# CORTICAL PROCESSING OF PAIN PERCEPTION IN HUMANS

# CORTICAL PROCESSING OF PAIN PERCEPTION IN HUMANS: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

By

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# ABSTRACT

There have been numerous studies of pain perception in humans using a variety of brain imaging methods. The majority of the past research has focused on the use of positron emission tomography (PET) as the primary imaging method. The present study examines the cortical mechanisms of pain perception in humans using a recently developed imaging technique called functional magnetic resonance imaging (fMRI). The primary interest in this study concerns how behavioural aspects of pain are reflected by cerebral cortical activity during noxious stimulation. As pain involves a combination of sensory, emotional, and cognitive responses, the extent and degree of activation in cortical areas associated with these responses can be affected. To address this issue, a behavioural experiment was first performed to assess the sensory, emotional, and cognitive components of tonic pain induced by a cold foam-pack (0°C). Subsequently, three subjects from the behavioural study pool participated in the imaging study of pain. In the imaging experiment, a cold foam-pack (0°C) and a non-cold foam-pack were applied to the left hands of these subjects. Activation produced by the noxious stimulus was compared with that produced by the innocuous stimulus. The results revealed inconsistencies in cortical activation among the three subjects and this could be related to each subject's behavioural measures. Individual and experimental variables may also account for the differences in results.

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# INTRODUCTION

Pain is essential for the survival of an organism. Although pain may be frequently associated with unpleasant or agonizing sensations, research in the past several decades has demonstrated that pain involves a network of neural structures which integrate sensory, affective, motivational, attentional, and motor responses to produce behaviours that are aimed at stopping pain immediately (Melzack & Katz, 1992; Jones & Derbyshire, 1996). The participation of the central nervous system (CNS) in pain perception has been of great interest. Studies with animals and humans have yielded a great deal of information on the central anatomical pathways involved in pain (Willis, 1989). However, it remains unclear how the interactions among many physiological and psychological events pertaining to pain takes place.

Recently, with the development of functional imaging devices such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), the study of the central mechanisms of pain perception in living human beings has become possible.

As these techniques are non-invasive, they provide a way of understanding the dynamic activities occurring in the brain during a variety of experimental pain conditions.

The present research was designed as an examination of the brain mechanisms of pain perception in humans. Chapter one reviews the fundamentals of pain anatomy and physiology, and the studies and hypotheses of how the CNS is involved in pain perception. Chapter two presents an experiment examining the behavioural aspects of cold-induced pain in humans. Chapter three extends these results in a brain imaging study of cold-induced pain in a subsample of these subjects.

# 1

# THE BIOLOGICAL BASES OF PAIN

Pain is a complex phenomenon that involves more than the integration of peripheral information from sensory receptors. It is now widely known that pain produces a host of sensory and emotional responses that are the result of cortical processing (Melzack & Katz, 1992). The purpose of the present study is to understand further the cortical mechanism of pain perception in humans using brain imaging technique.

The involvement of the cerebral cortex in pain perception in humans was once a subject of debate. Penfield and Boldrey stimulated 800 cortical locations in the primary motor cortex, and only in 11 of them did the patient use the word "pain" to describe the perceived sensation (Penfield and Boldrey, 1937). The result clearly downplayed the importance of the cortex in pain perception. However, animal studies on pain physiology and numerous clinical cases involving psychosurgery and electrical stimulation in humans have since demonstrated the involvement of certain cortical areas in pain processing, although how these areas integrate normal pain responses has yet to be explored (Jones &

Derbyshire, 1996). Advancements in brain imaging technology in recent years have allowed researchers to examine the relationship between behavioural and central mechanisms of pain, enabling them to draw functional relationships between psychological experiences of pain and cortical regions of interest. However, only a few of these imaging studies include some form of behavioural assessment to characterize those psychological elements associated with noxious stimulation. Therefore, inferences concerning the functions of the activated brain regions associated with noxious stimulation are mostly based on the findings in animal and human physiology research. The current study uses functional magnetic resonance imaging (fMRI) to examine cortical mechanism of cold-induced pain perception in humans. A behavioural assessment of cold-induced tonic pain is also included to aid the interpretation of pain imaging data.

Much of what is known about pain pathways is derived from studies with animals such as monkeys, rats, and cats (Willis, 1989). However, many findings are applicable to humans as well since humans share many biological characteristics with these species (Jones & Derbyshire, 1996).

The anatomical substrates of pain involve the following structures: 1) the peripheral pain system, 2) the central pain pathways, 3) the endogenous pain control system, and 4) the cerebral cortex.

**The Peripheral Pain System**

*Pain receptors and fibers*

Both tactile and noxious signals are conveyed by dorsal root ganglion neurons in the periphery (Jessell & Dodd, 1989). These dorsal root ganglion neurons project afferents to both the periphery and the spinal cord of the CNS to mediate the transmission of sensory information. Some of these neurons transduce tactile information, others convey nociceptive information and are called primary afferent nociceptors (Fields, 1990). Together, these innocuous and nociceptive fibers are called the primary afferent fibers. They are characterized according to their cross-sectional diameter, degree of myelination, and conduction velocity (CV) (Meyer et al, 1994). The tactile sensation is conveyed by the heavily myelinated Aβ fibers which respond to low-intensity mechanical stimulation. Pain arises from stimulation of two types of primary afferent nociceptors: 1) Aδ mechano-heat nociceptors (AMHs) which have thinly myelinated fibers with cross-sectional diameter of 2-5μm, and CV of 5-30m/s, and 2) C mechano-heat nociceptors (CMHs) which have unmyelinated fibers with a cross-sectional diameter of 0.3-3μm and CV of 0.5-2m/s (Burgess & Perl, 1971; Mountcastle, 1980). Both types can respond to cutaneous thermal, mechanical, and noxious stimulations.

Cells release naturally made chemicals at the site of an injury. These chemicals can cause or facilitate pain by binding to receptors on the naked nerve endings of the primary afferent nociceptors (Fields, 1990). Some of these chemicals include bradykinin,

potassium, serotonin, and histamine. Others such as prostaglandin, leukotrienes, and substance P sensitize the primary afferents at the injurious area.

**Central Pain Pathways**

The ascending pain pathways begin with the primary nociceptive afferents making synaptic contact with second order neurons in the grey matter of the dorsal horn of the spinal cord (Fields, 1990). These neurons send axons that cross the midline to the other side of the spinal cord, and then travel upward to the supraspinal regions via the anterolateral pathway in the white matter. Several spinal tracts make up this pathway, including the spinothalamic tract (STT), spinoreticulothalamic tract (SRT), and spinomesencephalic tract (SMT). The spinocervical tract (SCT) has also been found to play a role in nociceptive transmission (Guilbaud et al., 1994). These fibers either synapse directly on nuclei in the thalamus or indirectly via the brain stem connections. These thalamic nuclei in turn project to other areas in the cortex. The cortex can also exert its influence on pain perception by forwarding signals via the descending pain pathway in the brain stem to the dorsal horn to modulate neuronal activity.

*The dorsal horn*

The dorsal horn is divided into several layers or laminae according to cytoarchitecture (Rexed, 1954). The primary nociceptive afferents mainly synapse on neurons in laminae 1 (marginal zone), 2 (substantia gelatinosa), and 5 (Fields, 1990).

The marginal zone is the most superficial layer within the grey matter of the dorsal horn (Fields, 1990), and receives inputs from the small myelinated A and C fibers (Fitzgerald, 1989). The neurons there exhibit either nociceptive specific (receive input from nociceptors only) or wide dynamic range (receive inputs from both noci- and low threshold mechano-receptors) response (Albe-Fessard et al., 1985). These neurons project to the contralateral midbrain and thalamus.

The substantia gelatinosa is the termination site for C fibers and some Aδ fibers (Fields, 1990). It contains interneurons and receives dendritic inputs from cells in lamina 5. Neurons in lamina 5 receive direct input from the Aδ fibers (Fields, 1990) and exhibit a wide dynamic range response (Albe-Fessard et al., 1985). Also, their receptive fields are larger than those in lamina 1, suggesting that they receive greater convergence of afferent input. The neurons also send dendrites dorsally into both laminae 1 and 2, suggesting that they can receive direct inputs from C and Aδ fibers and indirect inputs via the interneurons in lamina 2. Finally, cells in the deeper layer (laminae 6-8) also play a role in nociception. They have very complex receptive fields and possess variability of input (Albe-Fessard et al., 1985).

*The Spinothalamic Tract (STT)*

The spinothalamic tract arises from neurons in lamina 1, outer part of lamina 2, and laminae 4-8 in the spinal grey (Guilbaud et al., 1994). The fibers synapse on either the lateral or medial region in the thalamus. The lateral region consists of the ventrobasal complex (VB), which includes the ventroposteromedial (VPM) and ventroposterolateral

nuclei (VPL), the ventroposteroinferior (VPI) nucleus, and the posterior nuclei (Po) (Guilbaud et al., 1994; Apkarian & Shi, 1994). The medial region includes the central lateral nucleus (CL) of the intralaminar complex, central median (CM), and parafascicular nuclei (Pf) (Kenshalo et al., 1980; Casey & Morrow, 1983; Guilbaud et al., 1994; Apkarian & Shi, 1994). Thus, the STT can be divided into lateral and medial components according to their destinations in the thalamus (Roland, 1992).

The lateral pain system delivers pain signals rapidly because it is composed of monosynaptic projections from the dorsal horn (Jones & Derbyshire, 1996). Therefore, it is believed to be involved in the transmission of the first pain which is considered stabbing in nature. The ventroposterior nuclei receive input from laminae 1 and 5 neurons of both nociceptive specific and wide dynamic range (Albe-Fessard et al., 1985). The receptive fields are maintained and organized somatotopically in VB. The VPI receives its input from lamina 1 (Apkarian & Hodge, 1989). Nociresponsive neurons recorded from VB in the awake monkey were shown to respond maximally to noxious stimuli delivered within small contralateral receptive fields (Casey & Morrow, 1983). This property makes these neurons ideal for the encoding of both spatial and temporal features of noxious stimuli. Neurons from VB and VPI send projections to the somatosensory cortices (SI and SII) where the same nociceptors are also found. The somatosensory region may be important in the sensory-disminination of pain. Apkarian and Shi (1994) studied the lateral thalamic projection in the squirrel monkey and proposed a parallel transmission system of pain to

the somatosensory cortex; one goes from VPL to SI, the other from VPI to SII. Finally, there are nociceptive projections from Po to SII (Stevens et al., 1993).

The medial pain system is believed to be involved in the transmission of the second pain, which is chronic, unpleasant, and elicits the burning, deep aching sensations (Jones & Derbyshire, 1996). This system is likely to be of greater relevance to the present study and others involving tonic pain in comparison to the lateral system (Chen et al., 1989b). Nociresponsive cells within the medial thalamic nuclei often have large and bilateral receptive fields with a non-somatotopic organization (Bing et al, 1990). There is evidence that many of these medial structures project to area 24 of the anterior cingulate cortex and the prefrontal cortex (Vogt et al., 1993; Sikes et al., 1992). These cortical regions are believed to be involved in the motivational-emotional aspects of pain (Devinsky et al., 1995). For example, using the HRP retrograde labeling method, Jones and Leavitt (1974) showed that the intralaminar nuclei (including Pf and CM) project densely to the striatum and sparsely and diffusely upon the frontal, parietal, and limbic areas of the cerebral cortex. The central lateral nucleus (CL) receives STT input from the deep laminae of the spinal grey (laminae 6-8) where neurons show large complex receptive fields (Albe-Fessard et al., 1985). It also receives input from the region of the mesencephalic reticular formation (MRF) that in turn receives nociceptive input from the cord (the pathway is called the spinomesencephalic tract). Neurons in CL project to a number of cortical areas, such as frontal and somatosensory areas.

In humans, it is believed that the VPL and ventrocaudal nucleus (Vc) of the lateral thalamus, and the central lateral nucleus of the intralaminar complex are the termination sites of the STT (Mehler, 1962). There have been microstimulation studies on humans in the last decade in an attempt to locate the "pain" areas in the brain. Davis et al. (1995) have shown that microstimulation within and below the Vc in the human thalamus can evoke visceral pain. Similarly, Lenz et al. (1993) have used the microstimulation method and demonstrated that the ventral posterior nuclei can mediate pain and temperature sensations in humans. It should be pointed out that the region in VPL where STT terminates overlaps wtih the termination area of the dorsal column nuclei (which mediates the somatosensory pathway). As expected, information transmitted via the STT is sent to the SI and SII (Willis, 1989). Based on this information, one may suspect that the lateral thalamus and the somatosensory cortices in humans are involved in the sensory-discriminative aspect of pain, as they are in primates and some other well-studied animals such as rats. Brain imaging studies (presented later) seem to indicate this possibility.

*Spinoreticulothalamic Pathway (SRT)*

Nociceptive information can also be transmitted via the spinoreticulothalamic pathway from cells in the laminae 7 and 8 (Kevetter et al., 1982; Kevetter & Willis, 1982). Some fibers cross the midline to the other side of the spinal cord, and some travel up the spinal cord on the ipsilateral side. Others send branches that terminate in various brain stem nuclei (Guilbaud et al., 1994). Neurons in the medullary reticular formation also project to the CL. Finally, there are projections to the medial structures of the thalamus.

The medial thalamic nuclei have massive projections to the striatal structures involved in motor and arousal responses under stressful conditions. This again indicates that the medial thalamus could be involved in affective-motivational responses.

*Spinomesencephalic Tract (SMT)*

The SMT arises from neurons in laminae 1 and 5, and terminates in the mesencephalic reticular formation (MRF), lateral region of periaqueductal grey (PAG), deeper layers of the superior colliculus and in the intercollicular nucleus (Mehler, 1962; Guilbaud et al., 1994). The PAG neurons project to the hypothalamus which in turn sends axons to the limbic system. The limbic system also sends projections back to the PAG via the hypothalamus. Thus, it appears that the SMT is involved in affective-motivational response as well.

*Spinocervical Tract (SCT)*

The SCT arises from neurons in lamina 4 which mostly respond to tactile stimulation, but some also respond to noxious input (Jessell & Kelly, 1991). The SCT ascends the spinal cord via the dorsolateral white matter on its ipsilateral side to the lateral cervical nucleus. This nucleus further projects to the contralateral midbrain nuclei and thalamus (VPL and posterior medial nuclei) through the medial lemniscus in the brainstem.

**Endogenous Pain Control System**

Pain perception mediated by the ascending pain system can be modulated by a descending inhibitory pathway originating from the periaqueductal grey (PAG) in the

brainstem (Basbaum & Fields, 1984). The PAG has extensive connections to a number of cortical, subcortical, and spinal areas. In particular, the spinal cord is the location for the modulation of nociception. Pain inhibition begins with the release of endorphins, the endogenous opioids in the CNS. The PAG receives inputs from various sources such as the frontal cortex, amygdala, and hypothalamus, and it is believed that the endogenous opioids are released by these cortical neurons into the PAG (Beitz, 1982; Mantyh, 1983). Also, both the PAG and MRF are the termination sites for the spinomesencephalic and spinoreticulothalamic tracts, respectively (Fields & Basbaum, 1994). Thus, these terminations are in the position to activate the descending inhibitory pathway as well.

**Functional Significance of these Structures**

The distinction among the ascending pain pathways should not be taken as a rule as there appears to be overlapping functions. For example, some spinothalamic neurons in the spinal cord that give rise to the STT also send collaterals to the mescencephalic regions and the reticular formation of the brainstem (Willis, 1989). The multiple termination sites in these pain pathways suggest that pain is a multidimensional experience involving a host of sensory, motivational, and motor responses.

Pain consists of a sharp/stabbing component (first pain) immediately after the noxious stimulus is applied, and a slow, deep aching component which is more long lasting, poorly localized, and unpleasant (Jones & Derbyshire, 1996). Physiologically, the sharp/stabbing component is transmitted by the fast Aδ fibers, then through the STT to the

lateral structures of the thalamus (VB and Po) and eventually arrives at SI and SII (Meyer et al., 1994). Moreover, it is believed that this pathway is involved in the sensory-discriminative aspect of pain (Kenshalo et al., 1983; Casey & Morrow, 1983). The deep aching component is mediated by the C-fibers, and the message is transmitted via the medial structures of the thalamus to cortical regions involved in the affective-motivational aspect of pain, such as the orbitofrontal cortex, limbic system, and other motor areas. In light of functional anatomy, the sensory and psychological experiences of pain are the result of activation of many subcortical and cortical areas. A lesion in any one of these regions could therefore impair a certain aspect of pain perception.

## The Cerebral Cortex

*Psychosurgery:*

Psychosurgery has also given researchers insights into how pain is processed cortically. One controversial method that had once been performed on many patients from the 1930s to the 1970s is leukotomy (Bouckoms, 1989). In particular, the frontal lobe leukotomy had been a popular choice for patients suffering from a wide variety of pain syndromes and other psychiatric illnesses such as depression. It was discovered that this procedure reduced the fear, agitation, and depression associated with pain (Barber, 1959). However, it was soon realized that these patients were suffering from other psychological distresses such as disorientation and incontinence (White & Sweet, 1969). Despite such a

profound mental deterioration, the surgery remained a popular choice for pain relief until the late seventies.

Cingulotomy is another alternative for pain relief and it involves bilateral ablation of the cingulum deep to the anterior cingulate gyrus (Bouckoms, 1989). This results in less apathy and more lasting relief of suffering. Foltz and White (1962) performed this surgery on chronic pain patients and discovered that although patients reported that they still felt pain, the pain itself was no longer bothersome. Also, it seems that these patients did not exhibit any neuropsychological deficits after the surgery (Bouckoms, 1989). In fact, Corkin (1979) found that many patients who received the surgery had improved cognition, but this is possibly due to the fact that they became less anxious and distracted by the pain, which then led to improved motivation and concentration (Devinsky et al., 1995). Recently, a study of a patient who received cingulotomy and capsulotomy revealed an increase in sensitivity to thermal pain stimuli (both heat and cold), suggesting that the cingulate cortex may be involved in controlling the perception of thermal pain (Davis, 1995). Other cortical areas that have also been surgically ablated to relieve pain include the medial thalamus, the internal medullary lamina of the thalamus, the pulvinar, amygdala, pituitary, hypothalamus and its perventricular nuclei (Bouckoms, 1989). They have been shown to be effective in treating chronic pain but unsuccessful in treating acute pain.

*Brain Imaging Studies:*

The electroencephalogram (EEG) is a simple but valuable tool in the study of cortical pain processing. Since the use of EEG in pain studies as early as 1941, many pain

illnesses and pain-related syndromes have been shown to produce abnormal EEGs (see review in Chen, 1993). As the EEG technology has advanced, it has become possible to localize brain-evoked activity. Chen et al. (1989b) studied the changes of cortical power spectrum (CPS -- the measure of cortical magnetic activity over time as a function of EEG spectral frequencies) in response to experimental pain induced by the cold pressor test in normal subjects. There were two groups of subjects. In the pain-tolerant (PT) group, subjects were required to tolerate the cold stimulus (1°C) for three minutes, whereas in the pain-sensitive (PS) group, subjects were required to endure the cold pain for an average of less than one minute. Using CPS, they found that both PT and PS groups had increased delta and beta cortical power densities compared to baseline. However, the delta activity was significantly higher in PS subjects than PT subjects, whereas the beta power did not differ significantly between these two groups. The authors concluded that the strong delta activity may be related to the stress component of pain responsivity, and the beta activity reflects the vigilance scanning of pain processes. Backonja et al. (1991) examined the cortical evoked activities using CPS in subjects being treated with either cool or cold water. Similar to the findings by Chen et al. (1989b), these researchers noticed an increase of beta power bilaterally in the frontal and posterior regions. Many studies with patients suffering from migraines, chronic pain, and other pain syndromes show abnormal EEG patterns in the frontal and bi-temporal cortices, and in the thalamus (Chen, 1993). Although the technology can elucidate the cortical mechanism of pain, it does suffer from some drawbacks. In particular, there seem to be large individual differences in the power

of EEG spectrum densities, and this could affect the interpretation of the results (Chen, 1993).

The tomographic imaging technologies such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) enable scientists and clinicians to study a variety of dynamic events and structural pathologies in live human subjects. The main assumption behind the use of these techniques is that neural activity is correlated with blood flow (Hsieh et al., 1995). Thus, by correlating the changes in cerebral blood flow in brain areas with behaviour one may be able to map the functions of those brain areas.

Jones et al. (1991) were the first group to look at the processing of pain in the cortex using tomographic techniques. They investigated the cortical basis of acute heat pain perception using PET. The heat stimuli were generated by a thermal threshold stimulator applied to one spot on the back of the right hand. There were three conditions: Warm (ave. temp = 36.3°C), non-painful heat (ave. temp = 41.3°C), and painful heat (ave. temp = 46.6°C). Data were pooled, compared, and converted to a statistical parametric map. Two statistical comparisons were done: 1) between warm and non-painful heat stimuli, and 2) between non-painful heat and painful heat stimuli. The results showed no significant change in regional cerebral blood flow (rCBF) between warm and non-painful heat. However, a comparison between non-painful heat and painful heat showed significant increases in rCBF in the thalamus, cingulate cortex (area 24), and lentiform nucleus all contralateral to the stimulation site. Non-significant activation was also found

in the ipsilateral lentiform nucleus and prefrontal cortex. There was no increase in rCBF in the primary somatosensory cortex on either side of the cortex. The authors believe that the involvement of the anterior cingulate cortex (ACC) and thalamus reflected the "suffering" component of pain (Jones et al., 1992).

Talbot et al. (1991) published a similar study using PET, except that for the pain stimulus they used a double heat pulse with a contact thermode delivered to six spots on the subjects's right volar forearm. The stimuli were either "Heat Pain" -- painful but tolerable (48 to 49°C) or "Warm" -- warm but not painful (41 to 42°C). The "Warm" condition served as the control. The resulting images were obtained by pooling the data across subjects for each condition (Heat pain and Warm) and subtracted. They found a significant increase in activation in Brodmann's area (BA) 24, the more posterior region within area 24, SII, and the arm area of SI, all contralateral to the stimulated arm. These changes were not the result of anxiety or stress since the pulse rates accessed during the heat pain condition were within normal range and not significantly higher than those during the warm condition. The authors did not discuss any changes in activity in the thalamus in this study.

Talbot et al. (1991) did find activation in the ACC contralateral to the stimulated sites; however, they did not believe that it was responsible for the "suffering" aspect of pain since their noxious stimulus did not evoke anxiety in the subjects (Talbot et al., 1991; Duncan et al., 1992). Furthermore, they argued that the affective experience should be reflected in the bilateral activation of ACC rather than in unilateral activation only.

Instead, the authors postulated that the ACC is involved in the encoding of stimulus intensity. The activation of SI and SII was also at odds with Jones et al.'s results. Jones et al. (1992) believed that the multiple sites stimulation in Talbot et al.'s study might have produced the positional component which activates the somatosensory cortices. On the other hand, Jones et al. might have used a less painful stimulus than Talbot et al. did; therefore they did not see any change in activity in SI and SII (Talbot et al., 1991; Duncan et al., 1992).

In a PET study, Coghill et. al. (1994) presented three conditions to normal subjects: 1) neutral (control) -- 34°C, 2) heat pain (47-48°C), and 3) vibrotactile (110 Hz). The protocol was similar to the one Talbot et al. (1991 used before. When comparing the heat pain condition to the neutral condition, they found significant activation in the arm region of SI and SII in the contralateral hemisphere, anterior portion of the insular cortex and/or the frontaloperculum, BA 24 of the anterior cingulate cortex, and two foci within the SMA (area 6). Areas that showed decreases in rCBF during the pain condition compared to the control condition were in the region approximating BA 31, BA 10 near the anterior tip of the orbital gyrus, all contralateral to the stimulated arm. Finally, activation was observed in the area of basal thalamus contralateral to the stimulated arm. They also compared the heat pain condition with the vibrotactile condition and showed that the noxious heat produced more activation than did the vibrotactile stimulus, which only activated the SI and SII. They concluded that, unlike vibrotactile stimulation, pain perception involved multiple sites in the cortex. One final

note, the greater number of activation sites observed in this study, as compared to their previous study might be due to the fact that in this study they used a neutral stimulus instead of a warm stimulus as the baseline for subtraction. The authors argued that noxious heat probably inhibited the activity of warm fibers.

