 Susceptibility to Artifacts

Several sources of artifacts and noise may contaminate fMRI images and complicate their interpretation. The most common artifacts arise from the subject's head movements (Hajnal *et al.*, 1993). The high spatial resolution of MRI, coupled with its high intrinsic contrast, has the disadvantage that when activation-related signal changes are very small, even slight mis-registration creates significant artifacts following baseline subtraction. Head motion not only reduces the signal to noise ratio in activated regions but also produces pseudo-activations, especially at the edge of the brain and between large fissures. Precautions and clear instructions to the subjects prior to the scanning should be given to avoid such a bias.

1.3 OBJECTIVES

The first human pain imaging study was performed in the early 1970s by Lassen and colleagues (Lassen *et al.*, 1978) using the radioisotope Xenon^{133}. Despite the poor spatial resolution provided by this technique, the results did indicate that there was an increased blood flow to the frontal lobes during painful conditions. However, the three subsequent brain imaging studies of pain published in the early 1990s using PET (Talbot *et al.*, 1991; Jones *et al.*, 1991) and single photon emission computed tomography (SPECT) (Apkarian *et al.*, 1992) have produced inconsistent results, specifically regarding the role of S1 in pain processing (refer to section 1.1.2.4.1). Since then, this cortical structure and its relation to pain processing has remained the subject of debate as inconsistent findings continue to be reported among the numerous brain imaging studies. However, given the considerable differences in methodological approach among the different research groups, it is not surprising that discrepancies are present among all the studies.

In addition, most of the brain imaging studies done in the past have mainly addressed the issue of the spatial location of S1 activation sites. Studies have seldom been directed towards exploring the temporal aspect of the activation, and the possible underlying physiological attributes of the physical and perceptual aspects of the stimuli in relation to the observed activation in this particular region of the brain.

The resolution of the imaging system becomes critical when attempting to assign activity to areas of the cortex in close spatial proximity. The majority of previous pain imaging studies were performed with PET, which has a relatively low spatial and temporal resolution. The high spatial and temporal sensitivity offered by fMRI not only allow a more precise identification of the cortical regions activated during the application of a specific stimuli, but also permit assessment of the dynamic behaviour of neural populations over time. Using this powerful imaging tool, this research project investigates the functional significance of S1 in pain processing by performing a temporal assessment of S1 cortical activity in relation to painful and non-painful tactile stimulations. Particular emphasis was placed on verifying whether differences in the activity of S1 under these two conditions could be reflected in the time course of the activation within this cortical region, and if so, could that difference in time-course be explained by differences in the physical or the perceptual characteristics of the stimuli?

The same set of data used in this study has also been analysed to address issues concerning the inter and intra subject differences in pain- and tactile-related cortical activation. Results of such analysis are presented in a thesis entitled ***"Pain and Tactile Evoked Activations in Cerebral Cortex: Between and Within Subject Comparisons Using fMRI"*** by Brian J. Ha (Ha, 2000).

Chapter 2

METHODS

2.1 SUBJECTS

Six normal volunteers (four males, two females, age 23 to 47) participated in the study. However, data from two subjects were excluded due to the presence of large motion artifacts. The subjects were instructed in the basic design of the experiment and were fully aware of the duration and intensity of pain that they would need to endure. The study was approved by the Montreal Neurological Institute and Hospital (MNI) Research Ethics Committee, and written informed consent was obtained from each subject prior to each study session.

2.2 STIMULI

Two types of somatosensory stimuli were used in the present study:

Thermal. Thermal stimuli consisted of noxious (45-46°C) and neutral (35-36°C) stimulation applied to the inner left calf via contact thermodes (9-cm^2 aluminum blocks connected to recirculating water baths under thermostatic control).

These temperatures were chosen prior to imaging experiments during a preliminary session in which subjects were acclimated to thermal stimuli and trained to rate both their pain intensity and unpleasantness using five-point verbal scales in which "zero" represented no pain sensation or no pain unpleasantness, while "five" represented the most intense pain sensation, or the most unpleasantness pain that the subject would tolerate. For each subject, the painful thermal temperature was determined as that which produced a moderate but tolerable level of pain (a rating of four out of five on the pain-intensity scale). The temperature of the neutral stimulus was chosen as that which produced only a minimal sensation of warmth. During imaging sessions, the thermal stimuli (noxious heat and neutral warmth) were applied in an alternating cyclic fashion (by the circulating water bathes, described below) to the skin during stimulation periods and withdrawn during the inter-stimulus interval. The presentation of the neutral thermal stimuli served as a control for tactile and cognitive aspects fo the phasic stimulation paradigm.

Mechanical. Mechanical stimuli were presented to the same site used for thermal stimulation and consisted of light manual brushing at 2Hz, using a 2-cm wide soft artist's paint brush moving back and forth in a proximal-distal orientation, over a 10-cm region of the skin. The brush stimuli were also presented during the preliminary session in which subjects practiced rating the intensity of the brush using

a similar five-point scale, where zero represented no sensation and five represented very intense, but non-painful sensation. During imaging sessions, the brush stimuli were presented in separate scanning runs, without thermal stimulation; periods of stimulation and rest (inter-stimulus intervals) were identical to those used in the thermal stimulation experiment.

2.3 EXPERIMENTAL PROTOCOL

Each subject participated in three fMRI scanning sessions conducted on different days. Before being placed into the scanner, subjects were instructed to attend to the stimuli, to keep their eyes closed and to restrain themselves from movement as much as possible throughout the imaging session. After being placed in a comfortable position, the head was immobilized with padded ear-muffs to prevent movement. Additional supports, such as a foam headrest and a plastic bar for the bridge of the nose and a bite bar, were sometimes used to further restrict motion. Each scanning session consisted of 5 to 8 functional scanning runs and a high-resolution anatomical scan. During the scanning, thermal and brush stimuli were applied to the left calf on separate runs. Scanning sessions always started with brushing runs followed by the thermal runs to avoid the possible effect of sensitization induced by the noxious stimuli. Thermal runs consisted of 10 cycles of rest, painful heat, rest, and neutral heat stimulation, with each condition lasting 3 complete full-brain scans, ~10 s long. Brushing runs contained

20 cycles of brushing and rest, each with the same duration as that used during the thermal runs. Presentation of both thermal and brush stimuli were synchronized with data acquisition using auditory cues generated by the scanner at the beginning of each full-brain scan sequence.

In order to assess the issue of stimulus reliability and to control for possible stimulus sensitization and/or habituation, subjects were instructed, following each run to rate the intensity and unpleasantness of the stimuli perceived at the beginning and at the end of the run in the manner described previously. Subjects were also asked to rate any discomfort arising from sources other than the stimulus. All ratings were given non-verbally, using the fingers of one hand, to minimize head movement. Separate psychophysical experiments, following the same stimulus paradigms used in fMRI, were also performed after the scanning sessions in order to obtain a continuous rating of both pain and brush perception along the full course of the stimulation. During the psychophysical experiments, ratings were given on-line throughout the stimulus period using a mechanical visual analogue scale (VAS) that allowed the subject to make instantaneous changes in the ratings that were then sampled by the computer at 10 Hz.

2.4 DATA ACQUISITION

Imaging was performed in the McConnell Brain Imaging Center at the

Montreal Neurological Institute using a 1.5 Tesla Siemens Vision scanner with a standard 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 x128). Images were taken in 120 whole-brain volumes (or 'frames') per run (3.36 s/frame, ~7 min /run) with 10 to 13 contiguous axial slices of 7 mm thickness parallel to the AC-PC line (in-plane resolution 2.3 x 2.3 mm), covering the brain from the vertex to the base of the thalamus. High-resolution T1-weighted anatomical scans (TR = 22 ms, TE = 20 ms, flip angle = 30°, FOV = 256 mm) were acquired for all scanning sessions.

2.5 Data Analysis

2.5.1 Statistical Activation Map

Functional data were motion corrected and low-pass filtered with a 6 mm FWHM Gaussian kernel in order to increase the signal-to-noise ratio. The first two frames were excluded in each run since such scans do not represent the steady state of magnetization. Activation maps, comparing painful heat to neutral heat conditions and tactile to rest conditions, were generated using fMRISTAT-MULTISTAT (Worsley *et al.*, 2000) software developed at the MNI. This statistical analysis 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 6

seconds and a standard deviation of 3 seconds timed to coincide with the acquisition of each slice (Lange & Zeger, 1997). Polynomial covariates up to 3 degrees were added to the frame times in the design matrix to compensate for the tendency of the fMRI signal to drift, which in turn causes loss of sensitivity by increasing the standard deviation. The correlation structure was modelled as an autoregressive process of 1 degree to account for temporal correlation, which, if not considered, would result in an inappropriately large t value and inaccurate statistical maps (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, which was 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 order to produce average data across a single session, runs were combined using another linear model for the run effects (as data), weighted inversely by the square of their standard errors. In order to account for variability among the different subjects and study sessions, a random-effects analysis was performed by estimating the ratio of the random-effects variance to the fixed-effects variance (obtained from the individual runs analysis). The ratio was then regularized by spatial smoothing with 15 – 30 mm FWHM Gaussian filters to increase its degrees of freedom, thus

increasing sensitivity. The resulting t statistic images were thresholded ($p = 0.05$) using the minimum given by a Bonferroni correction and random field theory (Worsley *et al.*, 1996).

All images were resampled into stereotaxic space using an automated registration method based on a multiscale, three-dimensional cross-correlation with the average of 305 normal MR scans registered into Talairach space (Collins *et al.*, 1994). Functional and anatomical data were then merged to locate regions of significant activation.

2.5.2 Localization of the Central Sulcus

The central sulcus was identified using two anatomical landmarks (Kido *et al.*, 1980; Sobel *et al.*, 1993). First, on the lateral view of the anatomical scan in the standardized space, the central sulcus was identified as the sulcus immediately posterior to the perpendicular intersection of the superior frontal sulcus (anterior-posterior oriented) and the medial-lateral oriented precentral sulcus. Second, on the midline sagittal plane, the central sulcus was identified as the small sulcus oriented dorsal-ventral on the dorsal surface of cortex, located anterior to the ascending marginal branch of the cingulate sulcus. At the midline, the central sulcus was limited in extent, but a few millimetres lateral to the midline view it was readily identifiable as a deep sulcus.

2.5.3 Construction of S1 ROI

Once the central sulcus was located for each subject, directed searches were performed on identified S1 regions reliably activated by brush and noxious heat stimuli. For each subject, the session demonstrating the strongest significant S1 activation was selected for the purpose of marking the regions of interest (ROIs). S1 ROIs were defined for the two stimulus modalities in each subject as the highest peak of activation within the S1 cortex and the surrounding significant voxels.