In a study by Casey et al. (1994), one group of subjects was treated with heat (40°C) and painful hot stimuli (50°C) to the forearm. Using the volume of interest (VOI) approach, they found activation in the contralateral thalamus, cingulate cortex, medial dorsal midbrain, ipsilateral SI and contralateral SI, and contralateral SII. Another analysis using the Z-score method showed significant activation in thalamus, SII, and insula (all contralateral to the simulated site), cerebellar vermis and ipsilateral thalamus. No activation was found in the medial dorsal midbrain, cingulate cortex, or either ipsilateral or contralateral SI. Thus, the way the data were processed could be a factor in obtaining any meaningful result (Berman, 1995).

To demonstrate that activation was not due to the difference between perceived warmth and heat pain or between stimulus intensities only, another group of volunteers was selected and had both forearms cooled to a baseline temperature of about 21-25°C (Casey et al., 1994). Then, the thermal pulses of 32 or 42°C were applied (the same temperature difference as in their first experiment). They found no significant activation in brain structures. This indicated that an increase in CBF corresponded to the sensation the subjects were experiencing.

Casey et al. (1996) performed a more comprehensive study on the effect of differential quality and quantity of thermal stimuli on cerebral activation during pain and touch. Subjects receiving noxious heat stimuli (50°C) showed an increase rCBF in the thalamus, anterior cingulate cortex, premotor cortex, SII, posterior insula, and within the region of anterior insula and lenticular nucleus, all contralateral to the stimulated area. Ipsilateral activations were found in the premotor cortex, thalamus, the medial dorsal midbrain and cerebellar vermis. For discrimination between tonic innocuous cold and tonic cold pain, the cold pressor was used with the mean temperature of 6°C maintained during the pain treatment. An increased rCBF was found in the contralateral sensorimotor cortex, premotor cortex, anterior cingulate cortex, and the region of anterior insula and lenticular nucleus. Significant activity also occurred in the ipsilateral lateral prefrontal cortex (BA 10 and 46), anterior cingulate cortex, region of the insular and opercular precentral cortices, and thalamus. Both the heat pain and cold pain activated the cerebellar vermis, ipsilateral thalamus, the contralateral premotor cortex, contralateral anterior cingulate cortex, and region of the contralateral anterior insula and lenticular nucleus. Thus, when different forms and intensities of innocuous and noxious thermal stimuli were applied, there was an overlap of the patterns of increased rCBF distribution in the brain. This suggests that there is a common neural circuitry that is activated by various kinds of pain stimuli. The different areas activated by these two forms of noxious stimuli reflect the different physiological processes involved in the perception of pain.

Apkarian et al. (1992) studied the brain mechanisms of pain using tonic heat pain. Three subjects immersed their fingers into a hot water bath (mean temperature = 46.2°C) for 3 min, and which was perceived by the subjects as moderately painful. For the control stimulus the temperature of 36°C was used, and this was perceived as neutral. Single photon emission tomography (SPECT) showed a decrease in rCBF in the contralateral parietal cortex within and around SI. The authors argued that this decrease reflected a net synaptic inhibition. No changes in rCBF in ACC were observed.

In another study carried out by Di Piero et al. (1993), tonic cold pain was used. Seven subjects immersed their hands in freezing water while inhaling $Xe^{133}$ and being scanned by SPECT. The subjects were also scanned during the resting state. The results showed an increase in activation in the hand region of the contralateral SI, the contralateral frontal lobe, and the bilateral temporal regions. The authors believed that these findings demonstrated that deep aching pain (via the C-fiber) was mediated by both medial and lateral STT, and the somatosensory pathways were involved. This clearly contradicts the results obtained by Apkarian et al. Di Piero (1993) explained this discrepancy by suggesting that the stimulus used in Apkarian's study was not intense enough, whereas the cold stimulus used in their own study was perceived by the subjects as very painful. Another plausible explanation might be that Di Piero did not use a control condition as Apkarian did, and hence Di Piero saw more change in activity in SI.

Di Piero et al. (1993) observed no significant focal change in the frontal lobe [as Jones (1991), Talbot (1991), and Apkarian (1992) did] but they found an increase in the

average rCBF of the whole frontal lobe contralateral to the stimulated hand. They attributed this increase in CBF to a general arousal mechanism induced by pain. They also observed a bilateral activation in the temporal lobes which they believed was the adaptive response to pain-induced stress. Finally, a non-significant increase in rCBF in the cingulate cortex and thalamus was found. Researchers who studied acute pain found a significant increase in these regions (Jones et al., 1991; Talbot et al., 1991; Casey et al., 1994, 1996; Coghill et al., 1994). The authors reasoned that in the acute pain situation the rapidly adapting receptors and the Aδ fibers were stimulated, but in the tonic pain situation they were blocked. Also, they suggested that the PET used in the acute pain protocol might have had a higher spatial resolution compared to that of SPECT, and hence was able to pick up activation in smaller regions.

Finally, Hsieh et al. (1995) studied the central processing of traumatic nociceptive pain in normal subjects by injecting ethanol intracutaneously to the subjects' right upper arm. The results showed regions of activation in the hypothalamus and PAG revealed by PET. Other activated areas included the prefrontal cortex, insular, anterior cingulate cortex, posterior parietal cortex, primary motor cortex, SI, supplementary motor area, and cerebellum.

There are other studies on pain using tomographic methods summarized in Table 1.

*Summary*

Several conclusions can be drawn in light of the evidence gathered from the brain imaging studies. First, the central processing of pain involves many brain regions. This is consistent with the anatomical and physiological evidence that shows the branching of pain pathways to different areas in the brain, and with the studies of patients who received surgery and electrical stimulation. Second, these studies have uncovered a common set of cerebral structures involved in pain perception. They are the primary and secondary somatosensory cortices, ACC, insula, thalamus, and prefrontal cortex, all contralateral to the stimulated site, and hypothalamus and PAG. Third, although there are some inconsistences among different studies in terms of which structures were involved, these discrepancies could be the result of the difference in stimulus properties, the experimental protocol, and the methods of analyses used in these studies. Stimulus properties such as the nature of the noxious stimulus (e.g., heat vs. cold), temperature, duration of application, and the amount of tissue exposed to the noxious stimulus, may all affect the extent or degree of cortical activation. Experimental manipulation, such as stimulation of one spot (Jones et al., 1991) versus multiple spots of a tissue (Talbot et al., 1991), may affect the pattern of activation in areas such as the somatosensory cortex. The methods of analysis used, such as a pixel by pixel analysis of heat pain versus warm images (Talbot et al., 1991) as opposed to pain versus neutral images (Coghill et al., 1994), can influence the extent and degree of cortical activation as well. Finally, there is still little understanding of the functions of the structures involved in pain perception. For example, although the

ACC is thought to be involved in the affective component of pain, anatomical and physiological studies have shown that the ACC is a heterogeneous structure that also participates in learning, memory and autonomic response (eg. Roland, 1992; Devinsky et al., 1995). Hence the functions of these structures still need to be elucidated.

**The Thesis**

This thesis is mainly concerned with the use of functional magnetic resonance imaging (fMRI) in accessing those brain areas that are involved in pain perception. There are two studies involved. The behavioural study evaluates the sensory and emotional-motivational aspects of tonic pain induced by a cold stimulus. Using this behavioural profile, a hypothesis concerning which cortical areas will be activated and the extent of activation can then be conceived. The imaging study tests this hypothesis by examining the cortical areas that are activated during painful stimulation.

# 2

# THE BEHAVIOURAL STUDY OF COLD-INDUCED PAIN IN HUMANS

Cold-induced pain was the focus in both the behavioural and imaging studies of this research. The purpose of the behavioural study was to assess certain psychophysical and behavioural characteristics of the noxious cold stimulation to be used in the imaging study. These characteristics included the sensory, emotional, and cognitive dimensions of pain induced by a foam-pack, and the coping strategies used by subjects when experiencing pain. Psychophysical characteristics such as subjects' sensitivity to the changes in pain intensity levels, pain threshold, and after-sensations duration were assessed to provide some basis for the experimental design of the imaging study. These characteristics were also required for the selection of candidates suitable for the imaging study (the selection criteria are stated in chapter 3). Much of the behavioural data would then be useful in the interpretation of the imaging results.

Research on cold-induced pain in humans has been conducted for a number of years. The most common cold stimulus used to generate pain is the Hines-Brown "cold pressor" test in which a subject's hand is immersed in cold water for no more than four minutes (Hines-Brown, 1932). The subject initially experiences cold sensations followed by a deep aching pain and an elevation of blood pressure. The cold pressor procedure has been widely used in many pain experiments and in clinical trials for the evaluation of the pain threshold and tolerance of patients suffering from pain and other disorders (Chen et al., 1989). Although some researchers consider the technique to be less reliable than other available methods, it is standardized and valid for measuring pain, and it readily produces pain which is similar to clinical pain (Wolff, 1986; Chen et al., 1989).

In both the behavioural and imaging studies, a foam-pack was used to produce cold pain instead of using a cold pressor because the cold pressor cannot fit in the MRI machine. The behavioural study was expected to offer some insights into the quality and quantity of pain produced by this foam-pack.

## Method

*Subjects*:

Thirty healthy subjects were recruited for the study (7 males and 23 females). Sixteen subjects were undergraduate students, nine of whom were recruited from a second year class and five from the first year introductory psychology for course credit. The rest of them (eleven were graduate students from the Department of Psychology; two were

volunteers outside of the McMaster community; and one was a medical student) received $10 and reimbursement for parking if applicable. All subjects were naive about the nature of this study. Ages ranged from 18 to 38 years with a mean of 25.50 and standard deviation (SD) 5.66 years. Before the subjects could participate in the study, they were told that they must be right-handed and have no medical problems. Those who did volunteer were further screened for handedness and past medical problems by completing a short version of the Waterloo Handedness Questionnaire (Steenhuis & Bryden, 1989; see Appendix I) and a medical history questionnaire (Appendix II). In addition, they also completed a demographic information sheet (Appendix III). Subjects who might participate in the fMRI study also completed a screening form to exclude those who were pregnant, had been exposed to metals, or had received metal implants (Appendix IV). All subjects were required to give an informed consent (Appendix V) acknowledging that 1) they would be exposed to the ice-pack which would induce a variety of sensations including pain, 2) they understood the methods and the risks involved in the experiment, and 3) they were free to withdraw from the experiment any time without prejudice. The study was approved by the McMaster Human Research Ethics Board and the Health Sciences Ethics Board.

*Exclusions*:

Four subjects had to withdraw from the study due to their inability to perceive any pain in either the left or right hand while exposed to the cold stimulus, and one subject was

excluded because the after-sensations durations on several trials exceeded 4 mins (see the description in the section Measures).

*Demographics:*

All thirty subjects who participated in this study had already attended or were attending university. Seventy percent of the subjects were single; 20% were married; one subject lived with a common-law spouse and another was divorced. Of those who were married, only two reported to have at least one child. Fifty-seven percent of the sample lived either alone or with roommates, while the rest lived with family members.

**Experimental procedure**

*Apparatus*:

The pain-inducing stimulus was a foam pack (12.5 x 18 x 4 $cm^3$) completely sealed by a plastic cover. Its temperature can be maintained at 0°C when kept in a freezer. During the experiment, a few of these foam packs were stored with crushed ice inside a cooler.

*Procedure*:

All subjects received a standard set of verbal instructions delivered by the experimenter. In general, they were asked to endure the sensations induced by the foam-pack (0°C) placed on the palm of the left hand for a period of time, and that pain might be one of the perceived sensations. They were not told the exact durations of the trials; instead, they were informed that the duration of each test trial would not exceed 4

minutes. They were also told that they could terminate the trial at any time if they could not tolerate the cold induced sensations.

Once the foam-pack was applied to the hand, the subject was instructed to pay attention to the onset of the first pain sensation if that happened. The first pain sensation was defined as the barely perceptible deep ache following the established definition presented by Wolf and Hardy (1941). Once the pain sensation occurred, the subjects hit the key ">" on a keyboard linked to an IBM-compatible computer. For any definite changes in pain intensity the subject pressed either "<" or ">" key, representing a subjective decrease or increase of pain intensity level, respectively. The duration for which the subject tolerated the pain sensations for all test trials was 35 seconds, after which the ice-pack was removed from the hand immediately. The hand was allowed to warm up back to its baseline temperature with the aid of a warm water bottle, which was kept in a bath of warm water (range: 42 - 46°C) throughout the experiment. At the same time, the experimenter initiated a timer once the pain trial was over to measure the duration of after-sensations. The subject was instructed to inform the experimenter the moment when those after-sensations dissipated.

The entire behavioural session consisted of one practice trial and 10 test trials. There were four minute breaks in between the test trials. The practice trial lasted 15 seconds. Its purpose was to help the subject become familiar with the experimental procedure and cold-induced sensations. At the end of the session, the subject was required to complete three questionnaires: 1) The McGill Pain Questionnaire (MPQ, see

Appendix VI), 2) the Spielberger's State Anxiety Inventory (SAI, Appendix VII), and 3) the Coping Strategy Questionnaire (CSQ, Appendix VIII). The entire experiment lasted approximately one and a half hours.

**Measures**

*Pain threshold, intensity level, and after-sensation duration*:

The pain threshold is defined as the time (in seconds) from the application of the foam-pack to the onset of the first pain sensation. Every time the subject struck either ">"or "<" key, the computer program recorded both the level of pain and the time the key was pressed. A strike of ">" key indicated one unit increase in pain intensity level, and a strike of "<" key indicated one unit decrease. Finally, the after-sensations duration is defined as the duration (in seconds) between the removal of the foam-pack from the hand and the moment the subject reports the dissipation of after-sensations.

*McGill Pain Questionnaire (MPQ)*:

The MPQ (Melzack, 1975; Melzack & Katz, 1992) was administered immediately after their last test trial. Subjects were instructed to choose, from each of 20 subclasses and three temporal subclasses, either a word that best described the quality of pain they had experienced during all the 10 trials, or none if the words provided could not apply. In addition, they had to rank the pain on a 0-5 rating scale called the present pain index (PPI), but they were instructed to rate it according to the maximum pain intensity they had experienced during any of those 10 trials. The pain rating index (PRI) was calculated for

sensory (PRI-S), affective (PRI-A), evaluative (PRI-E) and miscellaneous (PRI-M) categories by adding the rank values of the words chosen from each subclass in each of these 4 components. Total scores (PRI-T) were obtained by summing all the rank values. The number of words chosen (NWC) was also used. Together, these attributes provided a comprehensive description of the "cold-pain" induced by the foam-pack.

*State Anxiety Inventory (SAI)*:

The SAI (Spielberger, Gorsuch, & Loshene, 1970) was used to assess the subjects' anxiety state experienced during the test trials. It was administered to the subjects after they had completed the MPQ. The inventory consists of 20 statements, each describing an emotional state. The subjects were instructed to rate on a four point scale each of the 20 statements in relation to the anxiety state experienced during the test trials. The maximum score for each question is 4, and for the entire inventory 80.

*Coping Strategies Questionnaire (CSQ)*:

The CSQ (Rosentiel & Keefe, 1983) was administered after the SAI. This questionnaire assesses seven different pain coping strategies -- increasing behavioural activity, catastrophizing, praying/hoping, ignoring pain, self-statements, reinterpreting, and diverting attention. Each strategy consists of six different coping statements which subjects were instructed to rate on a six point scale. The maximum score for each coping strategy is 36. In addition, the subjects were asked to rate their belief in their ability to control and decrease pain on a seven point scale.

**Analysis**

Data obtained from the pain measures (pain thresholds and after-sensations durations), MPQ, SAI and CSQ were examined using descriptive statistics and correlational analysis (see Appendix IX). The p-value was set at 0.05.

**Results**

A summary of the data is presented in Appendix X.

*Subjective Pain Measurements*:

Pain threshold raw data for each subject is presented in Appendix XI. For those trials on which subjects did not perceive any pain, no value was assigned for the pain threshold, and therefore the trials were automatically excluded from the analysis (a value of 0 could not be assigned because the pain threshold did not exist). Pain threshold (APT) was calculated by averaging the obtained threshold values for each subject. In addition, the mean and standard deviation of the APT of all thirty subjects were calculated and are presented in Table 2.

All subjects' after-sensations durations (ASD) were recorded on all test trials except the last one due to the immediate administration of the questionnaires (see Appendix XI). Thus, the correlation between the ASD and pain thresholds was done without including the last trial. The APT was also correlated with the average after-sensations duration (AASD, $r = 0.40$, $p < 0.05$).

For threshold and duration of after sensation, data across all subjects for each trial were pooled, averaged, and the means were plotted (Figs. 1 & 2). All of these graphs revealed almost straight, flat linear trends, suggesting no substantial differences between the individual means and the overall means in these two measures. However, there were individual differences in responses in each of these measures.

*Profile of the MPQ, SAI, and CSQ:*

For the results of the MPQ, the sensory, affective, evaluative, and miscellaneous components were isolated and characterized (see Table 3). Comparisons of these scores with those of other cold-pressor studies are shown in Table 4. Table 5 shows the characteristics of cold pain induced by the foam-pack as assessed by the number of words chosen. Only those words that were chosen by more than 35% of the subjects (Keplac et al., 1981) are shown (for a more comprehensive list, see Appendix XII). In addition, the words chosen were also compared with those found in Keplac et al.'s (1981) cold pressor study (Tables 6 & 7) in which two separate groups (pain threshold and pain tolerance) were compared using the cold pressor task. Subjects in the threshold group withdrew their hands from a tank of ice-water at the pain threshold, whereas those in the tolerance group endured the noxious cold until tolerance was reached. Specific words that were chosen by more than one-third of the subjects in this study and in the Keplac et al. (1981) study are presented in Table 6. This comparison clearly reveals that more words were chosen by more than 35% of subjects in the pain tolerance group in Keplac et al.'s study than by the subjects in this study, but the number of words chosen was almost the same

between the pain threshold group in Keplac et al. and this study. This suggests that the quality of cold-pain experienced by subjects in this study was similar to that experienced by subjects in the pain tolerance group, and to some extent the pain threshold group, in Keplac et al.'s study, but the intensity as reflected by the number of specific words chosen was lower. Table 7 shows the percentage of subjects choosing each of the 20 word groups on the MPQ both in this study and in Keplac et al. (1981) study. The chi-square test cannot be used reliably because of the low frequencies in many of the cells. The low level of analysis adapted here is a common way of describing the quality of pain obtained by MPQ to allow cross-study comparisons (e.g. Keplac et al., 1981). The comparison between the two studies further demonstrated that the quality of cold-induced pain experienced by subjects in these two experiments was quite similar.

The mean SA score (SD) is 54.77 (5.98), respectively. Means and SDs for all 9 measures of the CSQ are presented in Table 8. Correlational analysis was performed among all subcomponents of the MPQ, CSQ, SAI, age, and APT. The results are shown in Appendix IX.

**Discussion**

The main purpose of this study was 1) to identify the quality and quantity of cold induced pain in humans, 2) to select those subjects who were suitable for the imaging study (see the sub-section "subject" under the section Method in chapter 3), and 3) to provide additional information for the interpretation of the imaging data. A concern in the

imaging study was physiological adaptation. Subjects might experience less pain through repeated exposure to the noxious stimulus trial after trial. Therefore, the procedures in both the behavioural and imaging studies were designed so as to minimize physiological adaptation. The selection of subjects for the imaging phase required that they could detect the pain thresholds within a reasonable time (20 sec or less) and experience pain on all test trials. Wolf and Hardy (1941) found that the adaptation to "cold pain" resulting from repeated exposure to a cold stimulus was due to a decrease in temperature gradient between the cold stimulus and the stimulated tissue area. When a cold stimulus was initially applied to the hand, the subject experienced more pain because of a large drop in temperature in the hand. However, if the hand was not allowed to warm up to the original baseline temperature, then when the cold stimulus was applied again to the hand there would be a smaller drop in temperature, and consequently less pain would be experienced. As the temperature gradient became smaller due to repeated exposures to the cold stimulus, adaptation became more apparent. In this study, all subjects were given a warm water bottle to warm their hands back to their baseline temperature to minimize adaptation. However, because skin temperature was not objectively measured, subjects had to decide subjectively when their hands' temperatures had returned to baseline.

During the study, subjects were asked to report their pain threshold, which was defined as a barely perceptible deep ache. Some subjects did not perceive this dull aching sensation as pain but rather as a cold sensation; some others defined pain as an excruciating, intolerable experience. In general most subjects considered the pain as

discomfort as reflected by their choice of word-rank value combination in MPQ. Clearly there were individual differences in the definition of pain, and this could have an impact on the measurement of both the pain thresholds and intensity levels. Furthermore, the average pain threshold (APT) for each subject was used in the correlational analysis instead of the pain thresholds of each trial. It was suspected that the foam-pack's temperature would increase after one or two uses. The situation was further complicated by the fact that different subjects were exposed to the stimulus for different lengths of time (due to the individual differences in the onset of pain threshold). Even within the same subject this difficulty arose, possibly due to variability in pain perception. In an attempt to control for this problem, the foam-pack was replaced by a new one every few trials to reduce the variability due to temperature change. Nevertheless, a number of subjects did show tremendous fluctuations in their pain thresholds, and it is not clear whether this is attributable to the changing of the stimulus's temperature or subjects' criterion. In view of these problems, it was decided that the APT was an appropriate index for the present study. The range of these APTs for all subjects was from 5.10 to 40.13 sec, indicating a substantial variability between individual subjects.

There were also individual differences in the durations of after-sensations (ASD) which ranged from 18 secs to 3 mins-50 secs. When the after-sensation durations for all nine trials were averaged for every subject, it was found that these durations were positively correlated with the APT, i.e., that the longer the pain threshold, the longer the after-sensation duration. This should not be a surprise since a longer pain threshold means

that the subject was exposed to the stimulus longer and so this should lengthen the duration of after-sensations.

To assess how the thresholds and the durations of after-sensations changed from trial to trial, data obtained from each trial in each measure were combined across subjects and averaged. Both plots revealed a somewhat flat linear trend, suggesting that as a sample there was little fluctuation in these two measures over the course of the trials.

A number of MPQ measures showed that the pain experienced by the subjects in this study was less severe than those in the studies by Keplac et al. (1981) and Chen et al. (1989a) who assessed cold-induced pain. Except for the sensory component, the other categories (affective, evaluative, and miscellaneous) had relatively lower scores in the present study. Both the Keplac et al. and Chen et al. studies used a standard cold pressor apparatus which allowed the hand to be completely immersed into cold water. In this study, only the palm of the hand was in contact with the foam-pack. Thus, the stimulus itself and the amount of body surface exposed to the noxious stimulus could influence a subject's perception of pain. Furthermore, there are apparent similarities among specific words and word groups chosen by subjects in the present study and those in the pain tolerance group in Keplac et al.'s study (1981), but the number of these specific words chosen was smaller in this study. This suggests that subjects in these two groups experienced a similar quality of cold-pain, but the intensity experienced by those in this experiment was less severe.

The present study also examined the coping strategies used by healthy subjects. Coping strategies that showed high scores include increasing behavioural activities, ignoring, self-coping statements, and diverting attention. Those that showed relatively lower scores are catastrophizing, praying, and reinterpreting pain sensation. Of particular interest is catastrophizing, which was found to be positively correlated with a number of pain intensity indices in MPQ, including NWC, PRI-T, PRI-E, PRI-A, and PRI-S. These results from the correlational analysis in the present study further substantiate the findings by Geisser et al. (1994) that catastrophizing tended to correlate with increased ratings of pain.

In summary, the data showed that the perception of cold-induced pain in humans differs interindividually. Differences may arise in assessing the pain thresholds and the durations of after-sensations. Using a foam-pack as the noxious stimulus can induce a similar strength in the sensory experience of pain as that induced by the standard cold pressor apparatus, although the quality may be slightly different due to the amount of tissue exposed to cold stimulus. However, it seems that a foam-pack is less capable of generating the emotional and cognitive intensities that a standard cold pressor can produce. This means that those cortical regions that are connected to the medial pain system may show a lesser degree of activation in the imaging study. Finally, there seem to be individual differences in coping styles, but certain strategies are being used by many subjects, such as increasing behavioural activities, making coping self-statements, ignoring, and diverting attention. These differences in coping styles can influence an

individual's perception of pain as demonstrated by the correlations between certain coping styles, self-appraisal factors, and MPQ descriptors.

# 3

# IMAGING PAIN

The purpose of this study was to examine the activation within the human brain during noxious cold stimulation using the functional magnetic resonance imaging technique (fMRI), and to relate the imaging results with the behavioural data. The behavioural results demonstrated that subjects experienced moderate intensity of pain similar to studies by Keplac et al. (1981) and Chen et al. (1989a). However, the emotional-motivational intensity was very much weaker compared to the findings in these two studies. In this imaging experiment, the pattern of cortical activation during noxious cold stimulation was investigated. The results would be interpreted in light of the behavioural data found in the first experiment of the present study, and the findings by two imaging studies on tonic cold-pain (Di Piero, 1994; Casey et al., 1996). Both of these studies used a cold-pressor; therefore, the cortical structures associated with emotional-motivational aspects of pain (i.e. the anterior cingulate and frontal cortices, and insula) would show substantial activation. In Di Piero et al.'s study (1994), significant increases

in rCBF were found in the frontal and bitemporal lobes, and a non-significant increase was also shown in ACC. Casey et al. (1996) found significant activations in the anterior cingulate and frontal cortices, and insula. Because the present study used a foam-pack as the noxious stimulus, it could be hypothesized that the weaker affective response would be associated with a different pattern of activity, possibly a lesser amount of activity, in the insula, anterior cingulate and frontal cortices than that found in the other two studies (Di Piero et al., 1994; Casey et al., 1996).

**Magnetic Resonance Imaging (MRI)**

The fundamental principle of magnetic resonance imaging (MRI) is the excitation of some atomic nuclei, such that their return to the ground energy level after the excitation emits radiofrequency signals, which can then be analyzed and produced as an image (Young, 1989, Cohen & Bookheimer, 1994). Various atomic nuclei are present in the human body at different quantities, such as hydrogen nuclei (or simply protons), oxygen, and phosphorus. Each such nucleus is charged and spins about its axis at a characteristic angular velocity, and this gives rise to a magnetic dipole. Both the hydrogen (proton) and phosphorus nuclei are effective in generating MRI signals. The proton will be used as an example here. When a subject is placed in a strong and uniform magnetic field, a number of protons in the body align themselves with this field. This results in the net magnetization of the body, and the subject now possesses a net magnetic dipole in the direction of this external magnetic field.

In reality, when protons are experiencing this magnetic field they do not simply align themselves with this magnetic field but precess about it (Young, 1989). This precession can be likened to a spinning wobble placed in a gravitational field. Here, the angular momentum of the wobble is trying to keep the wobble upward while the gravitational field is pulling it down. Eventually, the wobble tilted at the equilibrium position where the two forces balance each other, causing the wobble to precess about this gravitational field. Similarly, the interaction between the magnetic field and protons' spin (or angular momentum) causes the protons to wobble or precess about the magnetic field at a characteristic frequency, and this frequency is unique for a certain magnetic field for different nuclei.

Once the protons are aligned with the external field, a low radiofrequency (RF) pulse is applied to disturb the protons from their thermal equilibrium (Young, 1989). As the protons relax back toward equilibrium in the main magnetic field, they generate magnetic fields which can be detected by a receiver coil, and the detected signals are then used to reconstruct an image.

**Functional MRI:**

In fMRI, the index for neural activity is depicted by blood oxygenation (Cohen & Bookeimer, 1994). An active neural region receives an increase in the flow of blood which increases the oxygen content in that region (Fox & Raichle, 1986). This increase in the oxygen content exceeds the oxygen consumption by the neurons, and this leads to an

increase in oxygen content of the venous blood. It was discovered that the oxyhemoglobin and deoxyhemoglobin have different magnetic susceptibility so that the signals emitted (called T2* in MRI) in a high deoxyhemoglobin environment are shorter than that in a high oxyhemoglobin environment (Cohen & Bookheimer, 1994). By using an ultrafast imaging technology, the changes in the oxygenation of the venous blood can be examined. The image contrast obtained by the changes in the deoxyhemoglobin level is called blood oxygenation level dependent (BOLD) contrast and it is the physiological basis for fMRI.

In fMRI, the signal-to-noise ratio (SNR) is weak -- only 2 to 5% of signal can be detected when a 1.5T magnetic field is used, but it increases to 15% at 4T (Cohen & Bookeimer, 1994). The fMRI has the ability to detect substantial signal changes within subjects during a variety of experimental treatments. Therefore, the functional data need not be combined across subjects to increase sensitivity as that in PET. The advantage is that it preserves individual differences both anatomically and functionally, which are then eliminated by pooling data across subjects. The temporal resolution is better than that of PET and SPECT, but inferior to EEG and MEG. In terms of spatial resolution, fMRI can, in theory, image the brain at the columnar level because the vascular responses have been shown to occur in the cortical columns (Forstig et al., 1990; Cohen and Bookheimer, 1994). However, it remains impossible at present to achieve the spatial resolution at the columnar level because the signal from each voxel becomes smaller as resolution increases, while the noise level remains unchanged [a voxel is a three-dimensional element

in space from which a signal occurs (Young, 1989)]. Thus, the resolution of a fMRI image is lower in comparison to that of MRI, but is still superior to that of PET and SPECT. However, the better spatial resolution makes the fMRI more susceptible to motion artifacts (Cohen and Bookheimer, 1994), as slight head movements can cause the misregistration of data such that artifacts are produced when a difference image is obtained from the baseline subtraction.

**Method**

*Subjects*:

Four subjects were selected from the behavioural study to participate in the fMRI study of cold induced pain perception. There were two males and two females chosen on the basis that they could perceive pain on all ten trials, and that the pain thresholds on at least eight of the ten trials were within 20 sec. Prior to the study, the subjects were informed that: 1) they would be confined in the MRI device and would remain immobilized for two hours, 2) they understood the methods and the risks involved in the experiment, and 3) they were free to withdraw from the experiment at any time without prejudice. The study was approved by the McMaster Human Research Ethics Board and the Health Sciences Ethics Board.

*Exclusion*:

One subject's data had to be excluded from the analysis because of head movement induced artifacts.

**Experimental Procedure**

*FMRI study*:

Before the test session began, each subject spent a few minutes resting in the MRI machine to allow him/her to become accustomed to the environment. If the subject experienced claustrophobia, then s/he would be removed from the MRI immediately. For the test session, there were eight trials, each consisting of four conditions: 1) motor condition, during which the subject was asked to flex his/her left hand at a constant frequency for 37 seconds, 2) rest condition, during which the subject was scanned for 37 seconds while resting, 3) block condition, during which the subject held a non-cold foam-pack in the left hand for 37 secs, and 4) cold condition, during which the subject held a frozen foam-pack (10 X 11 X 3.5 $cm^3$) at 0°C in the left hand. The duration for the cold condition for each subject included the 37 seconds scanning time after the onset of pain threshold. The subject indicated the onset of the pain threshold by raising a finger in the right hand to signal the experimenter to start the scanning immediately. Following the cold condition, the next trial occurred four minutes later as the temperature and sensations in the hand were allowed to return to their baseline levels. A warm water bottle was given to the subject to aid the warming process. Each subject was told s/he would be treated with 10 repeated trials of all of the above conditions (but they all only received 8 trials), and s/he would be warned about the impending stimulus before it was delivered. A structural scan was taken prior to the test trials. In addition, the subject was asked to indicate the stimulus intensity on a scale of 0 to 10 ("0" being no intensity, "5" being the

pain threshold, and "10" being extreme pain) after the block and cold conditions. Finally, the anxiety level was also taken on a scale of 0 to 10 after each those two conditions ("0" being no anxiety, and "10" being extremely anxious).

**Scans**

*MRI:*

The MRI scans were obtained with a 1.5 Tesla (T) scanner, and structural images were acquired in axial orientation. The following parameters were used for the structural scan: 2-D inversion-recovery (fast) with TI (time to inversion) = 160 msec, TR msec/TE msec (repetition time/time for echo) = 5000/44, NEX (number of excitation) = 2, FOV (field of view) = 180 mm, matrix size = 256 X 256 pixels, section thickness = 5 mm, 18 sections encompassing the cortical tissue from the superior tip of the brain to a portion of the temporal lobe.

*FMRI:*

For the functional scan, the spiral k-space imaging method was used to enhance the speed of data acquisition. The following pulse sequence was used to acquire the functional data: TR msec/TE msec = 1440/35, FOV = 180 mm, 128 X 128 pixels matrix, section thickness 5 mm, 18 sections accommodating the same brain regions as in the anatomical scan, each section was sampled five times, acquisition time = 37 sec, flip angle = 6°, and 4 spirals. The raw data from the spiral acquisitions were imported to a Sun Sparcstation (Sun Microsystems, Mountain View, California) for image reconstruction.

**Statistical Procedure**

*Stimulus intensity and anxiety ratings*:

The stimulus intensity and anxiety ratings for both the Cold and Block conditions for individual subjects were compared to determine if there were any significant differences in these two measures between the Cold and Block conditions.

*Image Processing and Analysis*:

For each subject, the split-half t-test was performed, pixel by pixel, among different stimulus conditions. The functional data were then superimposed upon the anatomical MR images to create a statistical t-map for the identification of the structures with significant rCBF change. The magnitude of activation was represented by a color scale. For the motor cortex activation study, the region of interest (ROI) was established within the primary sensorimotor cortex in the right hemisphere on the basis of the structural images. This region encompassed the pixels in the precentral gyrus, central sulcus, and postcentral gyrus (Ramsey et al., 1996; Yang et al., 1996). For the pain imaging study, the ROI was defined as a set of contiguous pixels exceeding a certain level of statistical significance for intensity on the basis of the split-half t-test. Once the ROI was identified, the size of significant rCBF change was then determined by counting the number of pixels in that ROI that exceeded a specified level of statistical significance. The significance of a given CBF change was determined by thresholding the t-statistic images at 3.00 which corresponded to $p = 0.0074$ (19 df, two-tailed, uncorrected for multiple comparisons). Significant areas were first obtained using the first half of the t-test

(Schneider et al., 1994; Worden & Schneider, in press). Those regions that were commonly found activated in the contrasting conditions Block - Rest and Cold - Rest were considered to be related to block stimulation. Those areas that showed changes in rCBF in both the Cold - Rest and Cold - Block were considered to be related to pain. The same analysis was then performed for the second half of the t-test to determine if those significant areas observed in the first half of the t-test were replicated (Schneider et al., 1994; Worden & Schneider, in press). Only those regions showing significant changes in rCBF in both halves of the t-test were considered. Anatomical brain atlases (Gademann, 1984; Bradley et al., 1985; Talairach & Tournoux, 1988; Patel & Freedman, 1997) were then used to identify the structures associated with these regions.

**Results**

*Psychophysical ratings:*

Tables 9 and 10 show the mean ratings for both pain and anxiety levels the subjects experienced during the Block and Cold conditions. All three subjects reliably perceived the cold stimulus as painful during the Cold condition and the block as nonpainful during the Block condition. The mean anxiety level in the Cold condition in one of the subjects was considerably higher than that in the Block condition, whereas in the other two subjects no difference was found.

*CBF distribution during hand movement:*

Table 11 presents the size and magnitude of activation in the hand region of the

sensorimotor region in the brain for all three subjects. The results indicated that the motor activation could be produced reliably in all three subjects, thus demonstrating the reliability of the functional scan. The functional images of motor activation are presented in Appendix XIII.

*CBF distribution during block stimulation:*

Table 12 shows the structures with significant rCBF changes due to block stimulation alone, their corresponding sizes, and t maximums in both halves of the split t-test. Among the three subjects, one did not show any significant change in rCBF, and the other two subjects showed significant changes in rCBF in different regions of the cortex. The functional images of innocuous stimulation are shown in Appendix XIV.

*CBF distribution during pain:*

Table 13 shows the structures with significant rCBF changes due to pain alone, their corresponding sizes, and t maximums in both halves of the split-t-test. Inconsistent findings on the regions of activation were observed among the three subjects. The functional images of noxious cold stimulation are presented in Appendix XV.

**Discussion**

This study examined the cerebral activation during cold-pain stimulation using the spiral k-space fMRI. Subcortical areas including the thalamus were not included in the analysis because the MR signal was too weak to be detected. In this study, a hand

squeezing condition was added at the beginning of each trial to illustrate the strength and size of an activation that could be produced from the functional scan. It has been shown by other studies that finger tapping can produce a robust and reliable elevated blood flow in the sensorimotor region of the brain (Bandettini et al., 1993; Ramsey et al., 1996; Yang et al., 1996). The results here demonstrated a consistent activation in the sensorimotor cortex in all three subjects, thus demonstrating the reliability of the functional scan that was used in this study.

The present study on pain revealed inconsistent results among the three subjects during both innocuous tactile and noxious cold stimulation. The cold stimulus used in this study does not seem to contribute to the inconsistent results. The stimulus intensity ratings clearly showed that the subjects perceived the pain as mild to moderate on all trials, and these subjects had also expressed the pain as more severe than it was during the behavioural study. For the anxiety measure, subject no. 7 showed higher ratings in the Cold than in the Block conditions, whereas for the other two subjects no statistical difference was shown. An increase in anxiety might be associated with increasing heart rates which might then affect the pattern of activation in the brain. However, PET studies have shown that high levels of anxiety are not associated with any specific regional increases in CBF (Reiman et al., 1989; Drevets et al., 1992). On the other hand, anxiety might modulate or enhance pain-evoked neural responses (Coghill et al., 1994). This may explain why those regions found to be activated in other pain imaging studies were substantially activated in subject no. 7 but not in the other two subjects.

To date, all imaging studies on pain showed differential activation in a number of brain areas. However, these studies also consistently found two brain areas activated during pain, namely the thalamus and anterior cingulate cortex. Other areas such as the somatosensory cortices (SI and SII), prefrontal cortex, and insula, were not consistently activated. Comparing the results of these studies is difficult because they involved different types of noxious stimuli and different brain imaging methods. The differential effects of the thermal and cold noxious stimuli on the pattern of cortical activation have already been demonstrated by Casey et al. (1996). Variable results among individuals have been found in several other pain imaging studies (Derbyshire et al., 1996; Jones et al., 1996; Tolle et al., 1996). Although a common set of structures was shown to be activated consistently with pain in these studies, the extent and localization of these activated sites varied from person to person. For example, the study by Jones et al. (1996) using fMRI revealed a contralateral activation of the cingulate cortex in two of the subjects, ipsilateral activation in one subject, bilateral activation in one subject, and no activation in another subject. In the present study, two of the subjects showed an increase in rCBF in the anterior cingulate cortex bilaterally, whereas the other subject showed no change at all in the same region. Also, the intensity of the painful stimulus could affect the pattern and magnitude of activation (Talbot et al., 1991; Duncan & Talbot, 1992). Derbyshire et al. (1996) presented subjects with four different intensity levels of thermal pain in their PET study. They found a differential activation at more severe levels of pain in the prefrontal area corresponding to the Brodmann area 10, insula, and anterior cingulate cortex. These

investigators believed that these structures were responsive to the changing psychological experience associated with the intensity of the noxious stimulus.

Individuals could have different psychological experiences when exposed to the same intensity of noxious stimulation. The total MPQ score for subject no. 12 was much lower than the scores for the other two subjects. This might explain why only one area was found to be significantly activated. Indeed, the total MPQ scores for all three subjects seemed to correlate with the amount of activity found in the fMRI study. In particular, both the sensory and evaluative scores for subject no. 7 were higher than those of the other two subjects. This may translate into an increase in activity in the anterior cingulate, somatosensory, and frontal cortices for this subject. Although this explanation seems plausible, more subjects would be needed to establish the relationship between these behavioural measures and cortical activation. Also, differences in coping with pain might be a factor. There were differences in the scores of the CSQ measures among the three subjects, but it is not clear how these differences might be relevant to the brain imaging findings. A separate study on the influence of coping strategies on the cortical activation during pain is needed in order to resolve this issue.

To date, there have only been two published studies which investigated brain activation due to noxious cold stimulation (Di Piero et al., 1994; Casey et al., 1996). Including the current study, the three studies demonstrated some differences in their findings. Di Piero et al (1994) used SPECT in their study, whereas Casey et al. (1996) used PET, and thus, the different imaging methods used could be a factor. Casey et al.

(1996) suggested that owing to the poor resolution inherent in SPECT, the bitemporal activation seen in Di Piero et al.'s results could be due to activation in the insula as observed by Casey et al. The experimental designs in the three studies were different from each other. Di Piero et al. (1994) asked their subjects to hold their hands in water kept at a temperature of 0°C for 1 min before the scan and for about 3 min thereafter during the scan. The subjects in Casey et al. study (1996) kept their hands in 6°C water for 15 sec before the scan and for 1 min during each scan. In the present study, there was a prescan period varying from about 5 to 20 sec during which the subjects were holding a foam-pack maintained at 0°C temperature before any pain was felt. The scan immediately took place after the subjects experienced the pain and lasted for 37 sec. Therefore, it seems likely that the differences in stimulus intensity and duration produced variable pain experiences. Also, unlike the other two studies which used the cold pressor to induce pain, this study used a foam-pack instead. As already assessed by the MPQ in the first phase of the study, the foam-pack did not seem to have as strong an emotional impact as the cold pressor would. This might explain why very little activation was found in these subjects in the present study. Adaptation could also account for the differences found among the three studies. In Di Piero et al.'s (1994) study, the maximum level of pain might have already been experienced by the subjects just before scanning started. During scanning, the pain sensation might have become less severe due to adaptation. This could explain why these researchers failed to see any significant increase in rCBF in the frontal lobe, cingulate cortex, and thalamus. In the current study, the subjects were required to hold a warm

water bottle in between trials to minimize adaptation. In the first phase of the current study, results showed that two of the three subjects experienced increased pain after the pain threshold on all ten trials, and adaptation did not occur during any one of these trials (see Appendix XVI). The other subject seemed to experience some degree of adaptation on only one trial. In view of the behavioural data, adaptation should also have been minimized during the imaging study as well. Thus, it is possible that the pattern of activation seen in the other two studies, and not here, was related to adaptation to the cold stimulus and not the pain itself.

**Methodological Difficulties**

One problem in the experimental design in this study is that the condition orders were not counterbalanced. Counterbalancing can eliminate sequential effect and limit subjects' expectation of the impending stimuli (Coghill et al., 1994; Worden & Schneider, in press). Hsieh et al. (1995b) have shown an increase in CBF in the prefrontal cortex during pain, but a decrease, if the subjects can expect when the pain would occur (Hsieh, 1995a). Counterbalancing is difficult to achieve in this study because of the 4 min after-sensation duration. Conditions that are used in contrasts should be blocked as close in time as possible to minimize artifacts due to movement and drift of the MR signal (Worden & Schneider, in press). It is not known whether there was a substantial sequential effect in this study.

Another problem in this study is the way the stimulus itself was applied. The subjects might have inadvertently moved while the experimenter was delivering the foam-pack to subjects' hands, thus introducing motion artifacts. Additionally, the temperature of the foam-pack might rise while being held in the hand. The Peltier device used by other researchers is a well-controlled method to deliver thermal stimulus and to avoid movements in subjects. However, it is a metallic device and hence cannot be used in a fMRI study. Clark et al. (1996) have developed a laser technology to produce heat pain for their imaging research and they have had some success in using it in a preliminary fMRI study. One advantage of this method according to the authors is that it does not produce mechanical stimulation. The heat pain does not involve a pre-pain-threshold period and after-sensation duration; therefore it can dramatically decrease the amount of time a subject spends inside the MRI machine. Subjects tend to become more uncomfortable the longer they stay in the MRI, and consequently are more likely to move.

**Future Directions**

Imaging pain using the tomographic method has been intensively investigated in the last six years and has greatly contributed to the understanding of the central processing of nociception. However, two issues remain to be resolved. First, as mentioned earlier, the role of a number of cortical and subcortical areas activated by painful stimuli are still not clear. Frequently, researchers resort to speculation about the functionality of these regions. A behavioural investigation like the one in this study could aid the interpretation

of the imaging results. For instance, the prefrontal cortex has been suggested to be involved in the modulation of cognitive appraisal, and thus, recruiting coping strategies could be one of its tasks (Hsieh et al., 1995b; Jones & Derbyshire, 1996). Utilizing the concepts of this study, investigators can examine how different coping methods can affect the extent and magnitude of prefrontal activation.

Second, researchers are still unsure as to how certain cortical areas react to painful stimuli. Some studies have shown an absence in rCBF change in the somatosensory cortices (SI and SII) during painful stimulation, whereas others found either an increase or decrease in rCBF in these same regions. Hsieh et al. (1995a & b) have shown both an increase and decrease in CBF in the prefrontal area depending on the behavioural paradigm. Thus, the challenge of future imaging studies is to use better controlled stimulation and behavioural design to characterize the response of these brain regions to pain.

**Conclusion**

The present imaging study did not yield any consistent results concerning the cortical areas involved in pain perception. Individual differences in pain perception, as assessed by behavioural measures such as MPQ, could account for the variability demonstrated in the present study. This suggests a need for a behavioural assessment of pain perception to aid the interpretation of the imaging results. However, other human,

technical, and experimental factors might have contributed to these inconsistencies, which might be eliminated by a better controlled experiment and larger sample size.

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# FIGURES & TABLES

**Figure Captions**

Figure 1. Average pain threshold (mean ± SE) combined across subjects on all ten trials in the behavioural study. The graph shows no dramatic fluctuation, implying the average pain threshold remains stable throughout the test session.

Figure 2. Average after-sensations duration (mean ± SE) across subjects on all ten trials in the behavioural study. The graph shows no dramatic fluctuation, implying the average after-sensations duration remains stable throughout the test session.