2.5.4 Extraction of Time Course

In a second step, the original raw functional data runs (i.e. unanalyzed) of like modality were averaged for individual subjects. The time course of activation was then extracted from these averaged functional runs by using the corresponding ROI as a mask denoting the appropriate S1 region. These data were further averaged to examine the mean time course of activation per stimulus cycle.

Chapter 3

RESULTS

3.1 PSYCHOPHYSICAL RESULTS

3.1.1 Post-Scanning Estimates

In the fMRI session, all subjects rated noxious thermal stimuli as painful (mean rating 4.1 ± 0.1 out of 5 on pain scale), and innocuous brushing stimulations were always rated as moderately intense but non-painful (mean rating 2.0 ± 0.5 out of 5 on non-pain scale). In addition, no significant differences were found between the pain ratings at the beginning and at the end of runs (p = 0.12, paired t-test; Figure 1).

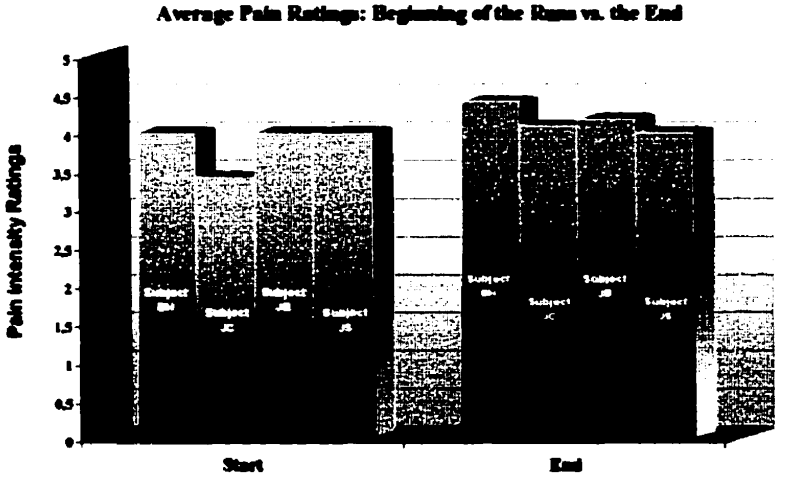

Figure 1. Pain ratings evoked by noxious heat stimuli presented during fMRI scanning. Following each scanning run subjects rated the perceived pain intensity associated with initial and final stimuli presented within that run. All noxious thermal stimuli were rated as painful (4.1 ± 0.1), and no systematic differences in pain ratings were observed within the scanning runs (start vs end ratings, paired *t*-test, p=0.12).

3.1.2 Continuous Ratings

Figure 2 shows the ratings of perceptual responses over time to both noxious heat and brush conditions obtained in a separate psychophysical session using online VAS following the same stimulus paradigm used for fMR scanning. During the heat pain condition, the perception of pain intensity (red) gradually increased over time, reaching a peak only at the end of the stimulation (~10 sec. after the onset of the stimulus), and eventually exceeding the duration of the stimulus (grey dotted line). By contrast, a response delay was not found under the brush condition (blue); its response curve was characterized by a nearly immediate response that remained constant throughout the stimulation period. Comparison of perceptual response to noxious heat and brushing revealed a significant difference in the occurrence of each respective peak, with thermal perception peaking significantly later than the perception of innocuous brushing ($p<0.01$, t-test).

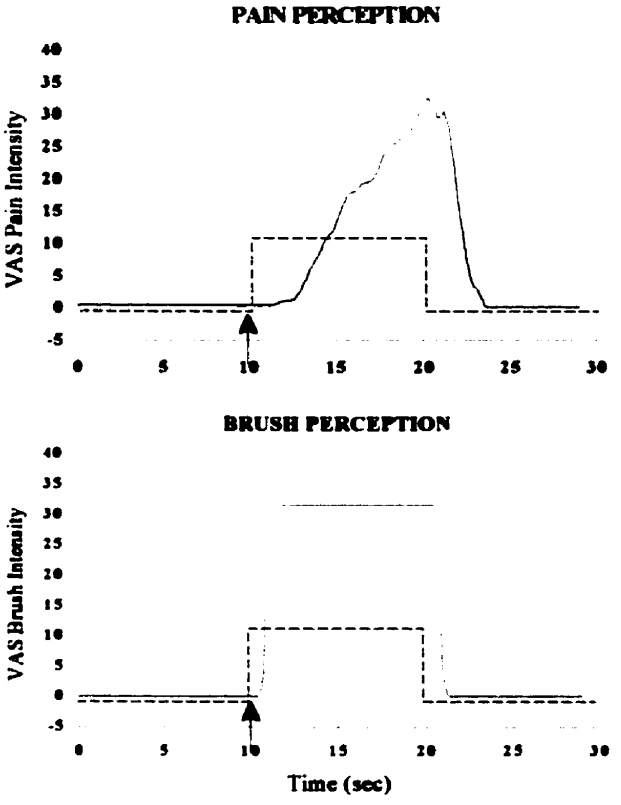

Figure 2. **Continuous VAS intensity ratings evoked by noxious heat and innocuous brushing stimuli. For this single subject, the perception of pain intensity (top, red line) evoked by noxious heat gradually increased over the duration of the stimulus (dashed grey line), reaching the peak only at the end of the stimulation, and eventually exceeding the duration of the stimulus. In contrast, the subject's perception of innocuous mechanical intensity (bottom, blue line) evoked by the brush stimuli showed an on-off pattern–i.e. an immediate response at the onset of the stimulus (indicated by an arrow; dashed grey line) which then remained at the same level throughout the stimulus duration, but returned to the baseline level as soon as the stimulus was withdrawn.**

3.2 PAIN- AND MECHANICAL TACTILE-RELATED S1 ACTIVATION

Single-session analysis revealed locally significant pain- and innocuous brush-related activations within S1 in all four subjects (Figure 3 and 4, Table 2). Sitesof S1 activation lay within anatomically relevant regions for each individual subject (Kido *et al.*, 1980; Sobel *et al.*, 1993). The position of the central sulcus varied across subjects (Figure 3, left), exhibiting 1 to ~4 mm anterior-posterior differences across the medial-lateral extent of the sulcus (mean SD = 3.8; Figure 3, right; Table 1, pp. 36).

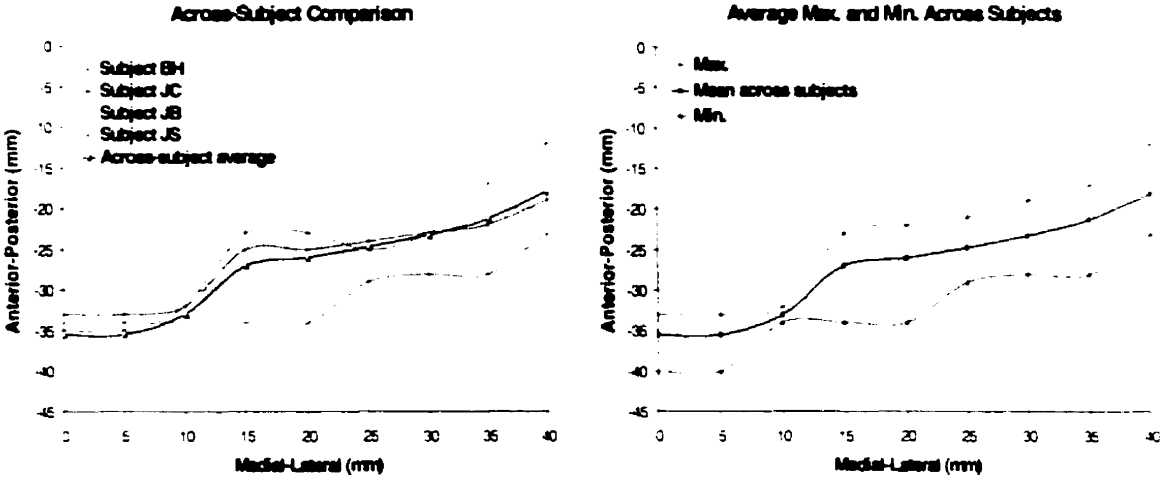

Figure 3. **Anatomical variability of the central sulcus among subjects.** Tag points were taken along the medial-lateral extent of the central sulcus and plotted against the anterior-posterior coordinates in each subject to demonstrate differences in the position of the central sulcus across subjects (left). In relation to the average, the anatomical variation ranged between 1 to ~4 mm anterior-posteriorly in the medial-lateral extend (mean SD = 3.8).

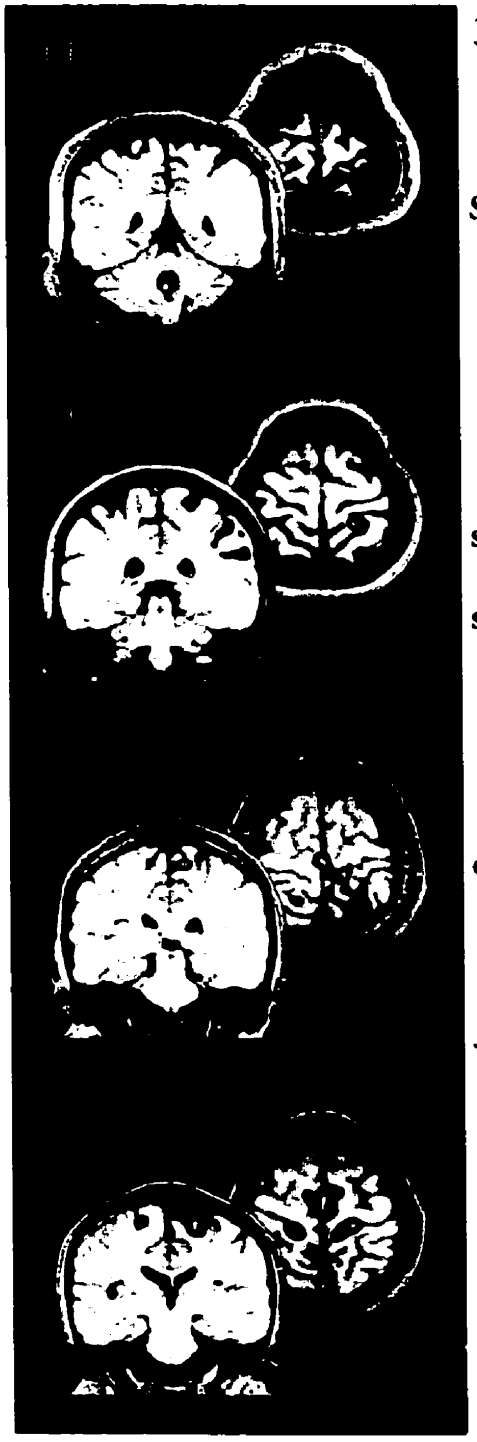

Figure 4. Significant pain-related S1 activation observed in all four subjects. Activation sites are found within anatomically relevant regions for each individual subject. While most of the activation sites are contralateral, one subject (SJ) showed bilateral activation. Variability of the central sulcus among the subjects is also observed. Coordinates are expressed in millimetres.