**Figure 1: Means of Pain Thresholds Combined Across Subjects for All Trials**

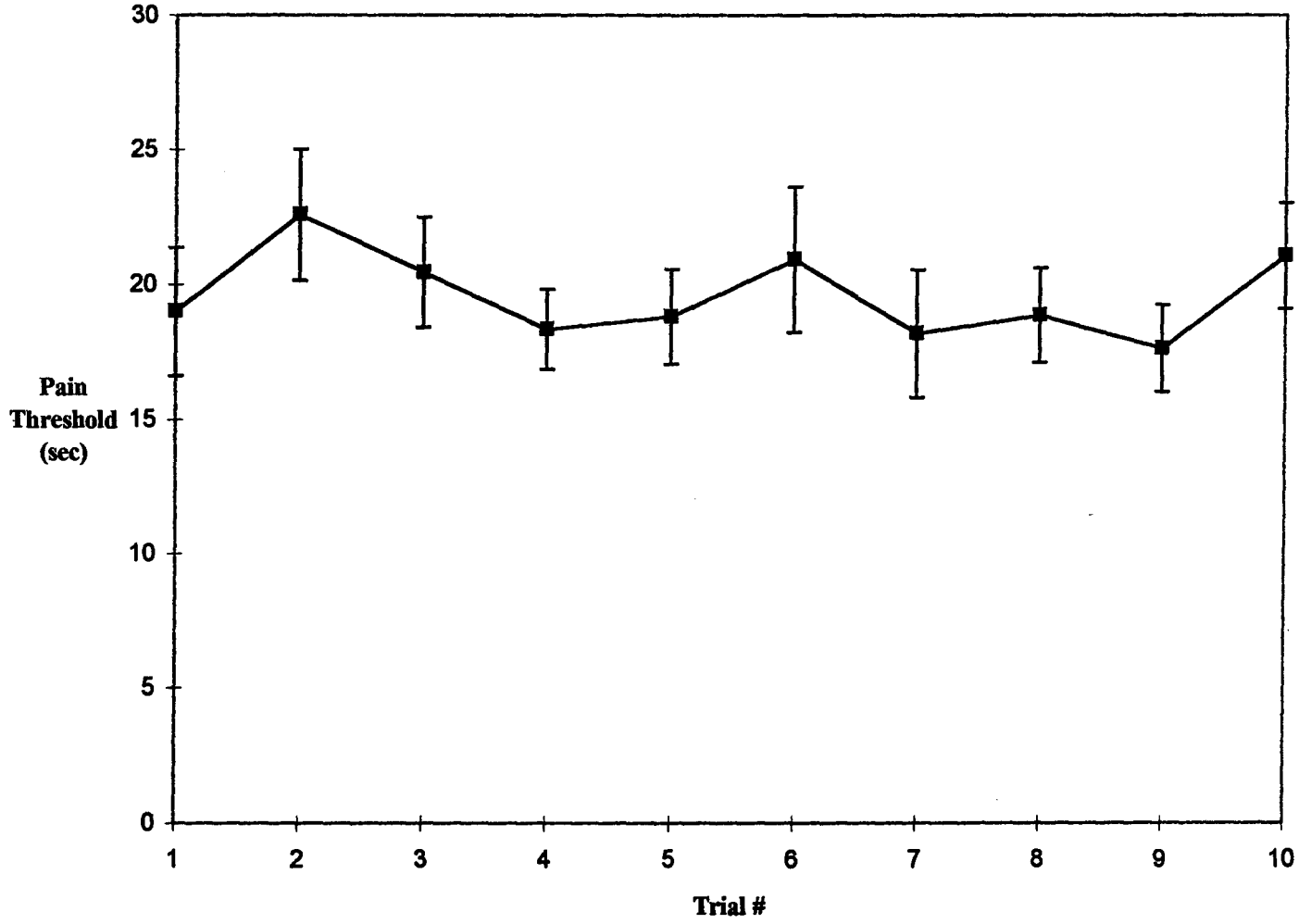

**Figure 2: Means of After Sensation Durations Combined Across All Subjects for All Trials**

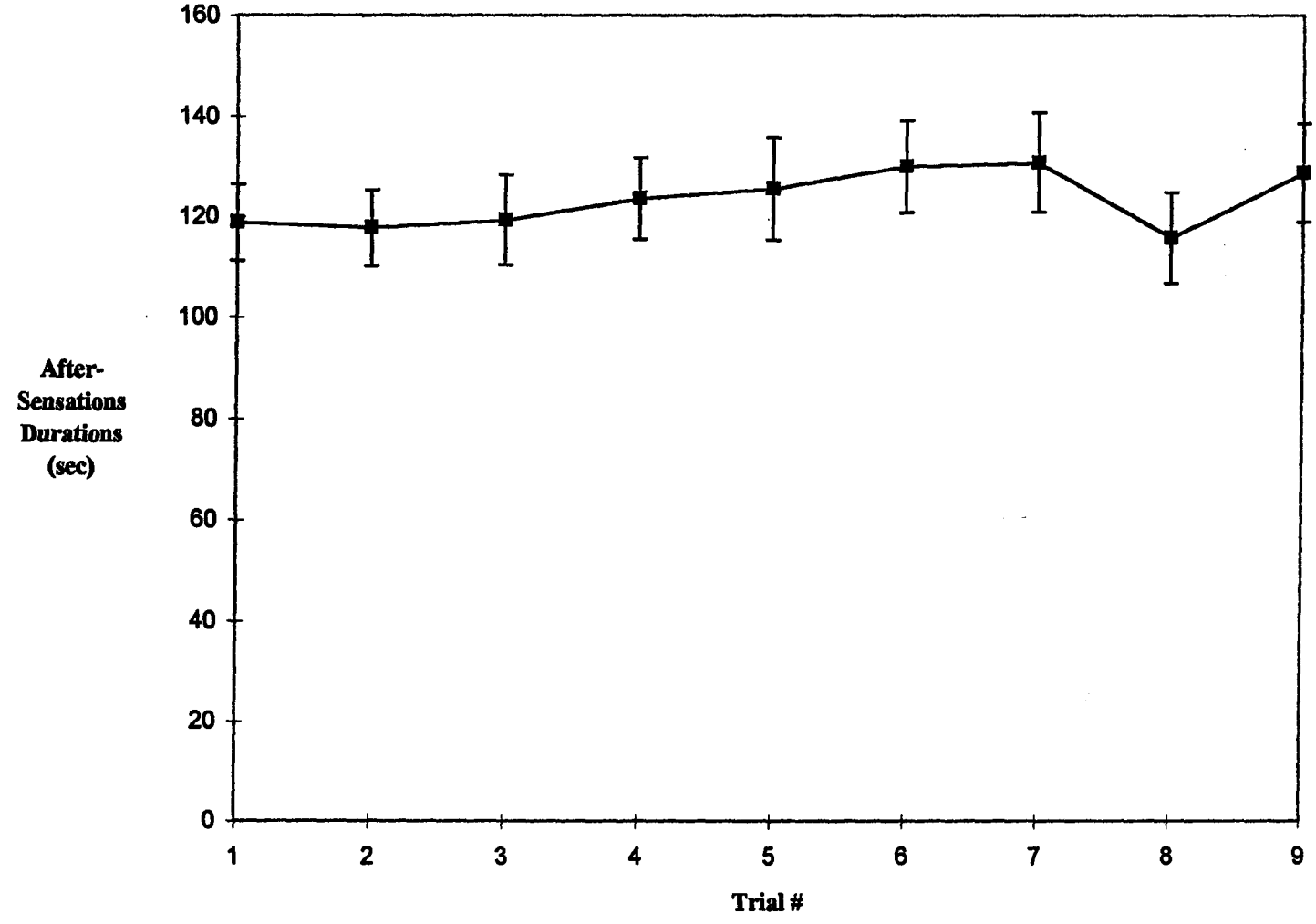

**Table 1. Summary of the findings on neuroimaging of pain studies (modified from the table by Hsieh et al., 1995).**

| Investigators | Methods of Study | Scan | Stimulus | SI | SII | ACC | Thala-mus | lenti-cular n. | MI | Insula | PFC | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jones et al., 1991 | acute thermal pain to a single spot of the arm | PET | 46°C heat pain non-painful hot | none | none | ↑ | ↑ | ↑ | none | none | ↑ 45*, 46* | |
| Talbot et al., 1991 | acute thermal pain to six spots on the arm | PET | 47-48°C heat pain vs warm | ↑ | ↑ | ↑ | na | none | none | none | na | |
| Coghill et al., 1994 | comparing neutral, acute heat pain ,and vibrotactile (110Hz) stimuli | PET | neutral (34°C), heat pain (47-48°C) vibrotactile (110Hz) | ↑ | ↑ | ↑ | ↑ | none | none | ↑ | ↑11 | |
| Casey et al., 1994 | acute thermal pain on multiple spots on forearm | PET | heat (50°C) vs warm (40°C) | ↑ | ↑ | ↑ | ↑ | none | none | ↑ | na | ↑medial dorsal midbrain, cerebellar vermis |
| Hsieh et al., 1995 | Traumatic pain | PET | ethanol | ↑ | none | ↑ | none | na | ↑ | ↑13 | ↑9, 10, 44 | ↑PAG, hypothala-mus |
| Apkarian et al., 1992 | tonic heat pain | SPECT | 46°C water, (moderate pain) | ↓ | na | none | na | na | none | na | none | |
| Di Piero et al., 1994 | tonic cold pain | SPECT | freezing cold water (0°C); resting state | ↑ | na | none | none | na | ↑ | na | na | ↑contra-frontal, bilateral-temporal |

* did not achieve significance level; ↑ = increase in rCBF; ↓ = decrease in rCBF; na = not available

**Table 1. (cont.)**

| Investigators | Methods of Study | Scan | Stimulus | SI | SII | ACC | Thala-mus | lenticular n. | MI | Insula | PFC | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Derbyshire et al., 1996 | $CO_2$ laser heat pain | PET | $CO_2$ laser | none | none | ↑ | ↑ | na | na | ↑** | ↑ 10** | ↑frontal/motor transition (BA6/44), 40 (inferior parietal)** |
| Porro et al., 1996 | prolonged noxious stimulation | fMRI | c-vitamin injected subcutaneously | na | na | na | na | na | na | na | ↑10 | |
| Jones et al., 1996 | tonic cold pain | fMRI | cold stone vs non-painful stone | na | na | ↑ | na | na | na | na | na | |
| Davis et al., 1996 | attention | fMRI | electrical | na | na | ↑ | na | na | na | na | na | |
| Tolle et al., 1996 | tonic heat pain | PET | neutral (37°C), warm, noxious heat | ↑ | none | none | ↑*** | na | na | na | na | ↑PAG, posterior cingulate gyrus, inferior frontal lobe (11,47) & basal part of temporal (20,38) |
| Svensson et al., 1996 | graded phasic heat | PET | 37°C, 45°C, 49°C | ↑~ | na | ↑~ | ↑~ | na | na | na | na | ↓in left & right medial temporal region #; ↑putamen~ |
| | tonic heat | | | ↑# | na | na | na | na | na | na | na | ↑putamen ~ |
| Casey et al., 1996 | heat and cold pain | PET | heat | ↑* | ↑ | ↑ | ↑ | ↑ | ↑* | ↑ | none | ↑cerebellar vermis, & dorsal midbrain |
| | | | cold pressor | ↑ | none | ↑ | ↑ | ↑ | ↑ | ↑ | ↑10, 46 | ↑cerebellar vermis |

↑ = increase in rCBF; ↓ = decrease in rCBF ; * did not achieve significance level; ** significant at higher intensity of pain; *** only between noxious heat & neutral; # high - low pain; ~ high pain - neutral; na = not available

**Table 2. Pain Measures** (N = 30)

| Measures | Mean | Standard Deviation | Range |
|---|---|---|---|
| **APT** | 19.80 | 8.32 | 5.10 - 40.53 |
| **AASD** | 125.15 | 42.73 | 29 - 197 |

APT = average pain threshold (in sec)
AASD = average after-sensations duration (in sec)

**Table 3. Measures of the McGill Pain Questionnaire** (N = 30)

| Measures | Mean* | Standard Deviation | Range |
|---|---|---|---|
| **Sensory** | 13.50 | 6.81 | 6 - 36 |
| **Affective** | 0.40 | 1.16 | 0 - 5 |
| **Evaluative** | 1.87 | 1.63 | 0 - 5 |
| **Miscellaneous** | 5.93 | 2.39 | 2 - 11 |
| **Total** | 21.67 | 9.52 | 9 - 50 |
| **Present Pain Index (PPI)** | 2.23 | 0.68 | 1 - 5 |
| **Number of Words Chosen (NWC)** | 10.80 | 2.99 | 4 - 16 |

* The sum of the rank values

**Table 4. Comparisons of the MPQ subcomponent scores among other cold pressor studies**

| Investigators | No. of subjects | PPI | PRI-S | PRI-A | PRI-E | PRI-M | PRI-T |
|---|---|---|---|---|---|---|---|
| Klepac et al., 1981 | 29 | 2.7 | 14.9 | 1.4 | 3.2 | 8.8 | 28.2 |
| * Chen et al., 1989 | 156 | 2.3 | 14.0 | 2.0 | 2.7 | 7.9 | 26.6 |
| This study | 30 | 2.23 | 13.50 | 0.40 | 1.87 | 5.93 | 21.67 |

* combined from five cold pressor studies
PPI = Present Pain Index
PRI = Pain Rating Index
S = Sensory
A = Affective
E = Evaluative
M = Miscellaneous
T = Total

**Table 5. Specific words chosen by 35% or more of the subjects**

| Word | Word Group | Rank* | % |
|---|---|---|---|
| Shooting | 2 | 3/3 | 37 |
| Sharp | 4 | 1/3 | 53 |
| Tingling | 8 | 1/4 | 43 |
| Aching | 9 | 4/5 | 63 |
| Annoying | 16 | 1/5 | 37 |
| Numb | 18 | 2/5 | 43 |
| Cold | 19 | 2/3 | 53 |

* The first number denotes the rank of the specific word; the second is the total number of words in that subclass.

**Table 6. Comparison of the MPQ words chosen in this study and Keplac et al.'s (1981) cold pressor study. Only those being chosen by more than 35% of the subjects are shown. Words that are shared in common by the two studies are in boldface type.**

| **Present study** | **Keplac et al.** | |
|---|---|---|
| | **Pain Threshold** | **Pain Tolerance** |
| Shooting | Pricking | Pricking |
| **Sharp** | Pressing | **Sharp** |
| **Tingling** | **Tingling** | **Tingling** |
| **Aching** | Intense | Stinging |
| Annoying | Penetrating | **Aching** |
| **Numb** | **Numb** | Intense |
| **Cold** | **Cold** | Penetrating |
| | Freezing | Piercing |
| | | **Numb** |
| | | Freezing |

**Table 7. Percentage of subjects choosing each word group on the MPQ Percentages equal to or greater than 70% in boldface type**

| Word group | Anchor words | This study | Keplac et al. | |
|---|---|---|---|---|
| | | | Threshold | Tolerance |
| | | % | % | % |
| Sensory | | | | |
| 1 | Flickering/pounding | **70** | 65 | 65 |
| 2 | Jumping/shooting | 47 | 25 | 50 |
| 3 | Pricking/lancinating. | 57 | 60 | 55 |
| 4 | Sharp/lacerating | 57 | 40 | 60 |
| 5 | Pinching/crushing | 53 | 60 | 55 |
| 6 | Tugging/wrenching | 27 | 5 | 25 |
| 7 | Hot/searing | 33 | 25 | 40 |
| 8 | Tingling/stinging | 67 | **80** | **100** |
| 9 | Dull/heavy | **97** | **70** | **75** |
| 10 | Tender/splitting | 20 | 40 | 60 |
| Affective | | | | |
| 11 | Tiring/exhausting | 10 | 10 | 10 |
| 12 | Sickening/suffocating | 3.3 | 5 | 10 |
| 13 | Fearful/terrifying | 0 | 10 | 35 |
| 14 | Punishing/killing | 6.7 | 20 | 40 |
| 15 | Wretched/blinding | 0 | 5 | 10 |
| Evaluative | | | | |
| 16 | Annoying/unbearable | **83** | **70** | **80** |
| Miscellaneous | | | | |
| 17 | Spreading/piercing | **77** | **90** | **95** |
| 18 | Tight/tearing | 60 | **80** | **95** |
| 19 | Cool/freezing | **90** | **100** | **90** |
| 20 | Nagging/torturing | 23 | 35 | 40 |
| Temporal | | | | |
| | Brief/Transient | 50 | na | na |
| | Rhythmic/intermittent | 53 | na | na |
| | Continuous/constant | 63 | na | na |

**Table 8. Subscales of the Coping Strategy Questionnaire (N = 30)**

| Measures | Mean | Standard Deviation | Range |
|---|---|---|---|
| Increasing behavioural activities | 17.07 | 7.17 | 2 - 30 |
| Catastrophizing | 8.30 | 7.24 | 0 - 27 |
| Praying | 11.40 | 9.26 | 0 - 30 |
| Ignoring | 17.20 | 6.30 | 4 - 33 |
| Self-coping statements | 21.60 | 5.30 | 13 - 32 |
| Reinterpreting pain sensation | 10.70 | 7.69 | 0 - 23 |
| Diverting attention | 16.03 | 8.13 | 1 - 32 |
| Ability to control pain | 4.13 | 0.73 | 3 - 5 |
| Ability to decrease pain | 3.63 | 0.93 | 2 - 6 |

**Table 9. Mean ratings of stimulus intensity during both the Block and Cold conditions.**

| Subject no. | Block (mean ± sd) | Cold (mean ±sd) |
|---|---|---|
| 5 | 2.88 ± 0.35 | 7.75 ± 0.71 |
| 7 | 3 | 7.88 ± 0.64 |
| 12 | 1.13 ± 0.35 | 7.13 ± 0.83 |

**Table 10. Mean ratings of anxiety during both the Block and Cold conditions.**

| Subject no. | Block (mean ± sd) | Cold (mean ± sd) |
|---|---|---|
| 5 | 0 | 1.13 ± 1.25 |
| 7 | 0 | 7.00 ± 0.76 |
| 12 | 1 | 1.25 ± 0.46 |

**Table 11. Motor-related foci of activation.**

| Subject no. 5 | | | | Subject no. 7 | | | | Subject no. 12 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| t1 max | size (pixels) | t2 max | size (pixels) | t1 max | size (pixels) | t2 max | size (pixels) | t1 max | size (pixels) | t2 max | size (pixels) |
| 8.70 | 33 | 8.21 | 54 | 6.66 | 158 | 7.02 | 128 | 11.67 | 240 | 13.87 | 187 |

t1 = first split-half t-test.
t2 = second split half t-test.

## Table 12. Block-related foci of activation.

| Subject no. 5 | Subject no. 7 | | | | | Subject no. 12 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Brain Region (BA) | Brain region (BA) | t1 max | size (pixels) | t2 max | size (pixels) | Brain region (BA) | t1 max | size (pixels) | t2 max | size (pixels) |
| *Right* | *Right* | | | | | *Right* | | | | |
| none | Precentral sulcus (44) | 4.67 | 11 | 3.90 | 1 | Parietal lobe (7) | 3.23 | 21 | 3.84 | 2 |
| *Left* | *Left* | | | | | *Left* | | | | |
| none | Middle frontal gyrus (45/46) | 6.55 | 9 | 4.25 | 3 | none | | | | |
| | Paracentral gyrus (8,6) | 4.41 | 5 | 3.32 | 1 | | | | | |

**Table 13. Pain-related foci of activation.**

| Subject no. 5 | | | | | Subject no. 7 | | | | | Subject no. 12 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brain Region (BA) | t1 max | size (pixels) | t2 max | size (pixels) | Brain region (BA) | t1 max | size (pixels) | t2 max | size (pixels) | Brain region (BA) | t1 max | size (pixels) | t2 max | size (pixels) |
| *Right* | | | | | *Right* | | | | | *Right* | | | | |
| Inferior frontal gyrus (47) * | 4.32 | 11 | 5.87 | 8 | Insula (14) | 3.15 | 2 | 5.25 | 6 | Inferior frontal gyrus (47) * | 3.12 | 3 | 4.53 | 7 |
| Insula (14) | 4.90 | 17 | 5.53 | 11 | Superior temporal gyrus (38) | 4.03 | 3 | 4.72 | 1 | | | | | |
| Postcentral gyrus (7/5) | 3.38 | 2 | 3.80 | 2 | Inferior frontal gyrus (47) * | 4.91 | 15 | 3.42 | 1 | *Left* | | | | |
| Anterior cingulate cortex (32) | 4.42 | 2 | 3.81 | 2 | Superior temporal gyrus (39) | 6.34 | 16 | 7.62 | 14 | none | | | | |
| | | | | | Central sulcus (SI/MI) | 6.88 | 7 | 4.54 | 3 | | | | | |
| *Left* | | | | | Central sulcus/ Postcentral gyrus (SI/MI) | 4.86 | 4 | 4.96 | 11 | | | | | |
| Middle frontal gyrus (46/10) | 4.77 | 6 | 3.87 | 17 | Central sulcus/ Postcentral sulcus (SI/MI) | 4.99 | 10 | 4.19 | 3 | | | | | |
| Anterior cingulate cortex (8/32) | 5.20 | 6 | 3.35 | 7 | Anterior cingulate cortex (24) | 3.71 | 4 | 4.59 | 1 | | | | | |
| Superior frontal gyrus (6/8) | -4.09 | 10 | -5.02 | 8 | Central sulcus to Paracentral Sulcus (6) | 4.90 | 8 | 5.46 | 15 | | | | | |
| Superior frontal gyrus (6) | 3.43 | 18 | 3.40 | 3 | Paracentral gyrus (4/6) | 3.68 | 2 | 4.94 | 2 | | | | | |
| | | | | | *Left* | | | | | | | | | |
| | | | | | Anterior cingulate cortex (32) | 3.40 | 2 | 3.65 | 1 | | | | | |
| | | | | | Paracentral gyrus (8,6) | 4.57 | 8 | 3.39 | 1 | | | | | |

* Sturctures commonly activated in these subjects. Negative t values indicate that blood flow was less during the Cold condition than during the Block condition.

# APPENDICES

# APPENDIX I

## Handedness Questionnaire

Subject #_____

Instructions: Answer each of the following questions as best as you can. If you always use one hand to perform the described activity, circle Ra or La (for right always or left always). If you usually use one hand circle Ru or Lu (for usually right or usually left), as appropriate. If you use both hands equally often, circle Eq.

Do not simply circle one answer for all questions, but imagine yourself performing each activity in turn, then mark the appropriate answer. If necessary, stop and pantomime the activity.

### Questions

| | | | | | |
|---|---|---|---|---|---|
| 1. Which hand do you use for writing? | La | Lu | Eq | Ru | Ra |
| 2. With which hand would you unscrew a tight jar lid? | La | Lu | Eq | Ru | Ra |
| 3. With which hand do you throw a baseball? | La | Lu | Eq | Ru | Ra |
| 4. With which hand would you pick a glass of water? | La | Lu | Eq | Ru | Ra |
| 5. In which hand do you hold scissors to cut paper? | La | Lu | Eq | Ru | Ra |
| 6. With which hand would you hold cloth when dusting the furniture? | La | Lu | Eq | Ru | Ra |
| 7. With which hand would you insert a pin into material? | La | Lu | Eq | Ru | Ra |
| 8. In which hand would you hold a match to strike it? | La | Lu | Eq | Ru | Ra |
| 9. Which hand would you use to dial a number on a push button phone? | La | Lu | Eq | Ru | Ra |
| 10. Which hand would you use to wave goodbye? | La | Lu | Eq | Ru | Ra |

# APPENDIX II

## MEDICAL HISTORY Subj#:____

Subject_____Date_____

Age_____Sex_____Do you smoke?_____Yes_____No

**Review of Symptoms**: Check any which you frequently experience:

Chills____Fever____Cold____Cough____Headache ____Fainting____Dizziness____

Chest Pain____Shortness of Breath ____Laboured Breathing when at rest ___ Laboured

Breathing on Exertion____ Palpitations ____Ankle Edema____ Blueness of Skin____Leg

Cramps____Nosebleeds____ Spitting Blood____Blood in Urine____Vomiting

Blood____Easy Bruisability____Infections - at present____other____

Pain of any sort. For example:

| | Y/N | | | See MD | Prescr Medic | Counter Drugs | Home Remedies |
|---|---|---|---|---|---|---|---|
| Headache | ___Mild | Mod | Severe | ___ | ___ | ___ | ___ |
| Low Back Pain | ___Mild | Mod | Severe | ___ | ___ | ___ | ___ |
| Menstrual Pain | ___Mild | Mod | Severe | ___ | ___ | ___ | ___ |
| Other Kinds of Pain | ___Mild | Mod | Severe | ___ | ___ | ___ | ___ |

Comments_____

# APPENDIX II (cont.)

**Past Medical History**: Check those which are applicable

Scarlet Fever ____Rhematic Fever____ Heart Trouble____Heart Murmur____

Elevated Blood Pressure ____Eczema____Asthma ___ Hay Fever____ Infectious

Mononucleosis____Liver Disease____Kidney Disease____Anaemia____Other____

Comment_____

**Family History**: Check if applicable to any member of your immediate family.

Easy Bruisability____Anaemia____Prolonged Bleeding____Haemophilia____

Sickle Cell Anaemia____Other Blood Disorders____ Other____

Comment_____

**Current and Recent Treatment**:

Currently pregnant? _____ When did you have your last period? _____

When did you last visit a physician?_____

For what purpose?_____

Have you visited a psychiatrist, psychologist, or counsellor in the last year?_____

When? _____ What was the general nature of the reason (e.g., academic problems, personal problems, mental illness, etc.)?_____

_____

What treatment have you received for such problems?_____

_____

Current medications and drugs of any type - Are you taking oral contraceptives?_____

_____

# APPENDIX II (cont.)

Other current treatment of any type (specify)_____
_____

If you are suffering from chronic pain, have you ever participated in a multi-disciplinary chronic pain management program?_____

# APPENDIX II (cont.)

## Medical Screening Rules for Excluding Subjects from Participation

A subject will be excluded from participation in the study under any of the following circumstances:

1. There is evidence of present medical disorder that the experimenter has a reasonable reason to believe it might be exacerbated by participation;

2. The subject reports a current serious medical problem or a serious medical problem recently enough that the subject may not yet have fully recovered his/her health;

3. The subject reports a significant, ongoing cardiovascular disorder or reports having had a cardiovascular problem that may recur;

4. The subject reports that she is or may be pregnant;

5. The subject reports a problem in the past that suggests she may be adversely affected than most people by a brief, stressful experience;

6. The subject has taken an analgesic or mood altering drugs within the past 24 hours, or has been receiving such medication regularly.

# APPENDIX III

**DEMOGRAPHIC INFROMATION SHEET Subj#____**

We would like to thank you for taking the time to fill out this information sheet. If there are any questions that you prefer not to answer, leave them blank.

Date:_____

Name:_____

Date of Birth:_____

Place of Birth:_____

How many years have you lived in Canada?_____

Please check the category that indicates your highest educational level.

Grade 1 - 6 _____

Grade 7 - 9 _____

Grade 10 - 12 _____

Grade 13 _____

Community College _____ # of years? _____

University _____ # of years? _____

Occupation_____

# APPENDIX III (cont.)

Marital Status -

Single _____

Married _____

Divorced/Separated _____

Common-Law _____

Widowed _____

Do you have children? _____ How many?_____

Living Arrangements -

Alone _____

With Family (Spouse, children, parents, siblings)_____

With Roommates _____

How many other people live in your household?_____

# APPENDIX IV

## EXPERIMENTAL SUBJECT PARTICIPATION and CONSENT FORM

**Cortical Processing of Cold Pain in Humans: A Functional Magnetic Resonance Imaging (FMRI) Study**

## ABSOLUTE CONTRAINDICATIONS TO MRI

Pacemaker/implanted defribilators
Ferromagnetic intracranical anerism clips
Shrapnel in vital locations
Ferromagnetic cochlear implants
Ferromagnetic eye prothesis
Nonremovable neurostimulators

1. Have you ever been a metal grinder, metal worker or welder? __yes __no

2. Have you ever had a metallic foreign body in your eye? __yes __no

3. Is there any chance you may be pregnant? __yes __no

4. Do you have:

   cardiac pacemaker? __yes __no

   artificial cardiac valve? __yes __no

   aneurism clip? __yes __no

   neurostimulator? __yes __no

   other implanted devices or metallic objects in body? __yes __no

5. Are you claustrophobic? __yes __no

6.. What is your weight? _____

Name of volunteer _____

Signature of volunteer _____

Date _____

# APPENDIX V

**(for subjects who participated in the behavioural experiment only)**

## EXPERIMENTAL SUBJECT PARTICIPATION and CONSENT FORM

**The Behavioural Study of Cold-Induced Pain in Humans**

You will be participating in an experiment which investigates the cold-induced pain perception in human. In this study, an ice-pack (at 0°C) will be applied to the palm of your left hand for a period of time not exceeding four minutes. During this time, the cold sensation may turn into painful feeling. When pain is experienced, you will inform the experimenter about its intensity by pressing the appropriate keys on a keyboard as described by the experimenter. Once the trial is ended, the ice-pack will be removed from your hand, and the next trial will begin four minutes later as your hand recovers to the normal baseline body temperature. You will also complete some questionnaires related to the task at the end of the session. This entire study will contain one practice trial and ten test trials. The purpose of the practice trial will be to familiarize you with the experimental procedure and the stimulus itself.

Upon completion of the entire experiment, you will receive one percent grade for your participation. Although your cooperation is entirely voluntary, it is essential that you take your job seriously. If for whatever reason you cannot give us your best effort, you can withdraw from the study, at any time, without fear of prejudice. You are free to ask any questions or express your views about the research at any point, and the experimenter will be pleased to address them. Finally, your medical and experimental records will be kept confidential, and your name will not be published with the research data. Thank you very much for your participation.

I, _____, have read the subject consent form and have agreed to participate in this experiment. I understand the potential risk described -- cold-induced pain and freely accept the risk.

# APPENDIX V (cont.)

**Your Student Number:** _____

**Signature** _____ **Date** _____/_____/_____

**Phone Number:** _____ **Subj#:** _____

**Experimenter:** Albert S.H. Ler

**Signature** _____


**Principal Investigators:**

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**Student Investigator:**

Albert S.H. Ler
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# APPENDIX V (cont.)

**(for subjects who might participate in both behavioural and fMRI studies)**

## EXPERIMENTAL SUBJECT PARTICIPATION and CONSENT FORM

**Cortical Processing of Cold-Induced Pain in Humans: A Functional Magnetic Resonance Imaging (FMRI) Study**

You will be participating in an experiment consisting of two studies -- the psychophysical study of cold-induced pain perception and the imaging study of the cortical processing of cold-induced pain perception using functional magnetic resonance imaging.

In the psychophysical study that examines the perception of cold-induced pain, an ice-pack (at 0°C) will be applied to the palm of your left hand for a period of time not exceeding four minutes. During this time, the cold sensation may turn into painful feeling. When pain is experienced, you will inform the experimenter about its intensity by pressing the appropriate keys on a keyboard as described by the experimenter. Once the trial is ended, the ice-pack will be removed from your hand, and the next trial will begin four minutes later as your hand recovers to the normal baseline body temperature. You will also complete some questionnaires related to the task at the end of the session. This entire study will contain one practice trial and ten test trials. The purpose of the practice trial will be to familiarize you with the experimental procedure and the stimulus itself.

After the psychophysical study, you will participate in the study that examines the cortical processing of cold-induced pain. You will be placed in a magnetic resonance imaging (MRI) device, and you will be exposed to a series of experimental manipulations. Three experimental conditions will be presented to you: 1) the rest condition -- scanning while resting; 2) the "tactile" condition during which you will hold an block in your left hand for 40 seconds; and 3) the "cold" condition during which you will hold an ice-pack at 0°C in your left hand and subject to a 40 secs scan.

Before the actual test trials of the imaging study, there will be a practice trial to help familiarize you with the experimental setting. If you experience claustrophobia during this trial, we will not proceed with the experiment. Both the practice and test trials will consist of the same experimental procedure as described above. The entire session will require you to stay in the MRI machine for at least one hour. While you are being scanned, you will be exposed to a magnetic field, but the exposure should not cause any danger to your health. Furthermore, since the experiment requires a large amount of data from each person, the experimental conditions mentioned above will be presented to you several times during the experiment. Finally, your pulse rates will be monitored throughout the experiment.

# APPENDIX V (cont.)

Upon completion of the entire experiment (both psychophysical and imaging), you will receive $40 for your participation. Although your cooperation is entirely voluntary, it is essential that you take your job seriously. If for whatever reason you cannot give us your best effort, you can withdraw from the study, at any time, without fear of prejudice. You are free to ask any questions or express your views about the research at any point, and the experimenter will be pleased to address them. Finally, your medical and experimental records will be kept confidential, and your name will not be published with the research data. Thank you very much for your participation.

I, _____, have read the subject consent form and have agreed to participate in this experiment. I understand the potential risks described -- the confinement in the MRI machine, the exposure to the magnetic field, claustrophobia, cold-induced pain and freely accept those risks.

**Your Student Number:** _____

**Signature** _____ **Date** _____/_____/_____

**Phone Number:** _____ **Subj#:** _____

**Experimenter:** Albert S.H. Ler

**Signature** _____

**Principal Investigators:**
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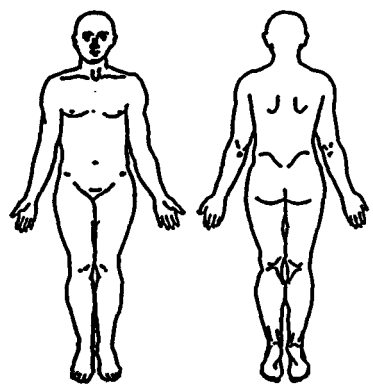
# APPENDIX VI

## McGill Pain Questionnaire

Patient's Name _____ Date _____ Time _____ am/pm

PRI: S _____ A _____ E _____ M _____ PRI(T) _____ PPI _____
(1-10) (11-15) (16) (17-20) (1-20)

| | | |
|---|---|---|
| 1 FLICKERING | 11 TIRING | BRIEF |
| QUIVERING | EXHAUSTING | MOMENTARY |
| PULSING | 12 SICKENING | TRANSIENT |
| THROBBING | SUFFOCATING | RHYTHMIC |
| BEATING | 13 FEARFUL | PERIODIC |
| POUNDING | FRIGHTFUL | INTERMITTENT |
| 2 JUMPING | TERRIFYING | CONTINUOUS |
| FLASHING | 14 PUNISHING | STEADY |
| SHOOTING | GRUELLING | CONSTANT |
| 3 PRICKING | CRUEL | |
| BORING | VICIOUS | |
| DRILLING | KILLING | |
| STABBING | 15 WRETCHED | |
| LANCINATING | BLINDING | |
| 4 SHARP | 16 ANNOYING | |
| CUTTING | TROUBLESOME | |
| LACERATING | MISERABLE | |
| 5 PINCHING | INTENSE | |
| PRESSING | UNBEARABLE | |
| GNAWING | 17 SPREADING | |
| CRAMPING | RADIATING | |
| CRUSHING | PENETRATING | |
| 6 TUGGING | PIERCING | |
| PULLING | 18 TIGHT | |
| WRENCHING | NUMB | |
| 7 HOT | DRAWING | |
| BURNING | SQUEEZING | |
| SCALDING | TEARING | |
| SEARING | 19 COOL | |
| 8 TINGLING | COLD | |
| ITCHY | FREEZING | |
| SMARTING | 20 NAGGING | |
| STINGING | NAUSEATING | |
| 9 DULL | AGONIZING | |
| SORE | DREADFUL | |
| HURTING | TORTURING | |
| ACHING | | |
| HEAVY | PPI | |
| 10 TENDER | 0 NO PAIN | |
| TAUT | 1 MILD | |
| RASPING | 2 DISCOMFORTING | |
| SPLITTING | 3 DISTRESSING | |
| | 4 HORRIBLE | |
| | 5 EXCRUCIATING | |



E = EXTERNAL
I = INTERNAL

COMMENTS:

# APPENDIX VII

## SELF-EVALUATION QUESTIONNAIRE

NAME:_____DATE: _____

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

| | | not at all | moderately so | somewhat so | very much so |
|---|---|---|---|---|---|
| 1. | I feel calm _____ | 1 | 2 | 3 | 4 |
| 2. | I feel secure _____ | 1 | 2 | 3 | 4 |
| 3. | I am tense _____ | 1 | 2 | 3 | 4 |
| 4. | I am regretful _____ | 1 | 2 | 3 | 4 |
| 5. | I feel at ease _____ | 1 | 2 | 3 | 4 |
| 6. | I feel upset _____ | 1 | 2 | 3 | 4 |
| 7. | I am presently worrying over possible misfortunes | 1 | 2 | 3 | 4 |
| 8. | I feel rested _____ | 1 | 2 | 3 | 4 |
| 9. | I feel anxious _____ | 1 | 2 | 3 | 4 |
| 10. | I feel comfortable _____ | 1 | 2 | 3 | 4 |
| 11. | I feel self-confident _____ | 1 | 2 | 3 | 4 |
| 12. | I feel nervous _____ | 1 | 2 | 3 | 4 |
| 13. | I am jittery _____ | 1 | 2 | 3 | 4 |

| | | not at all | moderately so | somewhat so | very much so |
|---|---|---|---|---|---|
| 14. | I feel "high strung" _____ | 1 | 2 | 3 | 4 |
| 15. | I am relaxed _____ | 1 | 2 | 3 | 4 |
| 16. | I feel content _____ | 1 | 2 | 3 | 4 |
| 17. | I am worried _____ | 1 | 2 | 3 | 4 |
| 18. | I feel over-excited and "rattled" _____ | 1 | 2 | 3 | 4 |
| 19. | I feel joyful _____ | 1 | 2 | 3 | 4 |
| 20. | I feel pleasant _____ | 1 | 2 | 3 | 4 |

## SCORING KEYS FOR STAI FORM X-1

Be sure you have the correct side of the stencil on the test sheet. Then simply total the scoring weights shown on the stencil for each response category. A simple hand counter or ordinary desk calculator will make the task easier, but it can be done mentally. Refer to the Manual for appropriate normative data.

| | not at all | moderately so | somewhat so | very much so |
|---|---|---|---|---|
| 1. | 4 | 3 | 2 | 1 |
| 2. | 4 | 3 | 2 | 1 |
| 3. | 4 | 3 | 2 | 1 |
| 4. | 4 | 3 | 2 | 1 |
| 5. | 4 | 3 | 2 | 1 |
| 6. | 4 | 3 | 2 | 1 |
| 7. | 4 | 3 | 2 | 1 |
| 8. | 4 | 3 | 2 | 1 |
| 9. | 4 | 3 | 2 | 1 |
| 10. | 4 | 3 | 2 | 1 |
| 11. | 4 | 3 | 2 | 1 |
| 12. | 4 | 3 | 2 | 1 |
| 13. | 4 | 3 | 2 | 1 |
| 14. | 4 | 3 | 2 | 1 |
| 15. | 4 | 3 | 2 | 1 |
| 16. | 4 | 3 | 2 | 1 |
| 17. | 4 | 3 | 2 | 1 |
| 18. | 4 | 3 | 2 | 1 |
| 19. | 4 | 3 | 2 | 1 |
| 20. | 4 | 3 | 2 | 1 |

# APPENDIX VIII

## COPING STRATEGIES QUESTIONNAIRE

Individuals who experience pain have developed a number of ways to cope, or deal, with their pain. These include saying things to themselves when they experience pain, or engaging in different activities. Below are a list of things that individuals have reported doing when they feel pain. For each activity, I want you to indicate, using the chart below, how much you engage in that activity when you feel pain, where a 0 indicates you never do that when you are experiencing pain, a 3 indicates you sometimes do that when you are experiencing pain, and a 6 indicates you always do it when you are experiencing pain. Remember, you can use any point along the scale.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Never do that | | | Sometimes do that | | | Always do that |

When I feel pain . . .

___ 1. I try to feel distant from the pain, almost as if the pain was in somebody else's body.

___ 2. I leave the house and do something, such as going to the movies or shopping.

___ 3. I try to think of something pleasant.

___ 4. I don't think of it as pain but rather as a dull or warm feeling.

___ 5. It's terrible, and I feel it's never going to get any better.

___ 6 I tell myself to be brave and carry on despite the pain.

___ 7. I read.

___ 8. I tell myself that I can overcome the pain.

___ 9. I take my medications.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Never do that | | | Sometimes do that | | | Always do that |

When I feel pain . . .

___ 10. I count numbers in my head or run a song through my mind.

___ 11. I just think of it as some other sensation, such as numbness.

___ 12. It's awful and I feel that it overwhelms me.

___ 13. I play mental games with myself to keep my mind off the pain.

___ 14. I feel my life isn't worth living.

___ 15. I know someday someone will be here to help me and it will go away for awhile.

___ 16. I walk a lot.

___ 17. I pray to God it won't last long.

___ 18. I try not to think of it as my body, but rather as something separate from me.

___ 19. I relax.

___ 20. I don't think about the pain.

___ 21. I try to think years ahead, what everything will be like after I've gotten rid of the pain.

___ 22. I tell myself it doesn't hurt.

___ 23. I tell myself I can't let the pain stand in the way of what I have to do.

___ 24. I don't pay any attention to the pain.

___ 25. I have faith in doctors that someday thee will be a cure for my pain.

___ 26. No matter how bad it gets, I know I can handle it.

0 1 2 3 4 5 6

When I feel pain . . .

___ 27. I pretend it's not there.

___ 28. I worry all the time about whether it will end.

___ 29. I lie down.

___ 30. I replay in my mind pleasant experiences in the past.

___ 31. I think of people I enjoy doing things with.

___ 32. I pray for the pain to stop.

___ 33. I take a shower or a bath.

___ 34. I imagine that the pain is outside of my body.

___ 35. I just go on as if nothing happened.

___ 36. I see it as a challenge and don't let it bother me.

___ 37. Although it hurts, I just keep on going.

___ 38. I feel I can't stand it anymore.

___ 39. I try to be around other people.

___ 40. I ignore it.

___ 41. I rely on my faith in God.

___ 42. I feel like I can't go on.

___ 43. I think of things I enjoy doing.

___ 44. I do anything to get my mind off the pain.

___ 45. I do something I enjoy, such as watching TV or listening to music.

___ 46. I pretend it's not a part of me.

___ 47. I do something active, like household chores or projects.

___ 48. I use a heating pad.

Based on all the things you do to cope, or deal, with your pain, on an average day, how much control do you feel you have over it? Please circle the appropriate number. Remember you can circle any number along the scale.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| No Control | | | Some Control | | | Complete Control |

Based on all the things you do to cope, or deal, with your pain, on an average day, how much are you able to decrease it. Please circle the appropriate number. Remember you can circle any number along the scale.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Can't decrease it at all | | | Can decrease it somewhat | | | Can decrease it completely |

## APPENDIX VIII (cont.)

### Coping Strategies Questionnaire

### Score Key

| Coping Strategies | Item numbers |
|---|---|
| Diverting attention | 3 + 10 + 13 + 30 + 31 + 43 |
| Reinterpreting pain sensations | 1 + 4 + 11 + 18 + 34 + 46 |
| Coping self statements | 6 + 8 + 23 + 26 + 36 + 37 |
| Ignoring sensations | 20 + 22 + 24 + 27 + 35 + 40 |
| Praying/hoping | 15 + 17 + 21 + 25 + 32 + 41 |
| Catastrophizing | 5 + 12 + 14 + 28 + 38 + 42 |
| Increasing behavioural activities | 2 + 7 + 39 + 44 + 45 + 47 |
| Filler items (not scored) | 9, 16, 19, 29, 33, 48 |

# APPENDIX IX
## The Correlation Matrix of the Behavioural Measures

| | | | MPQ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | SA | NWC | PPI | T | M | E | A | S | APT |
| Age | -0.23 | -0.068 | **-0.36*** | -0.050 | 0.041 | -0.060 | -0.0052 | -0.070 | -0.35 |
| CSQ | | | | | | | | | |
| B | -0.20 | **-0.44**** | -0.024 | **-0.38*** | 0.00 | **-0.40*** | **-0.37*** | **-0.38*** | 0.028 |
| A | -0.24 | **-0.46**** | -0.20 | -0.31 | -0.034 | -0.27 | -0.35 | -0.29 | 0.056 |
| 1 | 0.14 | 0.21 | -0.14 | 0.20 | -0.014 | -0.014 | 0.26 | 0.24 | -0.19 |
| 2 | 0.046 | **0.58**** | 0.30 | **0.62**** | 0.20 | **0.38*** | **0.63**** | **0.59**** | 0.00 |
| 3 | 0.010 | 0.17 | 0.13 | 0.25 | 0.049 | 0.017 | 0.22 | 0.29 | 0.19 |
| 4 | -0.32 | -0.15 | -0.25 | -0.090 | -0.0059 | **-0.36*** | -0.18 | 0.00 | 0.16 |
| 5 | -0.0085 | -0.022 | -0.29 | -0.14 | 0.030 | -0.21 | -0.15 | -0.13 | -0.090 |
| 6 | -0.20 | -0.21 | -0.15 | -0.017 | 0.051 | -0.25 | 0.00 | 0.013 | 0.34 |
| 7 | 0.23 | 0.18 | -0.070 | 0.19 | 0.023 | -0.028 | **0.36*** | 0.21 | -0.17 |
| APT | -0.31 | -0.11 | 0.054 | -0.13 | -0.19 | -0.18 | -0.14 | -0.055 | |
| MPQ | | | | | | | | | |
| S | -0.032 | **0.77**** | **0.37*** | **0.95**** | 0.33 | **0.44**** | **0.57**** | | |
| A | 0.29 | **0.61**** | 0.23 | **0.61**** | 0.035 | **0.39*** | | | |
| E | 0.35 | **0.49**** | **0.53**** | **0.64**** | **0.39** | | | | |
| M | 0.04 | **0.47**** | **0.50**** | **0.56**** | | | | | |
| T | 0.084 | **0.83**** | **0.51**** | | | | | | |
| PPI | 0.29 | **0.55**** | | | | | | | |
| NWC | 0.12 | | | | | | | | |

SA = state-anxiety; APT = average pain threshold; CSQ = Coping Strategies Questionnaire; CSQ 1 = increase behavioural activities; CSQ 2 = catastrophize; CSQ 3 = pray; CSQ 4 = ignore; CSQ 5 = coping self-statements; CSQ 6 = reinterpret pain sensations; CSQ 7 = divert attention; CSQ A = ability to control pain; CSQ B = ability to decrease pain; MPQ = McGill Pain questionnaire; S = sensory; A = affective; E = evaluative; T = total; PPI = present pain index; NWC = number of words chosen; all significant r values are in bold face; * $p < 0.05$; ** $p < 0.01$.

# APPENDIX IX (cont.)

| | CSQ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 7 | 6 | 5 | 4 | 3 | 2 | 1 | A | B |
| Age | -0.19 | 0.18 | 0.024 | 0.025 | -0.20 | 0.044 | 0.099 | 0.050 | -0.12 |
| CSQ | | | | | | | | | |
| B | 0.079 | **0.36*** | 0.060 | 0.10 | -0.010 | **-0.37*** | -0.043 | **0.63**** | |
| A | -0.012 | 0.21 | 0.11 | 0.13 | -0.069 | **-0.53**** | 0.018 | | |
| 1 | **0.66**** | 0.054 | **0.48**** | **0.36*** | 0.29 | **0.36*** | | | |
| 2 | 0.33 | 0.040 | -0.048 | -0.034 | **0.56**** | | | | |
| 3 | **0.49**** | 0.14 | **0.38*** | 0.18 | | | | | |
| 4 | 0.30 | **0.40*** | **0.37*** | | | | | | |
| 5 | **0.52**** | 0.013 | | | | | | | |
| 6 | 0.079 | | | | | | | | |
| 7 | | | | | | | | | |
| APT | | | | | | | | | |
| MPQ | | | | | | | | | |
| S | | | | | | | | | |
| A | | | | | | | | | |
| E | | | | | | | | | |
| M | | | | | | | | | |
| T | | | | | | | | | |
| PPI | | | | | | | | | |
| NWC | | | | | | | | | |

SA = state-anxiety; APT = average pain threshold; CSQ = Coping Strategies Questionnaire; CSQ 1 = increase behavioural activities; CSQ 2 = catastrophize; CSQ 3 = pray; CSQ 4 = ignore; CSQ 5 = coping self-statements; CSQ 6 = reinterpret pain sensations; CSQ 7 = divert attention; CSQ A = ability to control pain; CSQ B = ability to decrease pain; MPQ = McGill Pain questionnaire; S = sensory; A = affective; E = evaluative; T = total; PPI = present pain index; NWC = number of words chosenall significant r values are in bold face; * $p < 0.05$; ** $p < 0.01$.