3.2.1 S1 Pain-Related Activation

Three of the four subjects demonstrated S1 activation strictly contralateral to the stimulated body site, while one subject showed bilateral S1 activity (Figure 4, Table 2a). The majority of the contralateral S1 activation was detected on the surface of the post-central gyrus, except for one subject (Figure 4– JB), whose S1 activation was observed deep within the sulcus. The observed bilateral activity was also found deep within the central sulcus (Figure 4– JS).

3.2.1.1 *Other Cortical or Subcortical Regions of Activation*

Significant pain-related activity was also found in the secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insular cortex (IC) and supplementary motor area (SMA). Basal ganglia were also consistently found to be activated in all subjects (not shown; this study focusses on the S1 cortex).

3.2.2 S1 Mechanical Brush-Related Activations

Light mechanical brushing also produced significant activity within contralateral S1 in all subjects (Figure 5, Table 2b). The brush-evoked S1 activation was mainly found on the surface of S1, and in one subject, the area of activation is extended farther down into the cortex (Figure 5– JS). However, the same stimulation did not evoke a bilateral activation.

3.2.2.1 Other Cortical or Subcortical Regions of Activation

Bilateral S2 activation was also observed in all subjects. A number of other cortical areas were also activated, however these were not consistent across subjects. No subcortical regions of activation were found in any subject (data not shown; the present study focusses on the S1 cortex).

Figure 5. **Significant brush-related S1 activation observed in all four subjects. Single session analysis of responses to brush stimuli revealed significant contralateral S1 activation in all subjects. Coordinates are expressed in millimetres.**

Table 1. Anterior-Posterior Anatomical variability across subjects in the medial-lateral extent

M-L tag points (mm)	A-P variations (mm)			
	Subject BH	Subject JC	Subject JB	Subject JS
0	-34	-33	-40	-35
5	-34	-33	-40	-35
10	-34	-32	-34	-32
15	-34	-25	-26	-23
20	-34	-25	-22	-23
25	-29	-24	-24	-25
30	-28	-23	-19	-23
35	-28	-22	-18	-17
40	-23	-19	-18	-12

Tag points were taken along the medial-lateral (M-L ; positive = right) extend of the central sulcus to examine its variation in the anterior-posterior (A-P relative to the anterior commissure; positive = anterior) plane. Distance is expressed in millimetres.

Table 2. Stereotaxic coordinates and peaks of S1 pain- and brush-related activation

Table 2a. Pain-related S1 activation sites

Subject	Stereotaxic coordinates (mm)			Local maxima	Local threshold (p = 0.05)
	M-L	A-P	S-I		
HB	8	-46	74	6.0	3.55
CJ	24	-38	68	4.5	3.54
BJ	12	-32	66	7.7	3.57
SJ	20	-24	62	9.5	3.57

Table 2b. Brush-related S1 activation sites

Subject	Stereotaxic coordinates (mm)			Local maxima	Local threshold (p = 0.05)
	M-L	A-P	S-I		
HB	14	-40	74	9.6	3.55
CJ	22	-36	76	7.4	3.55
BJ	22	-34	74	5.9	3.57
SJ	24	-38	72	6.7	3.55

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 Overlap of Activation Site Within S1

A comparison of both pain- and tactile-related activations within S1 cortex revealed a close spatial proximity of activation sites across modalities in three of the four subjects (Figure 6). Although there is variability in location across subjects, activation was found in anatomically relevant positions for each subject.

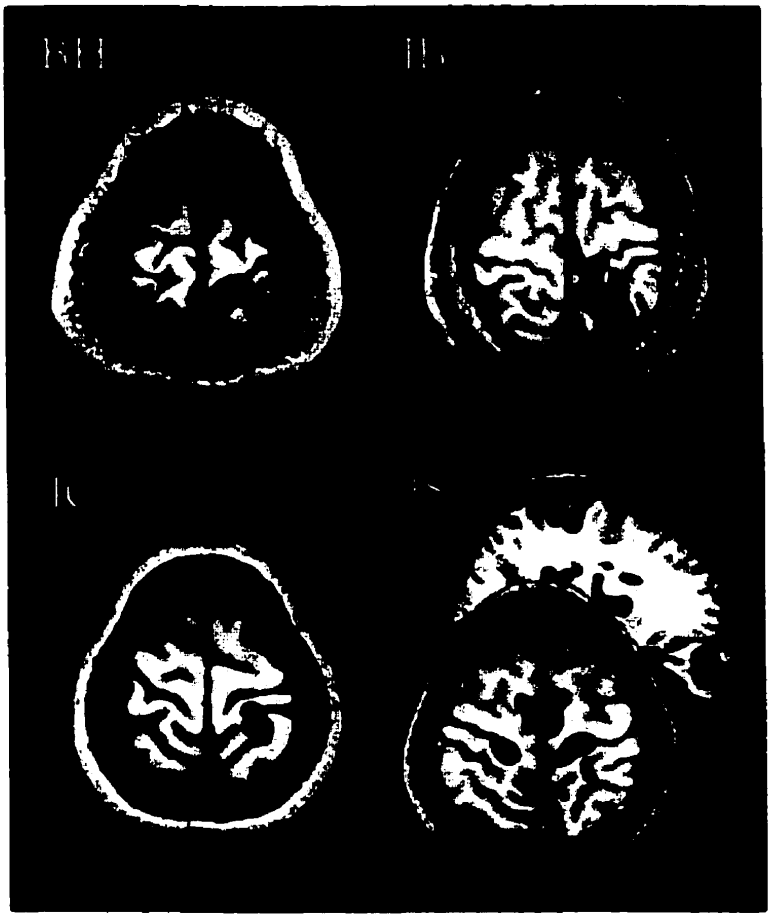

Figure 6. **Comparison of brush- and pain-related S1 activation.** Activity in S1 evoked by brush (blue) and painful heat (red) was observed to be overlapping in three subjects and in close proximity in the fourth (JS). Note also the anatomical variability of the central sulcus across subjects. Coordinates are expressed in millimetres.

3.3 TEMPORAL ANALYSIS OF S1 RESPONSES

The temporal properties of the fMRI response within the S1 region of interest were further analysed in order to investigate possible differences in S1 activation in relation to both physical and perceptual characteristics of the noxious thermal and innocuous mechanical stimuli.

3.3.1 Average Single Session Analysis

Analysis of the S1 ROI time series extracted from the average raw data of the session showed that S1 activations evoked by noxious heat and brushing could be differentiated by the time course of activation relative to the onset of stimulation. Figure 7 shows the ROIs and the corresponding time course extracted from the data for each subject. The time course revealed a consistent pattern of activation-related curves in each brushing and painful heat condition.

3.3.1.1 S1 Time Course Evoked by Light Mechanical Stimulation

The time course of brush-evoked responses (blue) in the S1 region revealed a single peak of activity approximately 10 sec. after the onset of the stimulus (indicated by the arrow), which rapidly diminished upon stimulus withdrawal. A significant difference was found when comparing the average peak response of brushing to the rest condition ($p < 0.05$, $\bar{x}$ activation brushing $=770.154$; $\bar{x}$ activation rest $=768.235$,

repeated measures ANOVA).

3.3.1.2 *S1 Time Course Evoked by Thermal Stimulation*

In contrast to the tactile fMRI time series, the S1 response to heat pain (red) was characterized by a double-peaked time curve, where the maximum response (the second peak) was consistently observed ~17 sec. after the onset of the stimulus (indicated by the arrow), parallelling the perception of increasing pain intensity that exceeds stimulus duration. Note that the minor peak in the heat pain response closely matched the peak of the brush-evoked response curve. Comparison of the average peaks revealed that response to painful heat was significantly greater than responses to neutral heat and to the rest condition ($p < 0.05$, $\bar{x}$ noxious peak response = 810.306; $\bar{x}$ neutral peak response = 801.898; $\bar{x}$ rest = 801.976, repeated measures ANOVA).

Further comparison was made between the peaks in the time course of noxious heat and brush stimuli in order to assess the significance of the time delay in the occurrence of the peaks as revealed by each respective time course. The result indicates that the maximum peak of the average response to the noxious heat stimulus occurred at a significantly later time than the average response to the brushing stimulus ($t_{(54)} = -5.809$, $p < 0.001$, linear model).

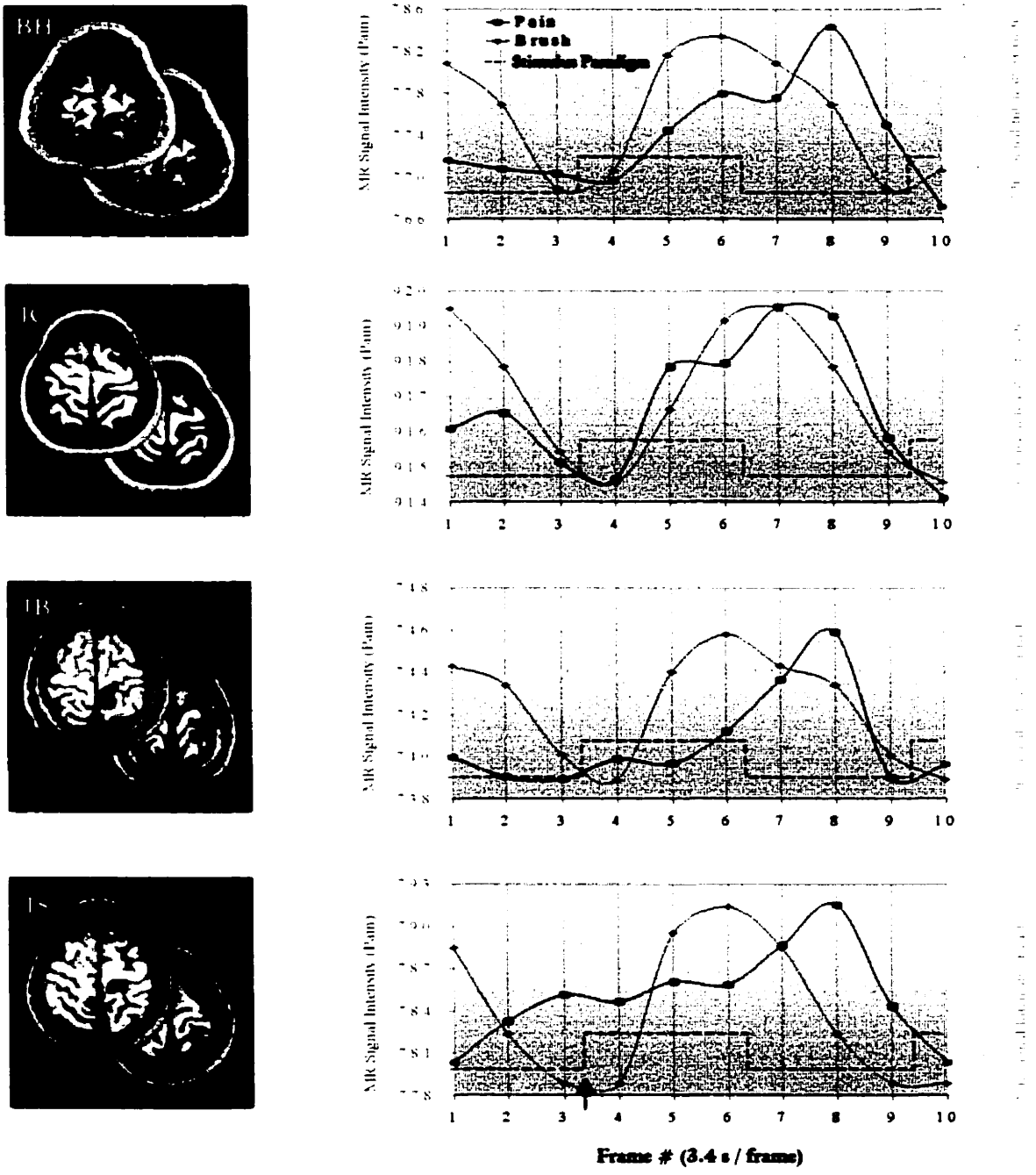

Figure 7. **Time course analysis of S1 activation per stimulus cycle (right) evoked by noxious heat (red) and brush (blue) extracted from selected ROIs in each subject (left) revealed a pattern of curves consistent for each type of stimulus across all subjects.** The time course evoked by brushing the skin produced a single peak that is consistently observed ~10 s after the onset of the stimulation (indicated by the arrow), which rapidly diminished when brushing ceased. Conversely, S1 time series of painful stimulation is characterized by a biphasic time curve where the maximum peak shows a prolonged response consistently ~17 s after the onset of the stimulation, exceeding the stimulus duration. Such observation parallels the perceptual consequence of painful stimulation reported in psychophysical studies. The minor peak, on the other hand, resembles the peak of the brush-evoked response. The time delay between the maximum peak of the heat pain response and the peak response of brush is statistically significant ($p<0.001$, linear model).

3.3.1.3 *Noxious Vs. Neutral heat*

Comparison was also made, for each subject, between the mean time course responses to noxious and neutral heat stimuli in order to assess for the possible contribution of a tactile component of the thermal stimulation (Figure 8). The time course of the response to the neutral stimulus is characterized by a single peak observed at ~7 sec after the onset of the stimulation, similar to that of the minor peak observed in the response to the noxious heat stimulus. In addition, the amplitude of signal intensity of the neutral stimulus is significantly lower than that of noxious stimulus ($p < 0.05$, paired t-test).

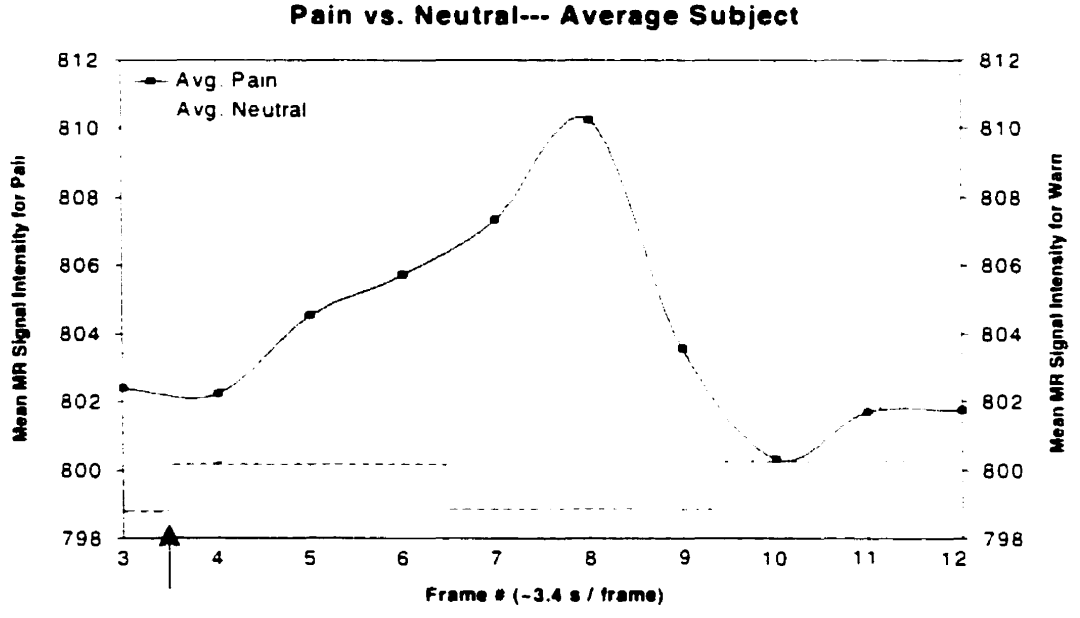

Figure 8. **Comparison of noxious and neutral heat time course shows two distinct temporal profiles.** The fMRI time course evoked by applying neutral temperature to the skin (orange) has a single peak occurring ~7 sec. after the onset of stimulation (indicated by the arrow). The response is maintained throughout the stimulation period. This peak resembles the first peak of the time course evoked by the painful stimulus (red), suggesting that the observed S1 activation is related to the processing of noxious information, and is not simply due to the physical characteristics of the stimuli.

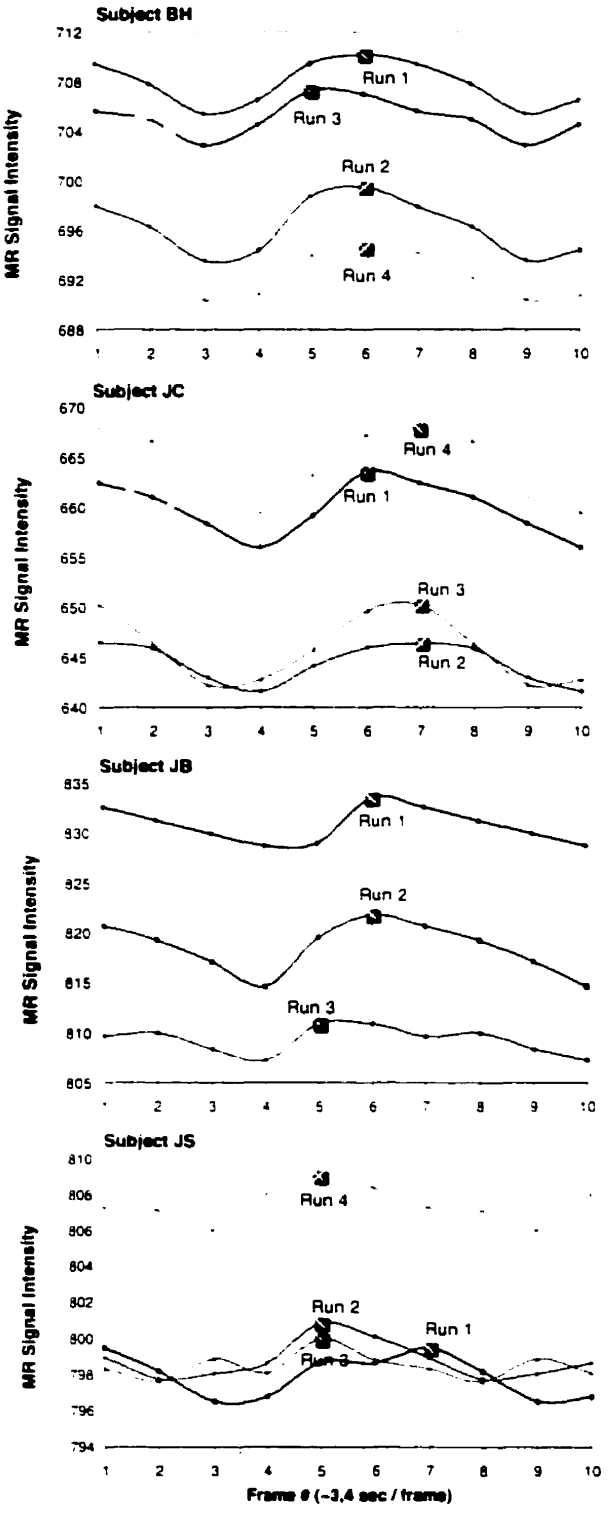

Figure 9. **Within-session analysis of individual runs for brush stimulation.** The responses evoked by innocuous brushing consistently demonstrated a mean peak of activity for each run at ~7 sec. ± 0.3 after the onset of the stimulus, as marked by the orange arrow. No significant differences were found in the time of peak activity across the different sessions ($p > 0.01$ single-factor ANOVA).

3.3.2 Within-Session Analysis of Individual Runs

In order to address the issue of response reliability for each type of stimulation, we further examined responses of each run within the course of a single session for both stimulus modalities (Figure 9 and 10, Table 3 a and b).

3.3.2.1 Individual-Run Analysis for Brushing Stimulus

Individual responses to brushing stimuli from run to run within a single session, revealed consistent mean peak responses across all the runs in all four subjects within their respective sessions (Table 3a). Within a single session, the mean peaks of each subject occurred consistently at ~10 sec. after the onset of the stimulus, with no significant

difference from run to run within the session (Figure 9; refer to Table 3a for the p values and mean peak response for each subject).

3.3.2.2 *Individual Run Analysis for Noxious Heat Stimulus*

Within a single session, individual responses to noxious heat were more variable from run to run than the average data. Nevertheless the peak responses were quite consistent across the runs within a single session (Figure 10; p values for each subject are shown in Table 3b, one-way ANOVA), with the mean peak response occurring at ~17 sec. after the onset of the stimulus. These data are consistent with the post-scanning pain ratings which showed no significant differences in perception.