# APPENDIX X

## The Summary of the Behavioural Data for All Subjects

| n = 30 | MPQ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subj# | S | A | E | M | T | PPI | NWC | APT (sec) | SAI |
| 1 | 19 | 0 | 0 | 5 | 24 | 2 | 9 | 18.23 | 53 |
| 2 | 22 | 0 | 4 | 7 | 33 | 2 | 11 | 26.79 | 50 |
| 4 | 14 | 4 | 4 | 7 | 29 | 3 | 14 | 17.47 | 65 |
| **5** | **11** | **0** | **1** | **8** | **20** | **2** | **8** | **8.82** | **52** |
| 6 | 6 | 0 | 1 | 2 | 9 | 2 | 6 | 5.10 | 55 |
| **7** | **16** | **0** | **4** | **9** | **29** | **2** | **9** | **15.06** | **50** |
| 8 | 12 | 0 | 4 | 10 | 26 | 3 | 11 | 13.77 | 61 |
| 9 | 6 | 0 | 1 | 5 | 12 | 2 | 6 | 24.58 | 60 |
| 11 | 18 | 0 | 2 | 5 | 25 | 2 | 8 | 23.34 | 49 |
| **12** | **8** | **0** | **1** | **3** | **12** | **2** | **8** | **14.89** | **60** |
| 13 | 17 | 0 | 1 | 6 | 24 | 2 | 11 | 18.76 | 53 |
| 14 | 36 | 5 | 4 | 5 | 50 | 2 | 14 | 11.48 | 61 |
| 15 | 20 | 0 | 0 | 7 | 27 | 2 | 10 | 21.93 | 52 |
| 16 | 11 | 0 | 2 | 5 | 18 | 3 | 7 | 22.98 | 50 |
| 17 | 9 | 0 | 4 | 4 | 17 | 2 | 7 | 38.54 | 53 |
| 19 | 11 | 0 | 1 | 3 | 15 | 2 | 11 | 29.06 | 56 |
| 20 | 7 | 0 | 0 | 3 | 10 | 2 | 4 | 40.53 | 51 |
| 21 | 9 | 0 | 4 | 4 | 17 | 2 | 7 | 11.31 | 67 |
| 23 | 9 | 0 | 2 | 3 | 14 | 2 | 7 | 9.51 | 63 |
| 25 | 15 | 0 | 0 | 6 | 21 | 2 | 10 | 23.32 | 53 |
| 26 | 13 | 0 | 2 | 5 | 20 | 2 | 9 | 12.78 | 54 |
| 27 | 8 | 0 | 1 | 6 | 15 | 2 | 8 | 20.27 | 59 |
| 28 | 27 | 1 | 5 | 11 | 44 | 5 | 15 | 24.43 | 59 |
| 29 | 5 | 0 | 0 | 5 | 10 | 1 | 6 | 19.91 | 44 |
| 30 | 9 | 0 | 0 | 8 | 17 | 2 | 9 | 24.69 | 59 |
| 31 | 6 | 0 | 1 | 9 | 16 | 2 | 7 | 12.91 | 56 |
| 32 | 17 | 1 | 2 | 6 | 26 | 2 | 13 | 18.12 | 40 |
| 33 | 13 | 0 | 0 | 6 | 19 | 2 | 8 | 25.65 | 49 |
| 34 | 17 | 0 | 4 | 11 | 32 | 3 | 11 | 10.52 | 57 |
| 35 | 14 | 1 | 1 | 4 | 20 | 3 | 11 | 29.29 | 52 |

SAI = state-anxiety inventory; APT = average pain threshold; MPQ = McGill Pain questionnaire; S = sensory; A = affective; E = evaluative; T = total; PPI = present pain index; NWC = number of words chosen. The bold-face subject numbers and their data indicate that these subjects have participated in the imaging study AND their fMRI data have been analyzed.

# APPENDIX X (cont.)

| n = 30 | CSQ | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Subj# | 7 | 6 | 5 | 4 | 3 | 2 | 1 | A | B | Age | AASD (sec) |
| 1 | 15 | 21 | 13 | 18 | 1 | 6 | 20 | 5 | 4 | 25 | 94.33 |
| 2 | 1 | 2 | 20 | 21 | 4 | 5 | 10 | 4 | 2 | 27 | 197.22 |
| 4 | 23 | 0 | 16 | 6 | 10 | 16 | 16 | 4 | 3 | 22 | 97.11 |
| **5** | **23** | **4** | **25** | **24** | **7** | **6** | **13** | **5** | **4** | **24** | **114.44** |
| 6 | 8 | 6 | 19 | 17 | 1 | 0 | 9 | 4 | 4 | 23 | 81.22 |
| **7** | **16** | **16** | **25** | **22** | **5** | **1** | **21** | **5** | **4** | **24** | **94.00** |
| 8 | 8 | 0 | 24 | 4 | 10 | 5 | 13 | 4 | 3 | 22 | 165.00 |
| 9 | 22 | 23 | 30 | 28 | 17 | 6 | 27 | 5 | 3 | 36 | 77.56 |
| 11 | 23 | 6 | 22 | 13 | 23 | 13 | 23 | 5 | 4 | 23 | 89.00 |
| **12** | **8** | **1** | **21** | **11** | **2** | **2** | **19** | **4** | **3** | **26** | **29.89** |
| 13 | 31 | 5 | 30 | 21 | 18 | 2 | 27 | 5 | 4 | 22 | 100.56 |
| 14 | 32 | 20 | 23 | 18 | 26 | 27 | 29 | 3 | 2 | 28 | 116.11 |
| 15 | 17 | 12 | 23 | 21 | 30 | 17 | 17 | 4 | 4 | 25 | 174.44 |
| 16 | 21 | 8 | 23 | 21 | 21 | 4 | 10 | 5 | 5 | 20 | 65.56 |
| 17 | 14 | 15 | 19 | 14 | 12 | 13 | 16 | 4 | 3 | 20 | 183.44 |
| 19 | 19 | 17 | 32 | 16 | 21 | 5 | 11 | 4 | 4 | 21 | 130.89 |
| 20 | 1 | 23 | 13 | 14 | 3 | 0 | 2 | 5 | 5 | 21 | 132.22 |
| 21 | 20 | 4 | 13 | 14 | 6 | 9 | 14 | 3 | 3 | 24 | 62.78 |
| 23 | 19 | 0 | 29 | 14 | 17 | 11 | 29 | 4 | 4 | 25 | 136.11 |
| 25 | 9 | 3 | 20 | 12 | 0 | 2 | 7 | 3 | 2 | 24 | 129.89 |
| 26 | 8 | 4 | 16 | 10 | 0 | 0 | 17 | 5 | 4 | 38 | 136.00 |
| 27 | 24 | 10 | 26 | 18 | 8 | 6 | 16 | 3 | 3 | 26 | 153.11 |
| 28 | 13 | 9 | 15 | 12 | 27 | 25 | 14 | 3 | 3 | 18 | 135.44 |
| 29 | 7 | 16 | 20 | 20 | 26 | 12 | 10 | 4 | 3 | 36 | 127.78 |
| 30 | 24 | 15 | 28 | 33 | 15 | 9 | 30 | 4 | 4 | 18 | 139.89 |
| 31 | 16 | 21 | 23 | 9 | 7 | 6 | 16 | 5 | 6 | 32 | 147.44 |
| 32 | 16 | 8 | 24 | 20 | 3 | 23 | 25 | 3 | 3 | 37 | 74.11 |
| 33 | 26 | 19 | 23 | 23 | 15 | 5 | 22 | 4 | 5 | 22 | 172.33 |
| 34 | 8 | 21 | 18 | 19 | 1 | 6 | 10 | 4 | 4 | 34 | 192.67 |
| 35 | 9 | 12 | 15 | 23 | 6 | 7 | 19 | 4 | 4 | 22 | 154.89 |

CSQ 1 = increase behavioural activities; CSQ 2 = catastrophize; CSQ 3 = pray; CSQ 4 = ignore; CSQ 5 = coping self-statements; CSQ 6 = reinterpret pain sensations; CSQ 7 = divert attention; CSQ A = ability to control pain; CSQ B = ability to decrease pain; AASD = average after-sensations duration. The subject numbers and their data in boldface type indicate that these subjects have participated in the imaging study AND their fMRI data have been analyzed.

# APPENDIX XI

## The Onset of Pain Thresholds for All Individual Subjects on All Trials

| Pain Threshold (sec) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Subj# | Trial # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1 | 10.27 | 39.60 | 12.25 | 23.12 | 22.91 | 14.01 | 10.60 | 13.13 | 12.64 | 23.73 |
| 2 | 12.08 | 25.54 | 26.53 | 33.40 | 29.66 | 15.21 | 36.47 | 23.62 | 35.15 | 30.27 |
| 4 | 10.06 | 21.64 | 18.45 | 13.73 | 10.94 | 22.85 | 19.55 | 19.50 | 18.18 | 19.82 |
| 5 | 9.94 | 8.68 | 9.01 | 12.08 | 8.79 | 7.09 | 7.47 | 7.85 | 9.17 | 8.07 |
| 6 | 5.93 | 4.77 | 4.23 | 3.57 | 5.38 | 4.01 | 6.04 | 6.92 | 4.84 | 5.32 |
| 7 | 12.03 | 20.11 | 11.87 | 14.01 | 17.41 | 6.81 | 11.87 | 18.90 | 19.23 | 18.34 |
| 8 | 12.19 | 14.88 | 17.25 | 16.87 | 15.60 | 8.08 | 12.03 | 11.64 | 12.85 | 16.31 |
| 9 | 20.76 | 22.68 | 25.32 | 18.89 | 21.86 | 38.45 | 10.82 | 37.85 | dne | dne |
| 11 | 17.63 | 30.81 | 27.41 | 26.80 | 19.67 | 19.67 | 19.27 | 35.09 | 19.60 | 17.41 |
| 12 | 6.48 | 12.68 | 21.20 | 10.05 | 18.45 | 9.78 | 13.18 | 25.76 | 11.32 | 19.99 |
| 13 | 14.17 | 11.53 | 22.74 | 13.07 | 26.81 | 11.54 | 13.01 | 25.98 | 25.10 | 23.62 |
| 14 | 8.24 | 4.94 | 11.37 | 9.06 | 12.13 | 12.53 | 8.90 | 9.50 | 12.96 | 25.16 |
| 15 | 17.25 | 30.65 | 24.93 | 13.46 | 16.21 | 34.50 | 17.41 | 18.62 | 30.98 | 15.33 |
| 16 | 17.30 | 37.96 | 15.71 | 15.03 | 14.50 | 14.22 | 19.39 | 19.93 | 24.88 | 50.87 |
| 17 | 21.53 | 30.37 | 41.24 | 28.12 | 35.81 | 71.62 | 43.83 | 43.83 | 32.95 | 36.14 |

dne = does not exist -- pain was never felt on that trial.

# APPENDIX XII

## The After-Sensations Durations for All Individual Subjects on All Trials.

| After-sensations duration (secs) Subj# | Trial 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | 82 | 62 | 72 | 58 | 161 | 96 | 92 | 166 |
| 2 | 148 | 165 | 200 | 175 | 206 | 210 | 237 | 206 | 228 |
| 4 | 90 | 120 | 97 | 100 | 83 | 87 | 105 | 102 | 90 |
| 5 | 83 | 128 | 123 | 80 | 132 | 176 | 68 | 85 | 155 |
| 6 | 79 | 88 | 70 | 90 | 72 | 90 | 72 | 75 | 95 |
| 7 | 96 | 117 | 82 | 94 | 70 | 85 | 98 | 112 | 92 |
| 8 | 150 | 192 | 136 | 180 | 202 | 180 | 195 | 148 | 102 |
| 9 | 87 | 85 | 74 | 90 | 69 | 66 | 90 | 80 | 57 |
| 11 | 100 | 75 | 87 | 94 | 82 | 85 | 79 | 105 | 94 |
| 12 | 45 | 21 | 18 | 42 | 30 | 24 | 38 | 31 | 20 |
| 13 | 105 | 83 | 97 | 86 | 83 | 103 | 144 | 94 | 110 |
| 14 | 88 | 118 | 122 | 140 | 130 | 112 | 117 | 105 | 113 |
| 15 | 105 | 137 | 168 | 181 | 176 | 175 | 210 | 200 | 218 |
| 16 | 88 | 68 | 59 | 68 | 66 | 63 | 68 | 58 | 52 |
| 17 | 147 | 160 | 148 | 188 | 210 | 158 | 222 | 206 | 212 |
| 19 | 210 | 83 | 110 | 122 | 125 | 163 | 136 | 100 | 129 |
| 20 | 84 | 138 | 117 | 94 | 154 | 168 | 147 | 101 | 187 |
| 21 | 70 | 52 | 63 | 73 | 58 | 77 | 47 | 67 | 58 |
| 23 | 145 | 150 | 87 | 152 | 114 | 156 | 164 | 114 | 143 |
| 25 | 124 | 135 | 165 | 121 | 108 | 132 | 146 | 108 | 130 |
| 26 | 186 | 178 | 170 | 118 | 109 | 87 | 163 | 93 | 120 |
| 27 | 160 | 143 | 218 | 181 | 160 | 124 | 149 | 128 | 115 |
| 28 | 143 | 141 | 107 | 171 | 183 | 170 | 98 | 68 | 138 |
| 29 | 138 | 171 | 175 | 111 | 107 | 115 | 113 | 119 | 101 |
| 30 | 131 | 101 | 112 | 124 | 166 | 149 | 150 | 152 | 174 |
| 31 | 111 | 135 | 133 | 131 | 150 | 184 | 163 | 164 | 156 |
| 32 | 82 | 80 | 73 | 82 | 69 | 62 | 81 | 70 | 68 |
| 33 | 178 | 80 | 152 | 171 | 222 | 168 | 160 | 220 | 200 |
| 34 | 138 | 170 | 213 | 215 | 144 | 228 | 230 | 198 | 198 |
| 35 | 196 | 138 | 145 | 167 | 233 | 147 | 143 | 78 | 147 |

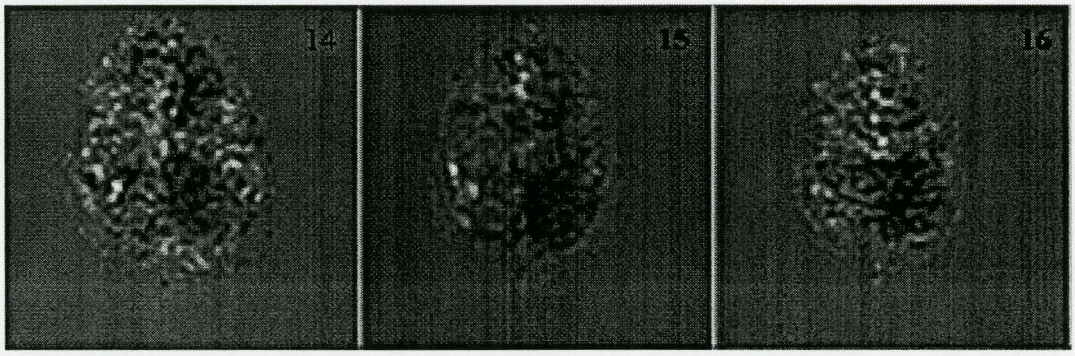
# APPENDIX XIII

## The Functional Images of the Motor Activation

Displayed are those sections that show activation in the motor cortex. The sections are arranged in order from the inferior regions of the cortex to the superior regions. The section number associated with each section is labeled at the top right corner of each figure. An increase in rCBF corresponds to bright signal intensities. The right hemisphere of the image is on the LEFT side of the figure.

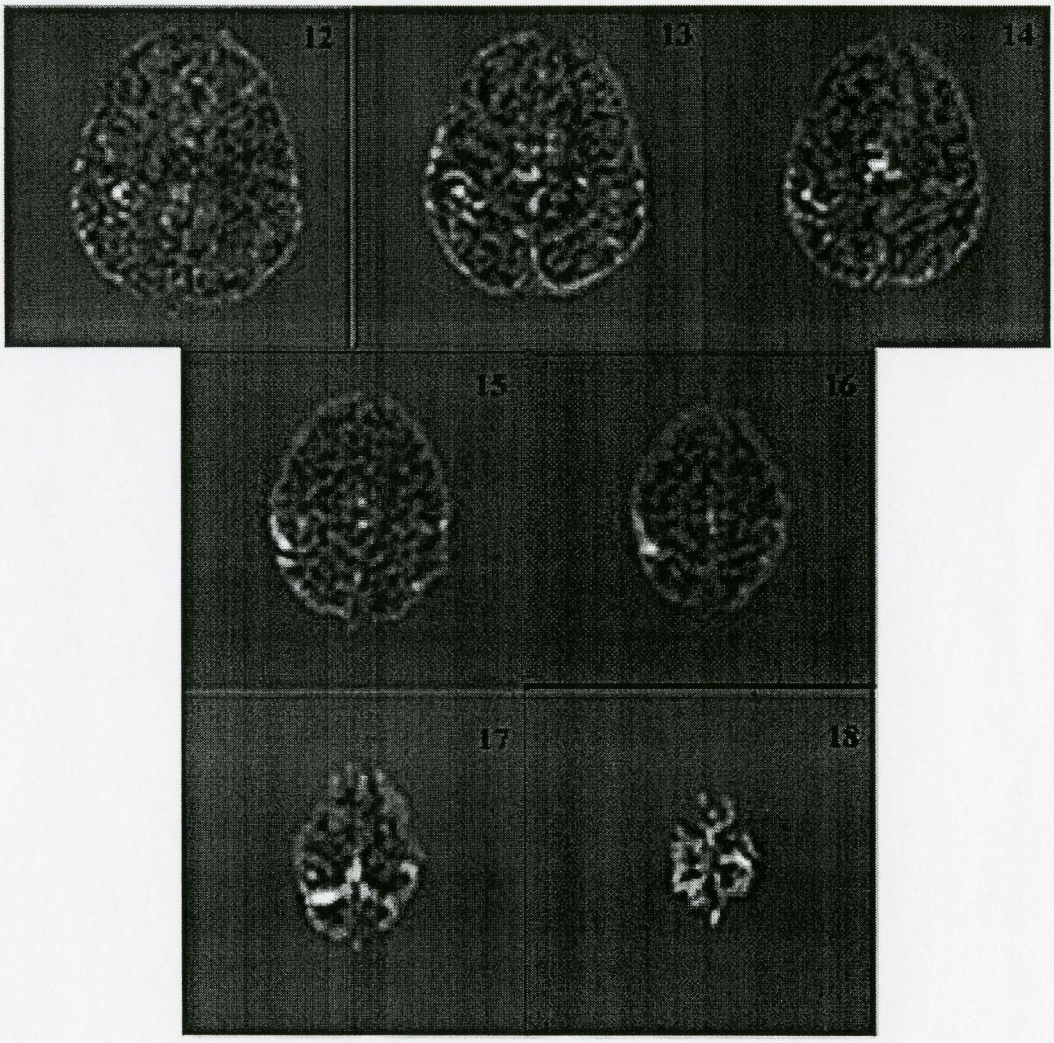
# APPENDIX XIII

**Subject no. 5**



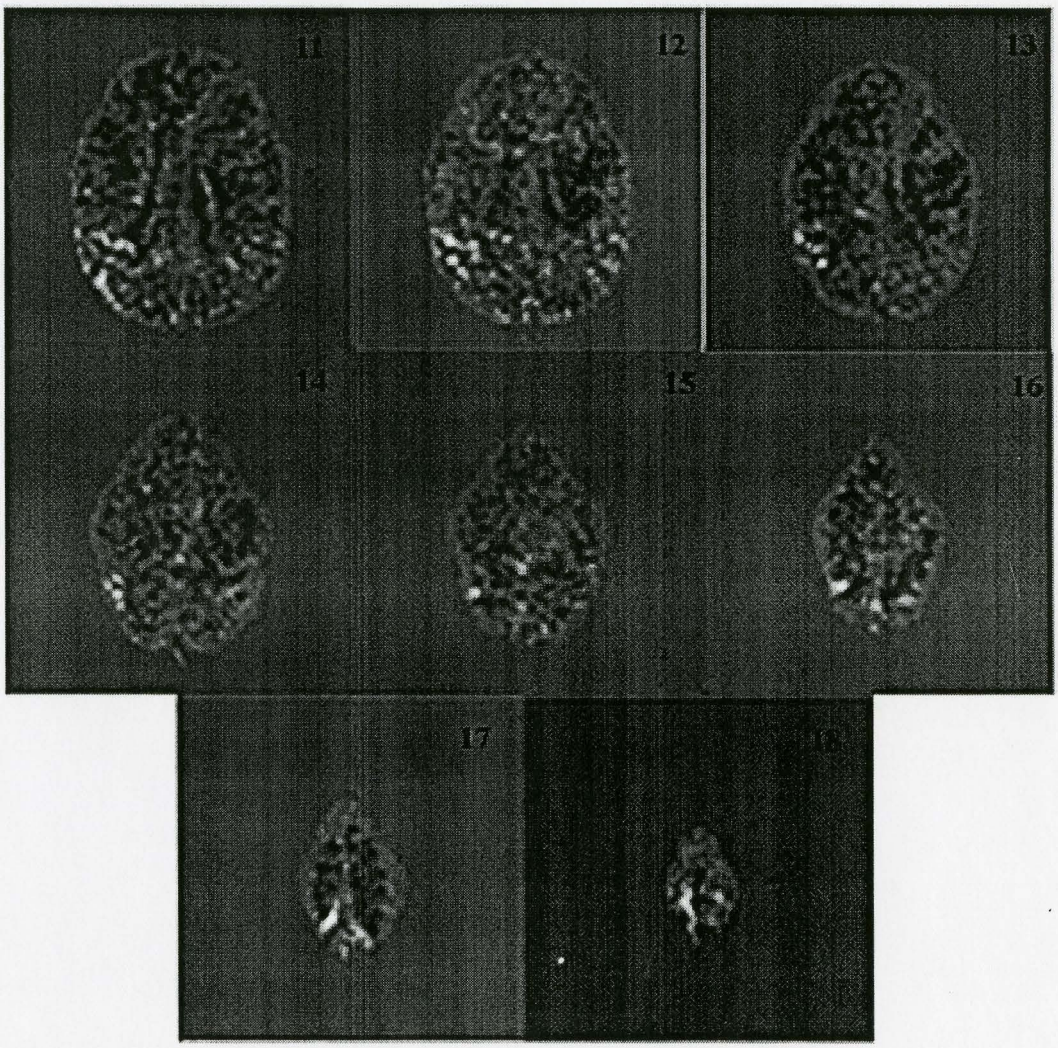
# APPENDIX XIII (cont.)