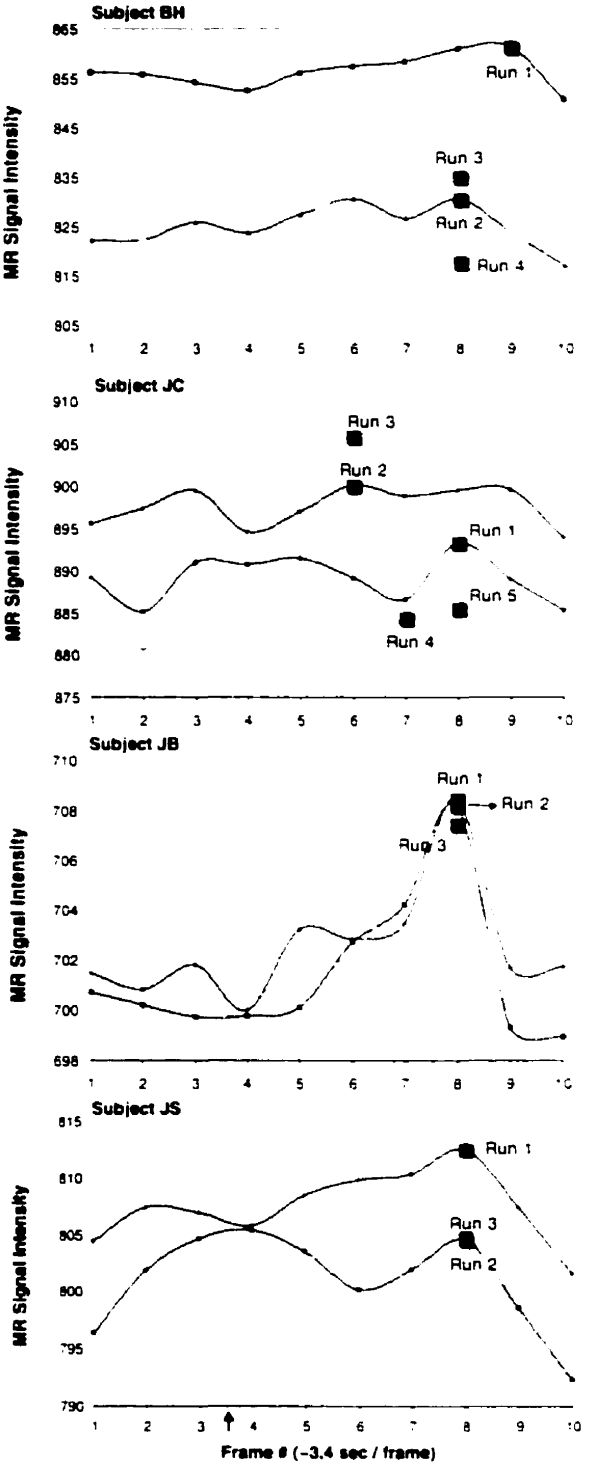

Figure 10. **Within-session analysis of individual runs for heat pain.** The peak responses evoked by heat pain, although more variable than the averaged data, were, nevertheless, quite consistent in all subjects across runs within the single sessions (~15 sec. ± 0.1 after the onset of stimulation, as marked by the blue arrow; $p>0.01$, single-factor ANOVA), suggesting that painful responses were reliable.

Table 3. Mean peak response of individual runs within single session

Table 3a. Mean peak responses for the 20 brush stimuli across individual runs

Subject BH

Run #	Mean peak occurrence (sec.)	Across-run comparison (single-factor ANOVA)
1st	9.52	P = 0.70
2nd	10.03	
3rd	11.05	
4th	11.05	
Average run	*10.41*	

Subject JC

1st	10.37	P = 0.97
2nd	11.22	
3rd	10.54	
4th	10.88	
Average run	*10.75*	

Subject JB

1st	12.58	P = 0.86
2nd	11.56	
3rd	12.24	
Average run	*12.12*	

Subject JS

1st	10.20	P = 0.62
2nd	8.33	
3rd	8.33	
4th	10.38	
Average run	*9.31*	

Mean average peak occurrence for brush across 4 subjects = 10.64 s; no significant difference was found among the averaged peak responses across 4 subjects ($p>0.01$; single-factor ANOVA).

Table 3b. Mean peak responses for the 10 noxious heat stimuli across individual runs

Subject BH

Run #	Mean peak occurrence (sec.)	Across-run comparison (single-factor ANOVA)
1st	16.32	P = 0.16
2nd	13.60	
3rd	15.30	
4th	17.68	
Average run	*15.73*	

Subject JC

1st	17.00	P = 0.12
2nd	17.34	
3rd	17.34	
4th	14.96	
5th	13.26	
Average run	*15.98*	

Subject JB

1st	15.98	P = 0.70
2nd	16.32	
3rd	17.00	
Average run	*16.43*	

Subject JS

1st	15.30	P = 0.94
2nd	15.30	
3rd	15.98	
Average run	*15.53*	

Mean average peak occurrence for pain across 4 subjects = 16.92 s; no significant difference was found among the averaged peak responses across 4 subjects ($p > 0.01$; single-factor ANOVA).

3.4 PERCEPTUAL VS. HEMODYNAMIC RESPONSE

In order to investigate whether differences in the time course across stimulus modalities could be attributed to differences in the perception of the two stimuli, we further compared the perceptual results obtained from the continuous VAS ratings to the fMRI time series under the noxious heat and brushing conditions. The comparison revealed a close temporal relationship between the perceptual response and the blood flow (Figure 11). The occurrence of the peak for the perceptual response and hemodynamic response under both mechanical brushing and noxious thermal conditions is approximately ~7 sec. of difference, suggesting that the fMRI defined activations evoked by these two stimuli were approximately 7sec. following the respective peak perceptual rating— a time difference that corresponds to the hemodynamic delay.

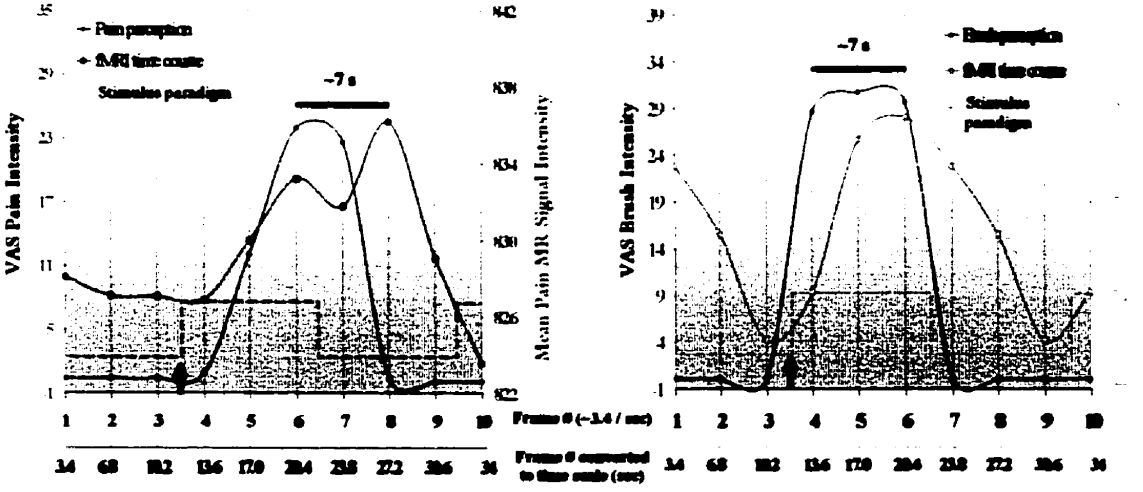

Figure 11. **Temporal comparison of S1-activity and perceived intensity evoked by experimental stimuli. The fMRI defined S1 activations evoked by both noxious heat (left) and innocuous brush (right) occur ~7 sec. later than the corresponding peaks of the perceptual responses. This seven-second difference corresponds to the hemodynamic delay known to exist between neuronal activation and the de-oxyhaemoglobin-dependent fMRI response, thus suggesting that S1 cortical activity evoked by noxious heat and innocuous brush may represent the cortical process underlying the perception of these stimuli.**

Chapter 4

DISCUSSION

The present study uses the temporal feature of BOLD-fMRI in an attempt to address the controversy surrounding the possible role of primary somatosensory cortex in pain perception. Activation of S1 by noxious stimuli has been observed in nearly half of the published human pain imaging studies using PET and in most of the fMRI pain studies, but its occurrence is quite variable (see review by Bushnell *et al.*, 1999) and has at times been attributed to procedural factors related to spatial features of stimulation (Jones *et al.*, 1991), rather than to the perception of pain itself. In addition, the spatial segregation of noxious and innocuous tactile stimuli in S1 cortex has been reported along with substantial overlap or proximity in various brain imaging pain studies (e.g. Coghill *et al.*, 1994; Gelnar *et al.*, 1999).

In search of the potential relevance of S1 activation associated with the different physical and perceptual characteristics of either innocuous tactile or noxious thermal stimulation, the present study examined whether differences in the activity of S1 under these two conditions were reflected in their respective time courses within this

cortical region. To this end, the time courses were compared with the actual perception evoked by those stimuli. The results of this study demonstrated that although the spatial extent of S1 activation evoked by innocuous and noxious stimuli was frequently overlapping and/or indistinguishable, the time course of the activation revealed a temporal signature specific to the perceptual characteristics of each stimulus modality. The following discussion describes: 1) results from the present study in relation to previous findings; 2) possible explanations for the discrepancies found in different studies and the role of S1 cortex in pain processing; 3) technical considerations influencing the design of this study; and 4) possible caveats and directions for future studies.

4.1 COMPARISONS WITH PREVIOUS FINDINGS

4.1.1 Activation Within S1 Cortex[1]

Although there were slight differences in the location of peaks among the four subjects, single-session analysis revealed locally significant pain- and innocuous tactile-related activations within S1. Such observations are consistent with the majority of previously reported findings using PET or fMRI imaging technique (Talbot *et al.*, 1991; Coghill *et al.*, 1994; Davis *et al.*, 1995). In addition, there is a substantial overlap

[1] A more complete and detailed discussion on the results of inter and intra subject analysis of pain and tactile evoked activations in the cortex pertains to the main topic of another thesis (Ha 2000, master's thesis). The present section will only discuss points that are relevant to the topics of this study.