**Subject no. 7**



# APPENDIX XIII (cont.)

**Subject no. 12**



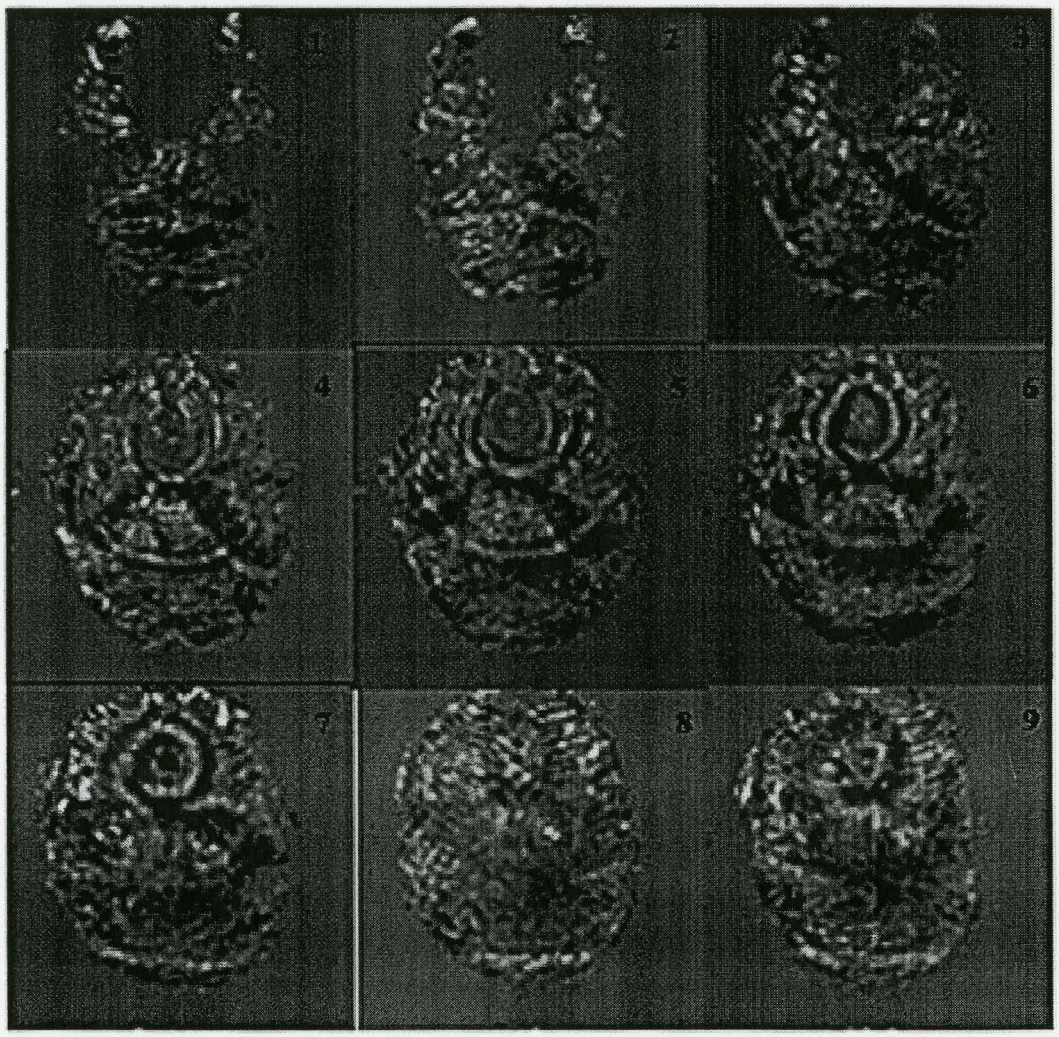
# APPENDIX XIV

## The Functional Images of the Block Stimulation

The volume is displayed as 18 sections. The sections are arranged in order from the inferior regions of the cortex to the superior regions. The section number associated with each section is labeled at the top right corner of each figure. An increase in rCBF corresponds to bright signal intensities, whereas a decrease corresponds to dark intensities. The right hemisphere of the image is on the LEFT side of the figure.

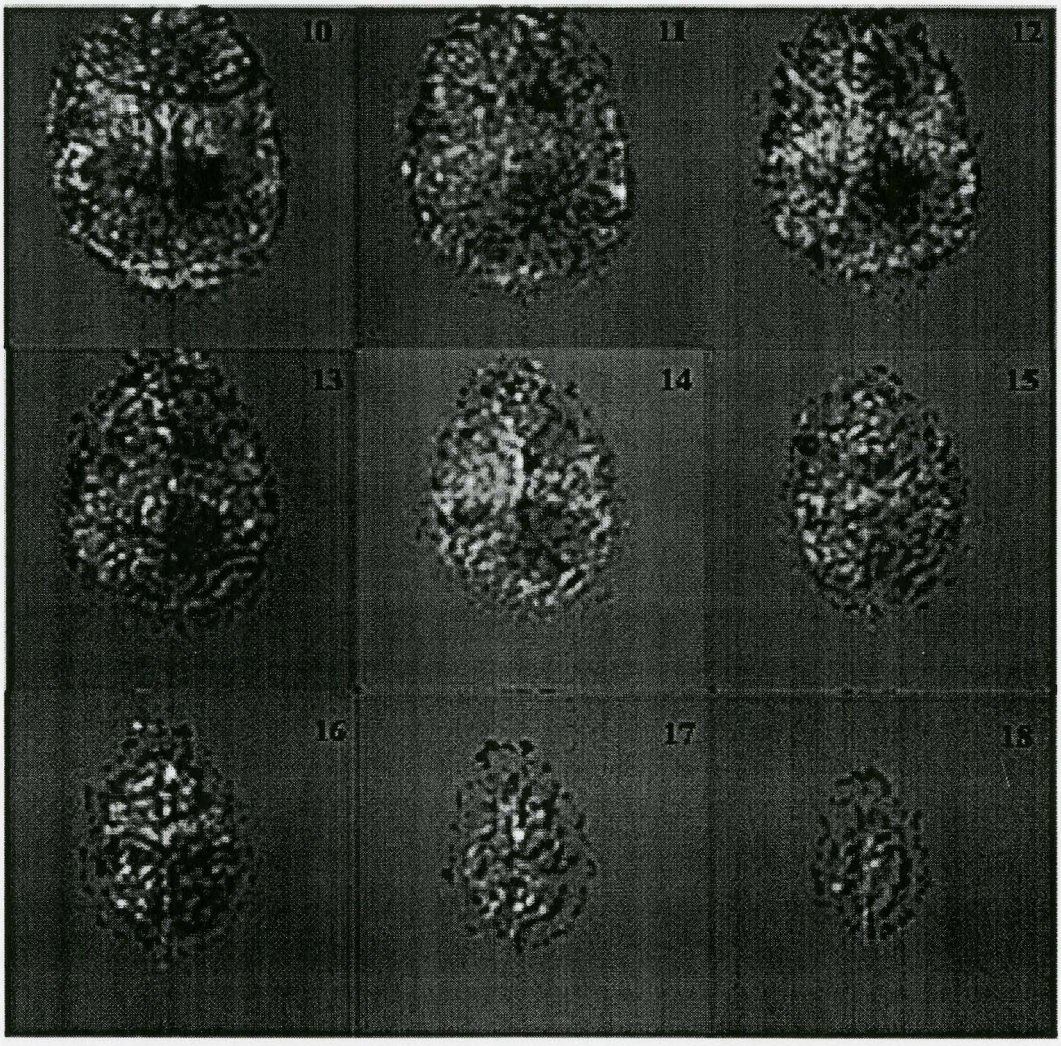
# APPENDIX XIV

**Subject no. 5**



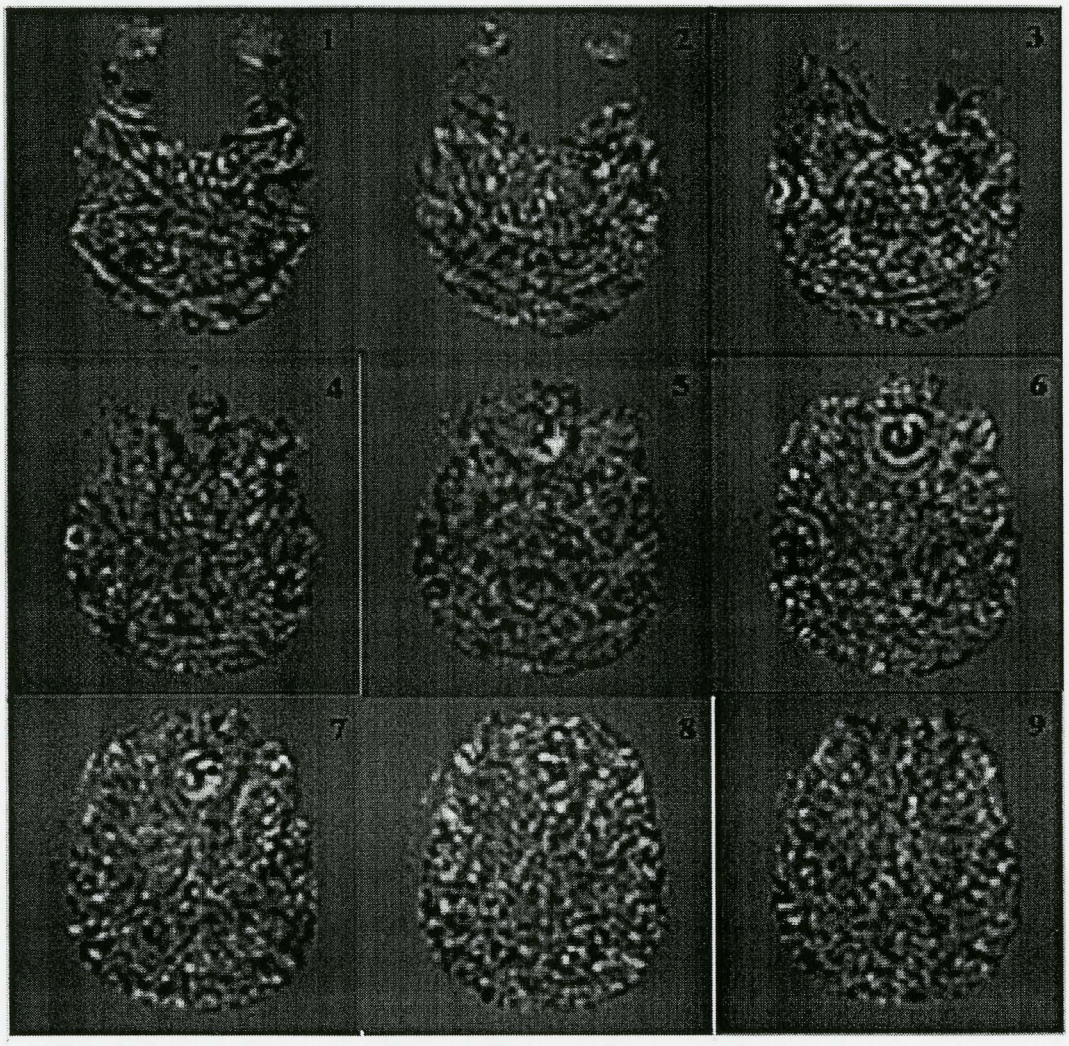
# APPENDIX XIV (cont.)

**Subject no. 5 (cont.)**



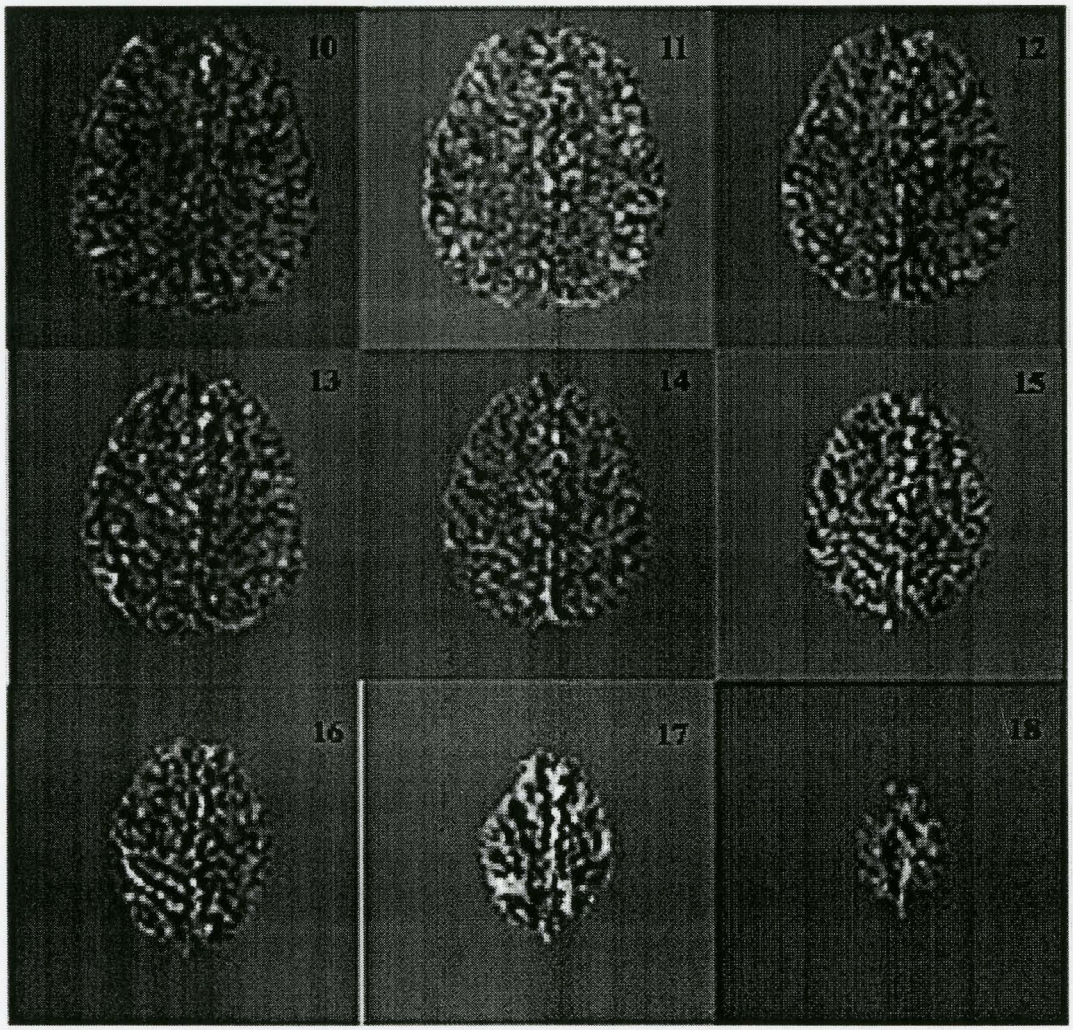
# APPENDIX XIV (cont.)

**Subject no. 7**



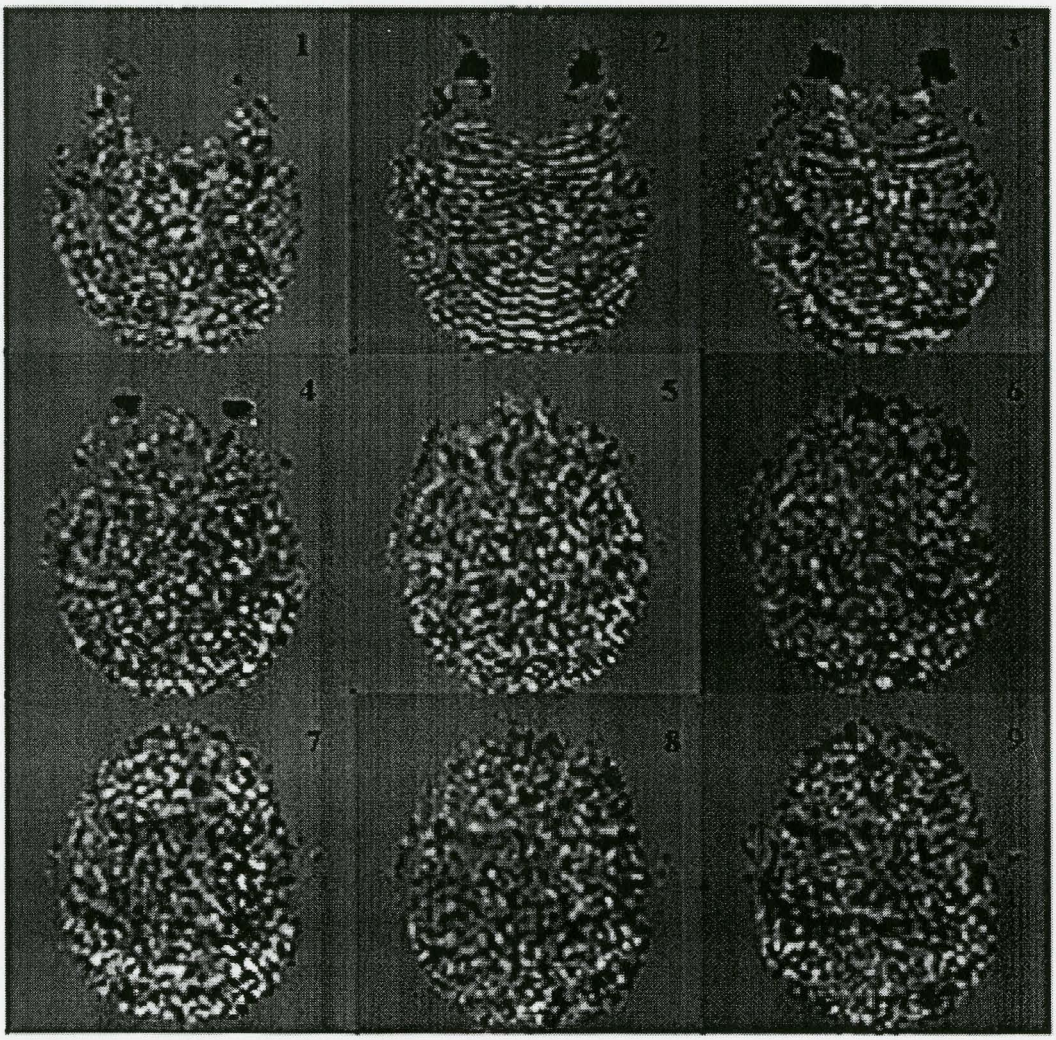
# APPENDIX XIV (cont.)

**Subject no. 7 (cont.)**

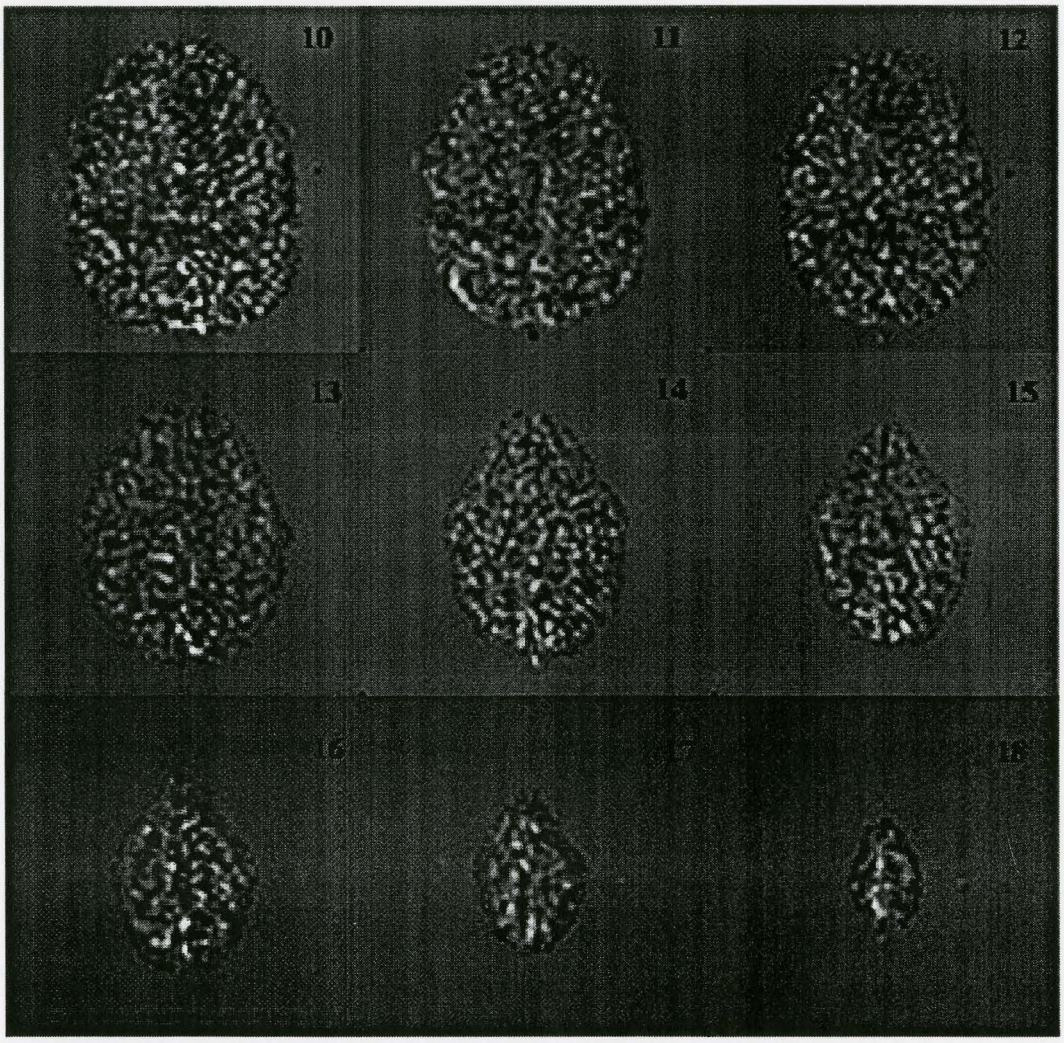


# APPENDIX XIV (cont.)

**Subject no. 12**



**Subject no. 12 (cont.)**



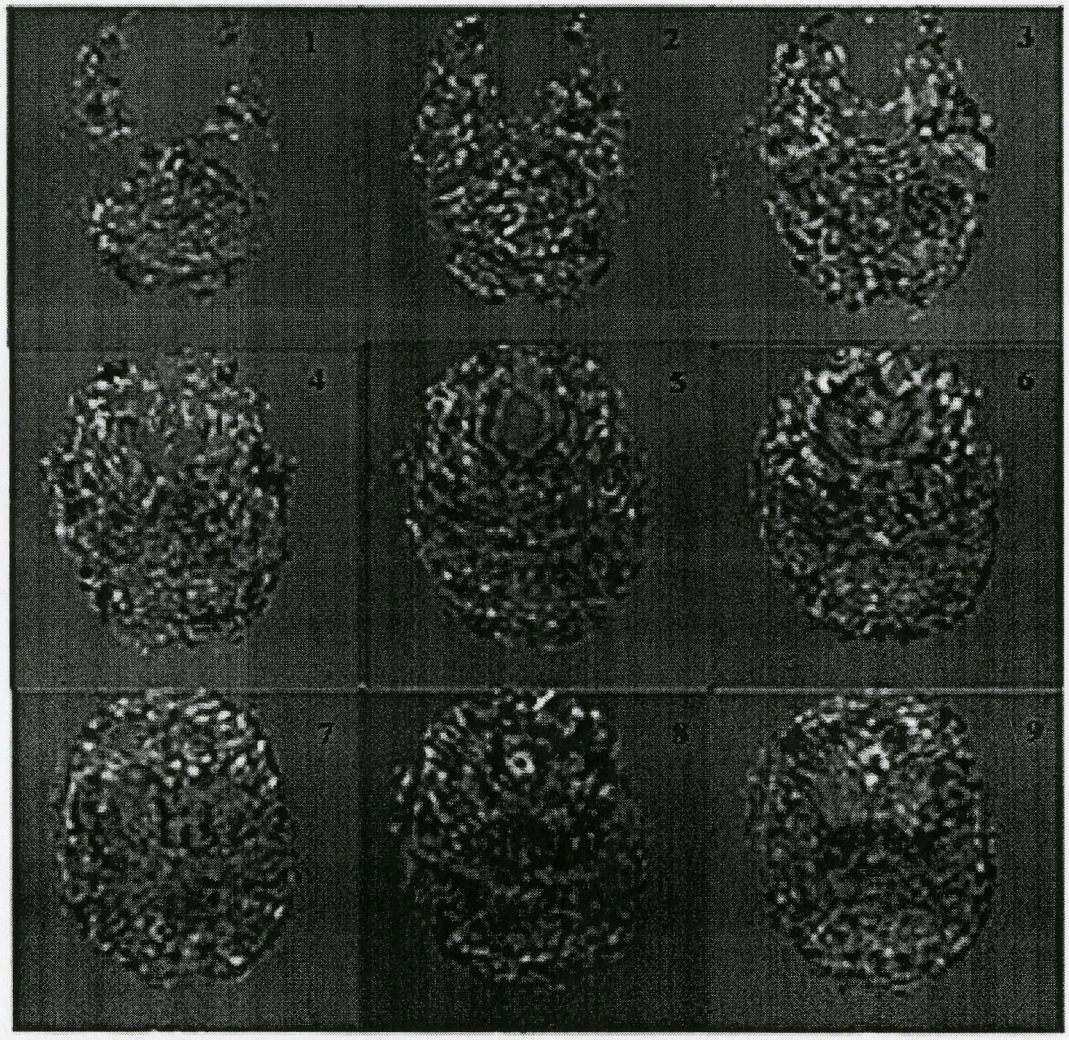
# APPENDIX XV

## The Functional Images of the Noxious Cold Stimulation

The volume is displayed as 18 sections. The sections are arranged in order from the inferior regions of the cortex to the superior regions. The section number associated with each section is labeled at the top right corner of each figure. An increase in rCBF corresponds to bright signal intensities, whereas a decrease corresponds to dark intensities. The right hemisphere of the image is on the LEFT side of the figure.