(Figure 6) between the activation sites associated with both noxious heat and innocuous tactile stimulation, as observed by previous reports (e.g. Coghill *et al.*, 1994). It should be noted, however, that the extent of the overlap does not exclude the possibility of separate sites of activation for each type of the stimuli. Previous PET studies lack the fine spatial resolution required to detect distinct S1 cortical regions in response to noxious thermal and mechanical tactile stimuli, and even the present fMRI study has rather low spatial sensitivity (2.3 mm x 2.3 mm) if compared with an imaging technique whose resolution is measured in nanometers. For instance, by using intrinsic optical signal (IOS) imaging, Tommerdahl and colleagues showed distinct cytoarchitectonic areas within the S1 cortex in response to pain and vibrotactile stimuli. Noxious heat was found to evoke intrinsic signal in area 3a, while vibrotactile stimulation evoked activity in areas 3b and 1(Tommerdahl *et al.*, 1996).

4.1.3 Time Course Analysis of S1 Activations

The most prominent difference revealed by the fMRI time course in the S1 response evoked by innocuous tactile and noxious heat stimulation was the extended period of activation associated with the thermal stimuli and the biphasic behaviour of the thermal response (Figure 7).

The prolonged S1 response to noxious heat stimuli, compared to that evoked by innocuous brushing, is consistent with the observed perceptual response patterns to

heat and brushing obtained from continuous VAS psychophysics. Perceptual responses to noxious heat and innocuous tactile stimulation showed that, despite the equal duration of stimulation, the perception of pain intensity increases gradually over time, exceeding stimulus duration, whereas tactile perception closely follows the stimulation (Figure 2). This finding, therefore, suggests that the observed S1 activation is related to the processing of noxious thermal information, and not simply to tactile information effected by skin contact with a thermode. Such observations are similar to results shown in recent studies using intrinsic optical imaging, where nociceptive neurons in area 3a of S1 cortex were found to exhibit slow temporal summation and post-stimulus response persistence after repeated cutaneous heat stimulation, which also parallel the perceptual consequences of the stimulation in humans (Tommerdahl *et al.*, 1996). Their prolonged response resembles a previously described psychophysical phenomenon termed "slow temporal summation", where it was shown that in normal human subjects, the intensity of pain evoked by a brief noxious thermal stimulus increases progressively with sequential stimulus applications presented at rates equal to or greater than 0.3Hz (Price *et al.*, 1977). Although the present study did not adopt a sequential stimulation paradigm, the observed prolonged pain-related response in the time course is nevertheless consonant with the phenomenon of temporal summation observed in previous studies, except that in the present case, it is most probably caused by the longer period of stimulation, rather than by the short pulses used in previous studies. Therefore, such commonality between the present study and previous findings demonstrates that S1 pain-related time course

activity closely follows the perceptual response.

Another temporal characteristic of S1 activity evoked by noxious thermal stimulation was the biphasic nature of the fMRI response. Although it did not appear to be very robust in some of the subjects, this double peak characteristic was present in all four subjects analysed, and statistical comparisons showed that the two peaks were significantly different in time. This observation is consistent with findings reported by a recent fMRI study using a similar type of thermal stimulus. Becerra *et al.* observed a double-peak characteristic associated with painful heat (46 °C) in the fMRI time course during the first two stimulations. Only the second peak remained in the subsequent 3rd and 4th stimulation in all regions of the cortex, including S1. In contrast, only the first peak was observed under neutral heat (40 °C) condition, suggesting that the second peak of the pair may represent painful sensation because it is only seen in the 46 °C (Becerra *et al.*, 1999). A close examination of the time course of neutral stimulus in the present study revealed a single peak that occurred at ~ 7 s after the onset of stimulation, which is similar to the minor peak observed in the time course of the pain-related S1 activity, but with lower signal intensity (Figure 8). Thus, results from the present study are in agreement with previous findings and further strengthen the conclusion that the observed S1 activation is related to the processing of noxious stimulation and is not simply due to the physical application of the thermode to the skin.

The double-peak characteristic and prolonged time course of S1 activity evoked by the 9-second noxious thermal stimulus is also consistent with the general perception of "first pain" and "second pain" reported during these experiments, namely, an initial recognition of a painful quality, followed by an increase in pain intensity over the duration of stimulation (Lewis & Pochin, 1937; Bishop & Landau, 1958). Assessments of the subjects' latencies for detecting painful stimuli have shown that the two pain sensations are subserved by separate peripheral afferent fibres with different transmission velocities, i.e., the fast-conducting Aδ myelinated and the relatively slower unmyelinated C-fibers, respectively (Lewis & Pochin, 1937; Campbell & Lamotte, 1983). In the present study, the early peak of pain-evoked activity approximates that observed with innocuous brushing, thus it may represent a response to the mechanical application of the thermode. Nevertheless, it does not rule out the possibility of representing the thermal component of the heat pain stimulus, as observed in the Becerra's study (Becerra *et al.*, 1999), where only the first peak was observed under neutral heat (40 °C). In the present study, we also noticed that the time course of the neutral temperature (~35 °C) did not show the biphasic characteristic of the noxious heat stimulus, but was represented by a single peak occurring at ~10 sec., i.e., within a similar time frame as that observed in the peak of brushing and the first peak of noxious heat after the onset of the stimulus. Taking such observations into account, the first peak in the present study may suggest the involvement of myelinated fibres, although the 3-sec. resolution of the fMRI paradigm limits identification of specific afferent

contributions to S1 activation. Since the perceptual consequence of C-fibre activation is a much longer duration of pain perception, the second peak of pain-related activation may be related to the slower C-fibre afferents, which are responsible for temporal summation of noxious information observed in second-order nociceptive neurons.

Yet another recent fMRI study performed using a similar type of thermal stimulus has reported different findings in its temporal analysis. By comparing the correlations of different regional cortical activities to the thermal stimulus and the associated pain perception convolved with cortical hemodynamic response function (Cohen, 1997), Apkarian and colleagues (Apkarian *et al.*, 1999) reported that the more posterior regions of the parietal cortex (Brodmann's area 5/7) better reflect the time properties of pain perception, and that the insular cortical activity best reflects the stimulus parameters. However, it should be noted that in that particular study, imaging was performed in the middle third of the brain encompassing different cortical regions including the posterior portion of the frontal cortex and most of the parietal cortex contralateral to the stimulation site, and that the comparisons were made in all the regions activated within this selected area. Thus the results observed could lead to a more generalized interpretation, as opposed to the present study, where a specific region of the brain (S1) was examined given the advantage of spatial resolution provided by the fMRI. In addition, direct comparison of the time profile in S1 under thermal and innocuous tactile stimulations between the Apkarian group and the present study is not

possible since Apkarian *et al.* only presented the time curves in S1 region for the motor task and not for the other two stimulations (vibratory and thermal).

4.1.4 Hemodynamic Response Vs. Perception

A comparison of perceptual and hemodynamic response of fMRI revealed a close temporal relation between pain perception and blood flow. This finding also suggests that the S1 activation observed under painful stimulation is related to the nociceptive component of the stimuli. The results indicated that the occurrence of the peak in the perceptual response and hemodynamic response differed by approximately ~7 seconds. A similar observation was found under innocuous tactile stimulation (Figure 11). In other words, the fMRI defined activations evoked by the innocuous tactile and noxious thermal stimulation followed the peak perceptual response by approximately 7sec.— a time difference that corresponds to the hemodynamic delay. Studies have indicated that hemodynamic changes occur relatively more slowly than neuronal activity or psychophysical responses, by showing that the length of time from the onset of stimulus to reach 90% peak BOLD response requires about 5 to 8 seconds, and that the time from the cessation of stimulus to 10% above baseline response is about 5 to 9 seconds (Bandettini *et al.*, 1995). Therefore, the observed time difference between the fMR time curve and the perceptual response may well be accounted for by the time lag of MR signal. In addition, the initial analysis, based on which the activation-related ROIs were chosen, assumed the same hemodynamic delay of 6 sec. for each of the

stimulus conditions. In spite of that assumption, the time curve still showed a substantially longer delay in the peak response evoked by the noxious heat stimuli, suggesting that the observed time course patterns are related to the S1 cortical activity evoked by both brush and noxious heat stimuli.

The observed temporal link between the hemodynamic response and the perceptual response reaffirms the significant difference between the stimulus property and the actual perception occurring at cortical level, and thus provides evidence for the involvement of S1 in both pain and innocuous tactile processing.

4.2 CONCLUSION

4.2.1 Discrepancies Among the Studies: Possible Explanations

Although a major proportion of human brain imaging studies have shown S1 activity in response to painful stimuli, inconsistent results have left the topic open to ongoing debate. In fact, 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 the different types of painful stimuli. Data in these previous studies may also be influenced by factors such as different methodological, instrumental and analytical approaches. For instance, the experimental stimuli vary considerably in terms of the type, duration and sites of application (see tables in appendix A). The types of stimuli,

which all differ in terms of intensity and quality, include chemical irritants and electrical shocks as well as hot thermodes and cold pressor tests. Moreover, subject populations range from normal subjects to patients with migraines, neuropathic pain, idiopathic pain, cancer and post stroke pain. In addition, the recording and analysis techniques as well as the types of instruments employed vary between laboratories. All these variables may cause discrepancies among the results of different studies especially when the sensitivity of the scanner's resolution and different thresholds for reporting statistically significant results are taken into account.

Instructions to subjects prior to scanning also vary among studies. Differences in experimental paradigms may result in varying cognitive states among subjects which could differentially influence S1, and thus contribute to discrepant results across studies. For example, Ha and colleagues noted remarkable differences in the extent and strength of pain-related cortical activation within a single subject across different scanning sessions. The strength of the response varied in relation to the subject's understanding of the instructions regarding his/her attention to and rating of the test stimuli (Ha, 2000).

Last but not least, studies have shown that there is great variability in the position of the central sulcus across different human brains and between the two hemispheres (Cunningham, 1892; Campbell, 1905). Since S1 cortex comprises the

portion immediately after the central sulcus (region of post-central gyrus), the differences in the location of S1 activation are most likely to be attributed to anatomical variability among the subjects. It has been hypothesized that this factor may further contribute to the negative findings in S1 activation reported in some of the previous studies using PET, which requires the averaging of multiple subjects and data smoothing in order to increase the signal to noise ratio (see Bushnell *et al.*, 1999). Since painful stimulation often produces a well-localized activation within S1 cortex, most probably due to its somatotopic arrangement (Lamour *et al.*, 1983; Koltzenburg *et al.*, 1993), such focal activation may be degraded with data averaging and a high degree of smoothing (Bushnell *et al.*, 1999). This hypothesis was confirmed in a different study originating from our laboratory using the same fMRI data. Averaging data across all subjects and applying the blurring kernel analogous to PET (~14 mm) to the fMRI data set, Ha and colleagues (Ha, 2000, master's thesis) demonstrated that significant sites of activation, especially S1, had disappeared. The high degree of anatomical variability in this post-central gyrus region may degrade the focal signal associated with painful stimulation when data are averaged across subjects and smoothed using a large blurring kernel, thus rendering inconclusive results reported in earlier studies using PET.

4.2.2 Functional Significance of S1 in Pain Perception

Based on all the evidence available from anatomical, neurophysiological and brain imaging studies, it is now clear that S1 cortex is involved in the processing of

painful information. Results from the present study reveal that innocuous and painful stimuli have distinct temporal response properties. They also indicate that differences in the perception of these stimuli over time can be reflected by their temporal differences in S1 activation. Insofar as the results concur with results reported in previous neurophysiological and psychophysical studies, this study reinforces the role of S1 in the sensory-discriminative aspect of pain perception.

In addition, a considerable amount of evidence indicates that S1 activations are highly susceptible to cognitive manipulations such as attention and hypnotic induction. It has been shown that 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). Hypnotic inductions that specifically alter perceived pain intensity modulate the activity in S1 (Hofbauer *et al.*, 1998), whereas suggestions directed toward changing the unpleasantness of the pain without altering the intensity had no effect on pain-related activity in S1 (Rainville *et al.*, 1997). Thus, the finding that S1 is modifiable by attention or hypnosis provides further support for the role of S1 in pain perception: if a brain region responding to noxious stimuli does not show changes in activity in accordance with cognitive factors that alter pain perception, then it is unlikely to contribute in a substantial way to the perception of pain.

Some evidence suggests that nociceptive input to S1 may also serve to

modulate tactile perception in S1 cortex by means of inhibition, as proposed in the "touch gate" theory (Apkarian *et al.*, 1992; Apkarian *et al.*, 1994). Similarly, intrinsic optical imaging studies report data that are in agreement with this proposal by showing the presence of inhibitory interaction between areas 3a, 3b and 1 of the S1 cortex in response to painful and vibrotactile stimuli (Tommerdahl *et al.*, 1996; Tommerdahl *et al.*, 1998). These studies found that while the presence of noxious heat evoked an intrinsic signal in area 3a, a reduced optical response in area 1 and 3b evoked by low-threshold mechanical stimulation during noxious stimulation was observed, which might be attributed to the suppression/inhibition of the neuronal activity in these areas. Such findings suggest that S1 activation may be related to a modulation of touch sensation that is proportional to pain perception, but it may not be necessary for the actual perception of pain itself, as evidenced by the continued perception of pain after this area is lesioned (e.g., Head & Holmes, 1911). A potential role for S1 nociceptive activity in the modulation of non painful cutaneous sensation does not rule out or preclude a role for this structure in sensory aspects of pain perception. In conclusion, all the available lines of evidence imply that S1 may be functionally segregated to participate in both the processing and modulation of painful and non painful somatosensory sensations.

4.3 TECHNICAL CONSIDERATIONS

4.3.1 Extraction of Time Course from Single Session

Most imaging studies using PET and fMRI have presented results from data averaged across a group of subjects or a series of scans /runs within a subject. However, as discussed earlier, possible confounding variables such as the varying cognitive state of the subject across the different scanning sessions may result in the differential S1 activation observed during each individual session. Therefore, for each subject, the current study examined the time course of data from a session that showed the strongest S1 activation under noxious thermal and brush conditions, in order to account for the issue of variability across different scanning sessions within a subject.

4.3.2 ROI Analysis

fMRI offers the advantage of high spatial resolution that reliably detects relatively small activated areas in the brain. Therefore, the present study confined the search area specifically to S1 cortex, and examined the time course of pain- and innocuous brushing-related activity in this particular region by assigning an S1 ROI for each stimulus modality in each subject (see Method). In addition, the present investigation did not adopt an *a priori* approach to examining the time course of S1 activation under both painful thermal and innocuous brush conditions. The initial analysis model did not assume any difference in the temporal response to the two types

of stimuli, i.e., we did not look specifically for the extended time period of pain-related S1 activations. This approach was taken to eliminate the possibility of adding a further confounding bias to the analysis.

4.3.3 Response Reliability

Repetitive noxious stimuli are likely to cause sensitization of peripheral afferents (Fitzgerald & Lynn, 1977; Meyer & Campbell, 1981). A recent fMRI study (Becerra *et al.*, 1999) using a similar thermal stimulus (41° C -warm; 46° C -noxious heat) applied to the dorsum of the hand showed a significant signal attenuation occurring in the last two stimuli in response to the noxious thermal stimulus in all cortical regions, including S1, possibly due to the extended period of stimulation. The present study took such issues into consideration by starting painful scans with a rest condition, under which no stimulus was applied, followed by the application of noxious heat for a duration of ~10 sec. The painful stimulus was given at an interval of every ~30 sec. with rest and neutral heat alternating in between. This paradigm design facilitated a reliable response to the stimulation, with little habituation; the ten painful stimulus cycles in which painful stimuli constantly elicited peak response ~17sec. after the onset of stimulus across all the runs within a single session in all subjects. This observation directly relates to the subjects' confirmation of the pain ratings at the end of each run, in which the early and late stimuli were rated at about the same intensity of pain.

4.3 LIMITATIONS

One disadvantage of the current study was the lack of more sensitive and precise on-line psychophysical measurements of subjects' perception. A reliable measure of pain perception not only permits identification of possible sources of variability, but also provides for a direct correlation study with the imaging data. The present study did not opt to use continuous ratings during the scan in order to eliminate possible motor and cognitive influence. While a recent study using fMRI and online rating has suggested that such an application is not a serious practical concern (Davis *et al.*, 1998a), future studies that employ online rating methods with a design that is compatible with the fMRI scanner will help clarify the effects of perceptual differences on neuronal activation and allow a more precise statistical comparison to be made.

The stimulus equipment presented another limitation to the present study. Thermal stimuli were delivered via a pair of non-Peltier MR compatible thermodes at fixed temperatures, and temperature adjustments were made only between runs, since fine monitoring during the scans was not possible. In addition, thermal stimuli were applied manually to the leg region by the experimenters, rendering the timing and duration of the stimulation imprecise. However, the possible human error in timing (less than one second) was very small compared with the 10-second stimuli and the relatively long temporal resolution (3-second acquisition time for a single brain volume)

of the fMRI. Future studies employing an fMRI-compatible, computer-controlled Peltier thermode that allows synchronization of the stimulus paradigm with the MR signal will help eliminate much of the variability in the timing and duration of thermal stimulation.

Although fMRI provides higher spatial and temporal sensitivity than the conventional PET imaging technique, some limitations inherent in the adopted fMRI technique must also be underlined. The three-second temporal resolution used in the current study was not optimal for further investigation of the particular fibers involved in the transmission of noxious and innocuous tactile information.

Finally, it should also be noticed that in all the brain imaging studies, statistical analysis is employed to *suggest* an involvement, by correlating the stimulus and the activation in a certain cortical region. It cannot, however, *prove* a cause-and-effect involvement in pain perception. Any activity that follows the perception of pain could be directly involved in some reaction that is directly related to pain perception. For example, activity in the motor cortex might follow the perception of pain because the more it hurts, the harder and faster the animal withdraws from the noxious stimulus. Thus, precautions should be taken when interpreting results in brain imaging studies, especially when the subject concerns the multidimensional pain experience.

4.4 FUTURE DIRECTIONS

fMRI provides higher spatial and temporal sensitivity than conventional PET techniques, allowing researchers to examine the dynamic behaviour of neural populations over time, and the different response pattern of adjacent cortical networks in individual subjects (Cohen & Bookheimer, 1994). Individual-based analysis, which does not require extensive spatial smoothing, also permits the quantification of activated areas and facilitates comparisons with psychophysical data. Although such features have allowed the present investigation to examine the time profile of possible brain processing mechanisms of painful and innocuous tactile stimuli, future studies will still be required in order to identify the specific nerve fibers that subserve these sensations. An imaging technique with an even higher temporal and spatial sensitivity (e.g., an fMRI scanner at higher magnetic strength) or an imaging parameter that involves smaller scan volumes, such as specifically scanning only S1 region might achieve this objective. Concentrating on only a few slices, and specifically altering the stimulation onset relative to the particular slice acquisition could probably allow a time resolution of only a few hundred milliseconds as compared to ~3 to 4 sec. with whole brain volume acquisition, therefore allowing more detailed temporal examination and analysis.

The only ROI investigated in the present study was the S1 cortex. However, other areas such as the secondary somatosensory cortex (S2), the anterior cingulate

cortex (ACC) and the insular cortex (IC), are also known to be reliably activated by a painful stimulus. Particularly, ACC and IC have been shown to participate in the affective-motivational aspect of pain experience (e.g. Rainville *et al.*, 1997). Future study concerning the time course of these areas and the way it compares with the S1 time profile (sensory-discriminative) would be helpful in clarifying the myth about cortical processing of pain.

Last but not least, given the characteristics of the temporal properties of painful stimuli revealed by the fMRI time course, it would be of great interest to examine the same time profile in patients suffering from congenital insensitivity to pain. These patients are born without the ability to feel pain, mostly due to the absence or damage of the nociceptive C afferents, or due to the abnormality of the large afferent fibers (Comings & Amronin, 1974). However, since this disease occurs at a relatively low incidence in the general population, alternative measurements could be assessed by replicating the condition via fibre blockade by means of pressure or anesthetics (Torebjork & Hallin, 1973). In this way researchers could selectively alter the Aδ and C-fibre responses, since Aδ fibres are known to fatigue faster with repetitive stimulation, therefore leaving only C-fibres responding at the end, since they, in contrast to the Aδ fibres, do not habituate but sensitize upon repetitive stimulation. Such response properties provide a way of carrying out a closer and more detailed examination of the fibre types involved in the biphasic response observed in the time course. Future

research conducted in that area could bring significant advances in our knowledge and understanding of the complex experience of pain.