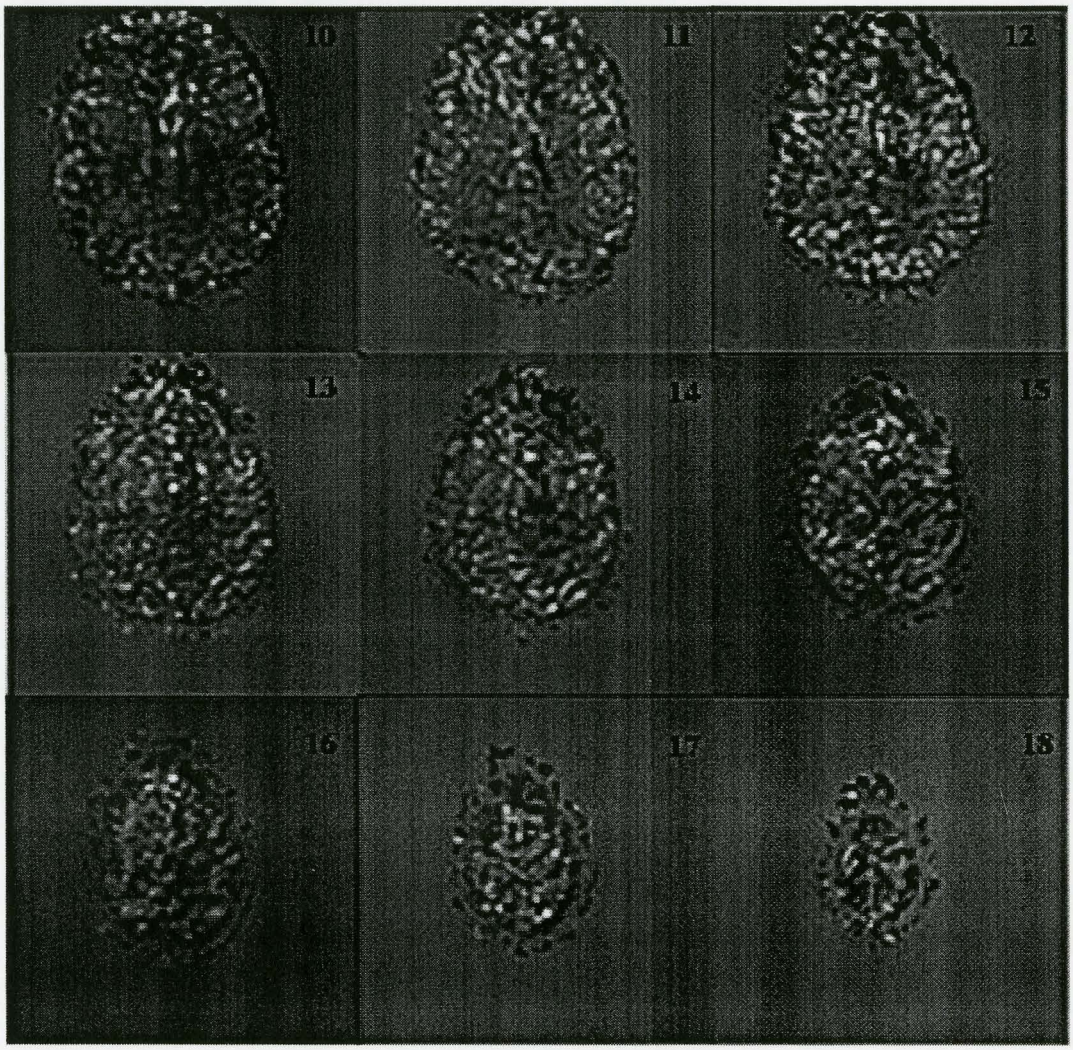
# APPENDIX XV

**Subject no. 5**



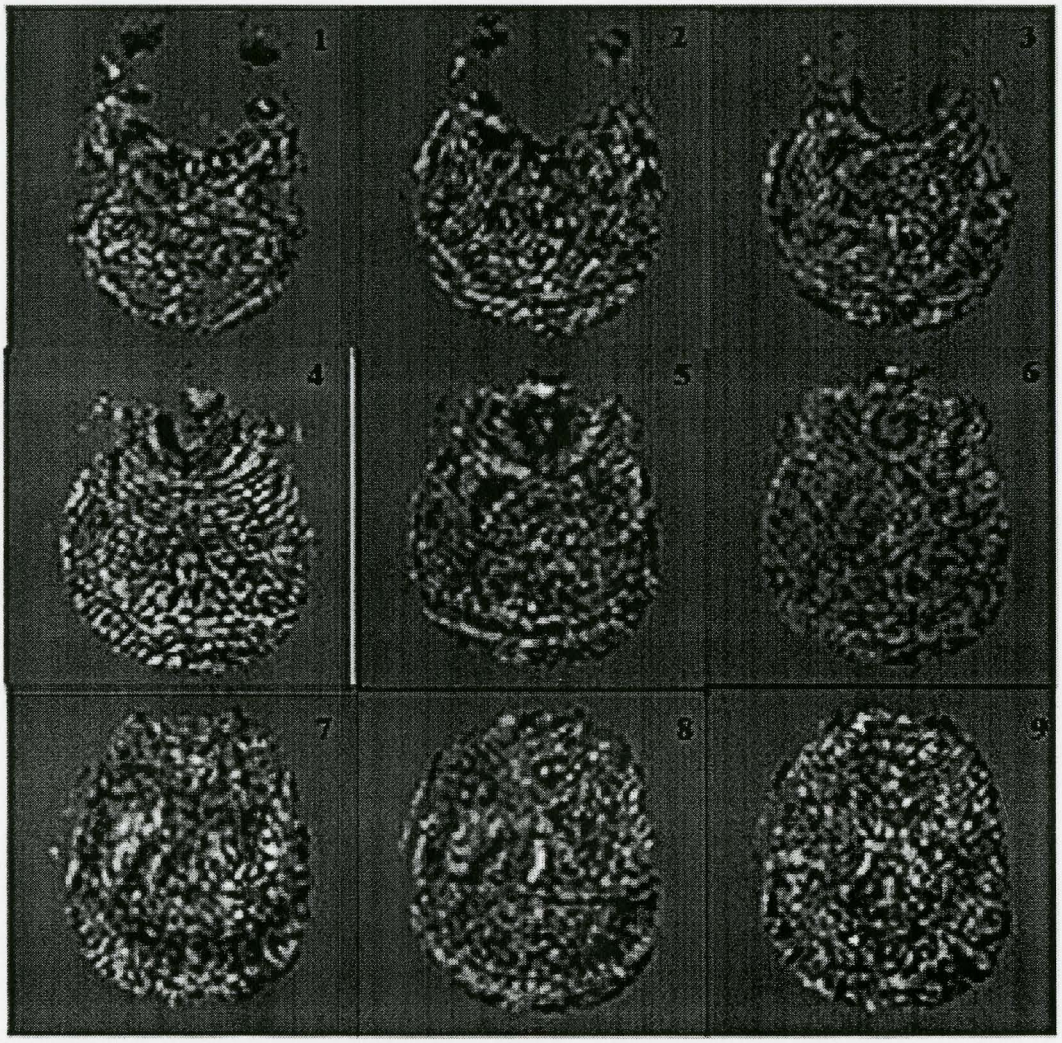
# APPENDIX XV (cont.)

**Subject no. 5 (cont.)**



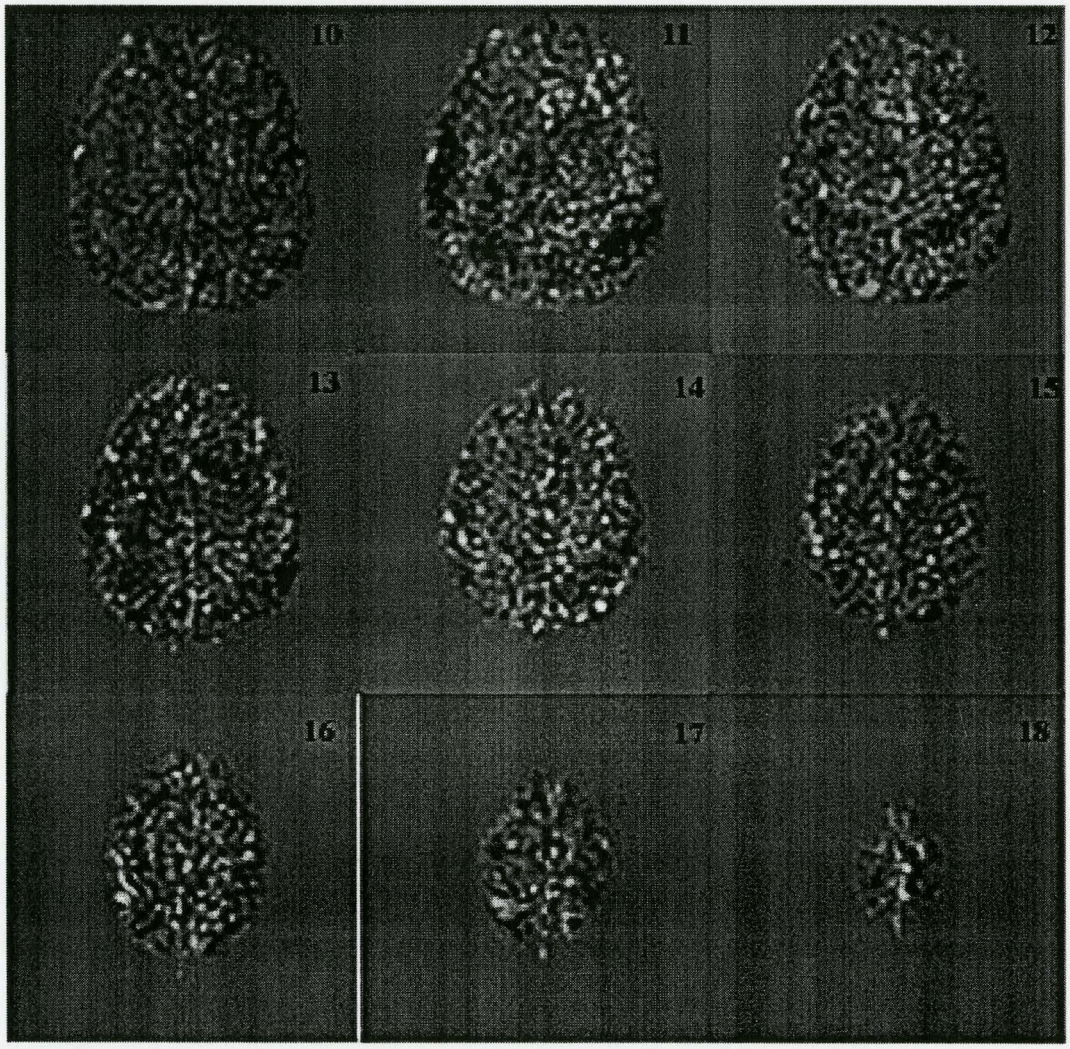
# APPENDIX XV (cont.)

**Subject no. 7**



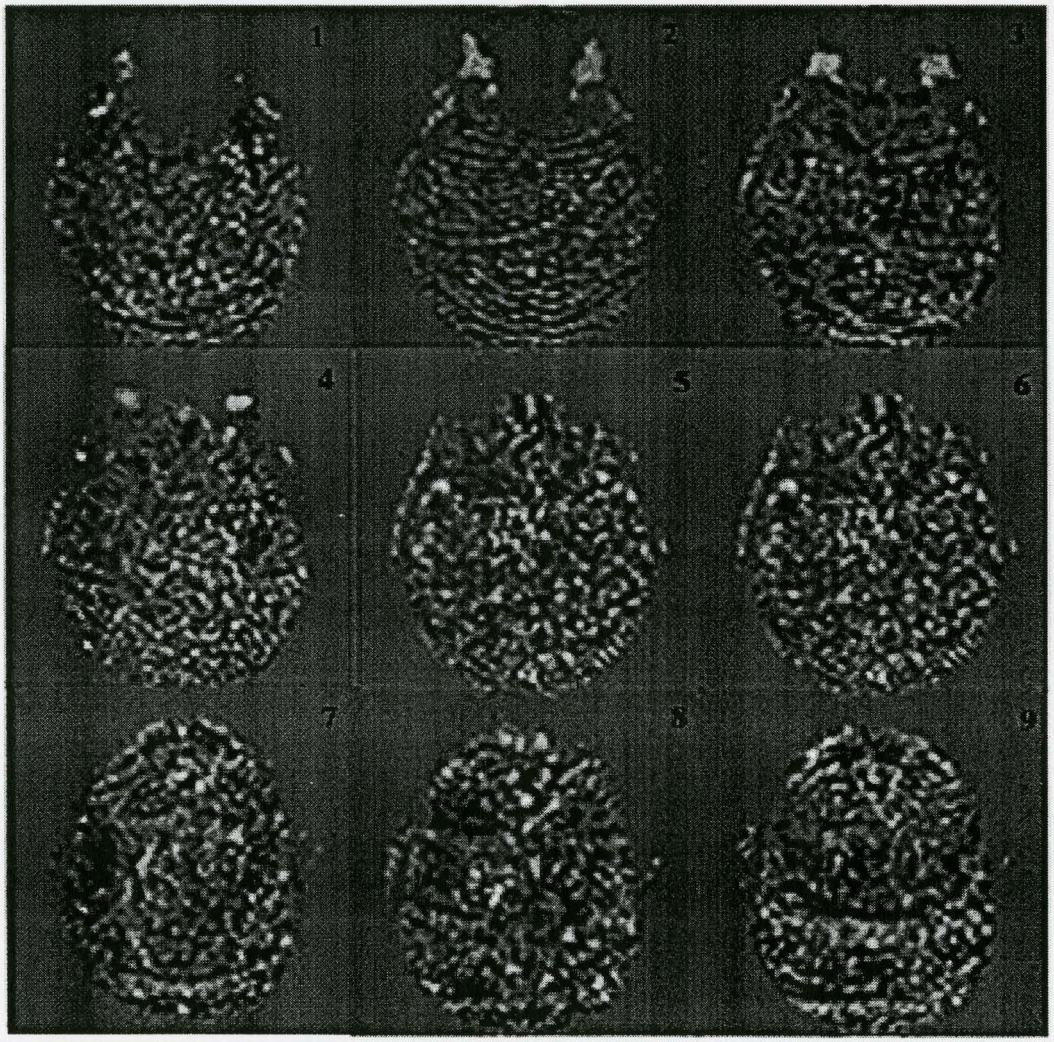
# APPENDIX XV (cont.)

**Subject no. 7 (cont.)**



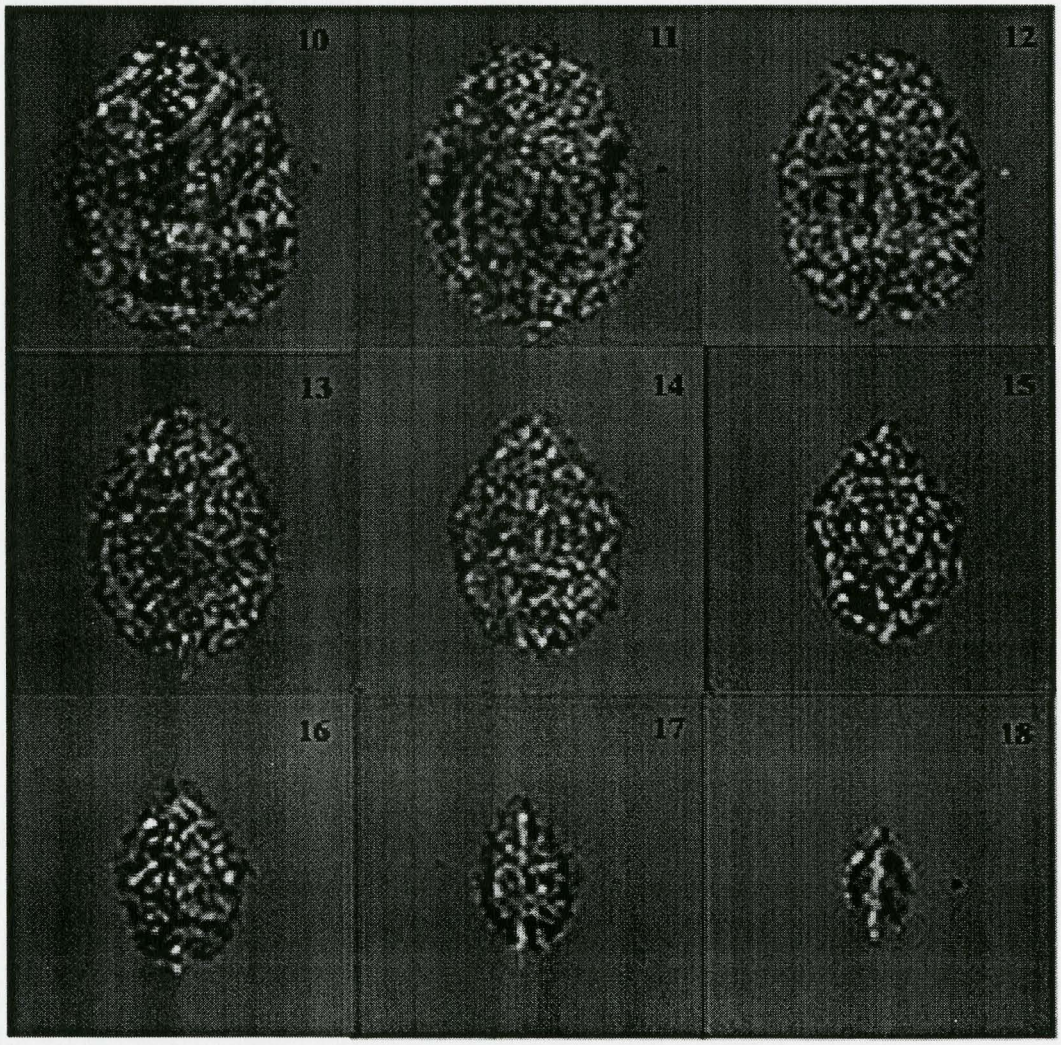
# APPENDIX XV (cont.)

**Subject no. 12**



# APPENDIX XV (cont.)

**Subject no. 12 (cont.)**



# APPENDIX XVI

## Subjects' Responses to the Changing Pain Intensity Level

**Subject no.5**

| Trial 1 | | Trial 2 | | Trial 3 | | Trial 4 | | Trial 5 | |
|---|---|---|---|---|---|---|---|---|---|
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 9.94 | 1 | 8.68 | 1 | 9.01 | 1 | 12.08 | 1 | 8.79 |
| 2 | 16.2 | 2 | 12.74 | 2 | 11.87 | 2 | 15.98 | 2 | 17.03 |
| 3 | 19.11 | 3 | 17.91 | 3 | 15.27 | 3 | 26.26 | 3 | 20.22 |
| 4 | 22.68 | 4 | 23.07 | 4 | 26.42 | 4 | 36.42 | 4 | 29.12 |
| 5 | 30.48 | 5 | 27.74 | 5 | 29.72 | 5 | 43.06 | 5 | 36.15 |
| 6 | 32.95 | 6 | 35.21 | 6 | 36.25 | 6 | 46.3 | 6 | 42.57 |
| 7 | 36.69 | 7 | 43.23 | 7 | 42.24 | | | 7 | 43.78 |
| Trial 6 | | Trial 7 | | Trial 8 | | Trial 9 | | Trial 10 | |
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 7.09 | 1 | 7.47 | 1 | 7.85 | 1 | 9.17 | 1 | 8.07 |
| 2 | 11.32 | 2 | 10 | 2 | 11.64 | 2 | 14.33 | 2 | 11.7 |
| 3 | 16.64 | 3 | 14.5 | 3 | 16.86 | 3 | 22.19 | 3 | 22.85 |
| 4 | 24.66 | 4 | 19.33 | 4 | 21.03 | 4 | 25.92 | 4 | 27.13 |
| 5 | 32.68 | 5 | 25.92 | 5 | 31.3 | 5 | 30.48 | 5 | 32.57 |
| 6 | 40.04 | 6 | 31.8 | 6 | 38.06 | 6 | 37.24 | 6 | 37.18 |
| | | 7 | 38.72 | 7 | 41.52 | | | 7 | 39.82 |
| | | 8 | 40.04 | | | | | | |

# APPENDIX XVI (cont.)

**Subject no.7**

| Trial 1 | | Trial 2 | | Trial 3 | | Trial 4 | | Trial 5 | |
|---|---|---|---|---|---|---|---|---|---|
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 12.03 | 1 | 20.11 | 1 | 11.87 | 1 | 14.01 | 1 | 17.41 |
| 2 | 18.12 | 2 | 31.8 | 2 | 18.79 | 2 | 22.58 | 2 | 26.47 |
| 3 | 25.21 | 3 | 39.38 | 3 | 28.45 | 3 | 34.82 | 3 | 34.6 |
| 4 | 36.14 | 4 | 50.53 | 4 | 39.22 | 4 | 44.11 | 4 | 43.66 |
| | | | | | | | | 5 | 48.94 |
| Trial 6 | | Trial 7 | | Trial 8 | | Trial 9 | | Trial 10 | |
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 6.81 | 1 | 11.87 | 1 | 18.9 | 1 | 19.23 | 1 | 18.34 |
| 2 | 10.77 | 2 | 16.37 | 2 | 26.2 | 2 | 29.11 | 2 | 24.22 |
| 3 | 15.98 | 3 | 21.2 | 3 | 32.08 | 3 | 35.1 | 3 | 32.19 |
| 4 | 21.81 | 4 | 27.52 | 4 | 36.47 | 4 | 41.2 | 4 | 39.6 |
| 5 | 29.88 | 5 | 34.55 | 5 | 46.03 | 5 | 50.09 | 5 | 51.35 |
| 6 | 40.21 | 4 | 44.88 | | | | | | |

# APPENDIX XVI (cont.)

**Subject no.12**

| Trial 1 | | Trial 2 | | Trial 3 | | Trial 4 | | Trial 5 | |
|---|---|---|---|---|---|---|---|---|---|
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 6.48 | 1 | 12.68 | 1 | 21.2 | 1 | 10.05 | 1 | 18.45 |
| 2 | 15.1 | 2 | 19.06 | 2 | 30.04 | 2 | 22.57 | 2 | 26.2 |
| 3 | 22.35 | 3 | 30.15 | 3 | 31.97 | 3 | 28.28 | 3 | 33.72 |
| 4 | 28.45 | 4 | 41.03 | 4 | 36.03 | 4 | 36.47 | 4 | 41.47 |
| 5 | 33.06 | | | 5 | 42.46 | 5 | 43.11 | 5 | 45.15 |
| 6 | 36.36 | | | | | | | 6 | 53.44 |
| **Trial 6** | | **Trial 7** | | **Trial 8** | | **Trial 9** | | **Trial 10** | |
| Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) | Pain intensity | time (sec) |
| 1 | 9.78 | 1 | 13.18 | 1 | 25.76 | 1 | 11.32 | 1 | 19.99 |
| 2 | 18.23 | 2 | 17.74 | 2 | 31.35 | 2 | 21.92 | 2 | 23.4 |
| 3 | 28.12 | 3 | 22.3 | 3 | 37.35 | 3 | 26.97 | 3 | 26.69 |
| 4 | 31.97 | 4 | 25.32 | 4 | 44.6 | 4 | 35.54 | 4 | 28.45 |
| 5 | 39.49 | 5 | 32.13 | 5 | 54.05 | 5 | 40.76 | 5 | 33.5 |
| | | 6 | 36.36 | | | | | 6 | 37.18 |
| | | 7 | 41.79 | | | | | 7 | 42.29 |
| | | 8 | 46.24 | | | | | 8 | 47.78 |
| | | | | | | | | 9 | 50.69 |
| | | | | | | | | 10 | 54.92 |