APPENDIX A

TABLE OF COMPARISON AMONG DIFFERENT BRAIN IMAGING STUDIES

I. fMRI Pain Studies

II. PET and Other Brain Imaging Studies of Pain

Appendix A. Comparison of brain imaging studies of pain

I. fMRI Pain Studies

Study	Stimulation	Scanning parameters	Analysis	S1
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 = 45E, FOV = 30 x 22 cm and 48 x 30 cm, matrix = 256 x 128	*t*-test, individual subject analysis (n = 6)	✔
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 = 45E, FOV = 48 x 24 cm, matrix = 256 x 128	*t*-test and correlation, individual subject analysis (n = 10)	
Davis *et al.*, 1998b	noxious thermal – hand, 2EC (40 s) and 47.5EC (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)	
Davis *et al.*, 1998a	noxious thermal – hand, 2EC (1 s) and 47.5EC (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)	
Oshuro *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 60E, FOV = 20 x 40 cm, matrix = 64 x 128	correlation (MRVISION), (n = ?)	✔
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 = 40E, matrix = 128 x 128	correlation, individual subject analysis? (n = 10)	
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 = 40E, FOV = 230 245 mm, matrix = 128 x 128	correlation, individual subject analysis (n = 24)	✔
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)	✔
Berman *et al.*, 1998	noxious thermal – hand and foot, 0.2EC (2 s) and 55.5EC (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 = 60E	*z*, individual subject analysis (n = 8)	✔
Becerra *et al.*, 1999	noxious thermal – hand, 46EC (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 = 90E	Kolmogorov-Smirnov, individual and multisubject analysis (n = 6/group)	✔

Apkarian *et al* , 1999	noxious thermal hand, temperature above pain threshold (35 s), heated surface	1 5 T, surface coil, EPI, eight 6 mm slices, TR = 3 5 s, TE 60 ms, flip angle = 90E, FOV = 40 x 20 cm, matrix = 256 x 128	time course analysis, multiple subject analysis (n = 10)	✔
Gelnar *et al* , 1999	noxious thermal finger, 45C (35 s), thermodes	1 5 T, surface coil, EPI, eight 6 mm coronal slices, TR = 3 5 s, TE = 60 ms, flip angle = 90E, FOV = 40 x 20 cm, matrix = 256 x 128	*t* test, individual and multisubject analysis (n = 9)	✔
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 = 60E, FOV = 40 x 40 cm, matrix = 128 x 128	correlation, individual subject analysis (n = 9)	

C = contralateral, I = ipsilateral, B = bilateral

II. PET and Other Brain Imaging Studies of Pain

Study	Imaging Technique	Stimulus	Subject	Analysis	S1
Talbot *et al.*, 1991	PET $H_2{}^{15}O$	thermal heat pulses (thermode 1 cm^2), warm– 42 °C, noxious– 49 °C, 6 spots volar forearm, 5 s	Healthy (n = 8)	t-statistic, Z-score thresholding	✔
Jones, *et al.*, 1991	PET $^{15}CO_2$	thermal heat (thermode 2.5 cm x 5 cm), warm– 36.3 °C, non-painful hot– 41.3 °C, noxious– 46.4 °C, dorsal hand, 15 s.	Healthy (n = 6)	t-statistic (SPM[t]) with correction for multiple repeated measures	
Apkarian *et al.*, 1992	SPECT	thermal heat (waterbath), control– 36 °C, noxious– mean temp 46.2 °C, fingers immersion	Healthy (n = 3)	ROI pixel subtraction between stimulus and control, calculation of mean % change and SD for each subtractive image	**Inhibited**
Crawford *et al.*, 1993	PET ^{133}Xe	Tourniquet, ischemic pain	Healthy n = 11	ANOVA, paired t-test	✔
Coghill *et al.*, 1994	PET $H_2{}^{15}O$	thermal heat (thermode 1 cm^2), neutral– 34 °C, noxious– 47 (5 s)-48 °C (1 s), 6 locations ventral surface of the forearm	Healthy n = 9)	substation, t-statistic, Gaussian random field theory (GRAFT)	✔
Di Piero *et al.*, 1994	SPECT ^{133}Xn	thermal (waterbath), cold pressor test, hand immersion	Healthy n = 7	ROI analysis, ANOVA for repeated measures, paired t-test for post-hoc comparison test	✔
Derbyshire *et al.*, 1994	PET $H_2{}^{15}O$	thermal tonic heat (thermide), ramp 25-43°C.	Facial pain n = 6), Healthy (n = 6)	t-statistics, SPM (t) data analysis.	
Rosen *et al.*, 1994	PET $H_2{}^{15}O$	Dobutamine infusion	Angina pain patients n = 12	t-statistics, Z-score.	
Casey *et al.*, 1994	PET $H_2{}^{15}O$	thermal heat pulses (thermode); control– 31.8 °C, innocuous heat– 40 °C, noxious– 50 °C, 6 locations volar forearm, 5 s	Healthy n = 9)	VOI comparisons with Bonferroni correction, t-statistic, Z-score	✔
Hsieh *et al.*, 1995	PET $H_2{}^{15}O$	spontaneous neuropathic pain	Neuropathic pain patients (n = 8)	student t-test, Z-score, directed search.	
Hsieh *et al.*, 1996a	PET $H_2{}^{15}O$	intracutaneous injection of ethanol	Healthy (n = 4)	student t-test, Z-score, directed search.	✔
Weiller *et al.*, 1995	PET $H_2{}^{15}O$	spontaneous migraine pain	Migraine patients (n = 9)	SPM, ANCOVA, t-statistic	
Howland *et al.*, 1995	MEG	Electric finger shock (electrical nerve stimulator)	Healthy (n = 5)	?	✔

Katamura *et al.*, 1995	MEG	Electric finger shock via electrical nerve stimulator	Healthy (n = 5)	?	✔
Craig *et al.*, 1996	PET $H_2{}^{15}O$	thermal (thermal grill), interlaced bars of cool– 20 °C, warm– 40 °C, palm of hand, 1 min.	Healthy (n = 11)	voxel-by-voxel subtraction, t-statistic	✔
Hsieh *et al.*, 1996b	PET $H_2{}^{15}O$	episodic cluster headache by sublingual administration of nitroglycerin.	Cluster headache (n = 7)	student t-test, Z-score max with multiple comparison adjustment	
Casey *et al.*, 1996	PET $H_2{}^{15}O$	thermal (thermode), warm– 40 °C, noxious– 50 °C.	Healthy n = 9)	voxel-by-voxel statistical subtraction analysis (Z-score)	✔ ns
Casey *et al.*, 1996	PET $H_2{}^{15}O$	thermal (waterbath), 6 and 20 °C.	Healthy (n = 9)	voxel-by-voxel statistical subtraction analysis (Z-score)	✔
Vogt *et al.*, 1996	PET $H_2{}^{15}O$	thermal (Peltier thermode 2.5 cm x 1.5 cm), 2 °C below tolerance, dorsal hand, 15 s	Healthy (n = 7)	t-statistic (SPM), analysis of covariance	
Andersson *et al.*, 1997	PET $H_2{}^{15}O$	intracutaneous capsaicin injection, hand of foot	Healthy (n = 6)	linear contrasts estimates of t-values, t-statistic, Z-score	✔
Aziz *et al.*, 1997	PET $H_2{}^{15}O$	esophageal distension (balloon)	Healthy (n = 8)	ANCOVA, t-statistic, z-score	✔
Di Piero *et al.*, 1997	SPECT	thermal (waterbath), cold pressor	Cluster headache n = 7) Healthy (n = 12)	ROI analysis, repeated ANOVA, unpaired Student's t-test and Duncan's multiple range test for post-hoc analysis	✔
Derbyshire *et al.*, 1997	PET $H_2{}^{15}O$	intermittent cutaneous heat pulses (CO_2 laser)– 100 ms, dorsal hand, every 2 s for total of 90 s.	Healthy (n = 12)	subtraction, correlation, SPM {t} data analysis.	✔
Rainville *et al.*, 1997	PET $H_2{}^{15}O$	thermal (waterbath), neutral– 35 °C, noxious 47 °C, hand immersion, 75 s	Healthy (n = 11	t-statistic, regression analysis, ANCOVA	✔
Silverman *et al.*, 1997	PET $H_2{}^{15}O$	rectal distension (balloon)	Patients with IBS (n = 6) Healthy (n = 6)	ROI analysis, SPM 95, t-statistic, Pearson correlation	
Svensson *et al.*, 1997	PET $H_2{}^{15}O$	cutaneous heat pulses (CO_2 laser)– 50 ms, elbow, 0.5 Hz., 100 s	Healthy (n = 11)	VOI analysis, paired t-statistic, Bonferroni correction, Z-score	
Xu *et al.*, 1997	PET $H_2{}^{15}O$	cutaneous heat pulses (CO_2 laser), 60 ms at 0.5 Hz, dorsum of hand or foot.	Healthy (n = 6)	SPM 95	
Derbyshire & Jones 1998	PET $H_2{}^{15}O$	thermal tonic pain via waterbath; painful and non painful temp ?, right hand immersion, 2 min 30 s	Healthy (n = 12)	t-statistic, SPM{t}	
Iadarola *et al.*, 1998	PET $H_2{}^{15}O$	capsaicin (subcutaneous arm injection)	Healthy n = ?	SPM{t}, pixel-by-pixel ANCOVA	✔

May *et al.*, 1998	PET $H_2{}^{15}O$	capsaicin (subcutaneous forehead injection)	Healthy (n = 7)	ANCOVA, general linear model (SPM 96); voxel-to-voxel comparison of stimulus conditions using t-statistic.	
Paulson P E *et al.*, 1998	PET $H_2{}^{15}O$	thermal (thermode 254 mm^2), warm– 40 °C, noxious– 50 °C, 5 s duration.	Healthy (n = 20)	Z-score, VOI analysis; 2-way ANOVA with repeated measure, t-statistic.	
Coghill *et al.*, 1999	PET $H_2{}^{15}O$	graded thermal pain (electrically heated probe, 1 cm diam); neutral– 35 °C, pain threshold– 46 °C, moderate pain 48 °C, substantial pain 50 °C, upper right arm, 6 spots, 5 s	Healthy (n = 16)	voxel-by-voxel multiple regression analyses (NIH-FIDAP); Wilk's Lambda statistic.	✔
Ploner *et al.*, 1999	MEG	nociceptive cutaneous laser (Tm:YAG)– 1ms; for 10-14 s, dorsum of hand	Healthy (n = 7)	goodness of fit	✔
Tolle *et al.*, 1999	PET $H_2{}^{15}O$	heat pulses (thermode, 1.6 x 3.6 cm); neutral– 37 °C, tonic pain– max. 1 °C above threshold, tonic heat– 1 °C below pain threshold, total time 5 min, volar forearm.	Healthy (n = 12)	z-score, Pearson's linear correlations, Fischer transformation to calculate z-values.	
Ploner *et al.*, 2000	MEG	cutaneous laser stimulation (Tm:YAG)– 1 ms, for 10 - 14 s, both hands.	Healthy (n = 6)	goodness of fit, 95 % confidence limits.	✔

ns= not significant; SPECT= single photon-emission computed tomography; MEG= magnetoencephalographic imaging

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
- Hear/Vascular Clip
- Prosthetic Valve
- Metal Prosthesis
- Pregnancy
- Current use of narcotic or other analgesic medication
- Cardiovascular or neurological disease
- Any chronic pain condition (more than 6 months)

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.

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