Sex Differences in the Perception of Capsaicin-induced Pain

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by

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Abstract

Previous research has demonstrated that although women may find post-operative pain more intense than men, males are more disturbed than females by low levels of pain that last over time. In these studies, females had a tendency to rate the intensity of pain higher than males, but males had stronger affective responses following the surgical placement of intra-oral implants. However, these findings have not been investigated in an experimental setting. This experiment examined the pain responses of 20 healthy subjects (10 males, 10 females), who were subjected to capsaicin-induced pain on the face and ankle (on separate sessions). During the experiment, all subjects rated their pain intensity, unpleasantness, and anxiety on visual analog scales (VAS). In addition, throughout the experiment, heart rate was monitored every five minutes and mood was assessed once before and after the experiment. Finally, subjects also completed the McGill Pain Questionnaires (MPQ) once at the end of every session. Results revealed that although there were generally no statistically significant sex differences in the pain ratings during the experiment, there was a sex * time interaction with males displaying increasing anxiety scores over time with the capsaicin patch on the face while the anxiety scores of females decreased over time with the capsaicin patch on the face ($F = 1.64$, $P = 0.02$). Also, there was a tendency for the relative unpleasantness (unpleasantness/intensity ratio) to be greater for males than females over time on the face ($F = 3.43$, $P = 0.08$). Males and females did not differ in both the mean number of words chosen and the pain rating index of the MPQ for all categories. In addition, there were no sex differences for heart rate and mood for both the ankle and face regions throughout the

experiment. Taken together, these results replicate previous findings that men may find low levels of pain more disturbing than women.

Résumé

Des recherches antérieures ont démontrées que bien que les femmes puissent trouver la douleur post-opératoire plus intense que les hommes, toutefois les hommes sont plus dérangés que les femmes par la douleur de bas niveau qui dure longtemps. Dans ces études, les femmes ont tendance à estimer l'intensité de la douleur plus haute que les hommes, mais les hommes ont une plus forte réponse affective après le placement chirurgical des implants intra oraux. Cependant, ces découvertes n'ont pas été examinées en détail dans un milieu expérimental. Cette expérience a examinée la réponse à la douleur de 20 sujets sains (10 hommes, 10 femmes), qui ont été soumis à la douleur provoquée par capsaicin sur le visage et la cheville (dans des sessions distinctes). Pendant l'expérience, tous les sujets ont évalués l'intensité de leur douleur, déplaisance et anxiété par des échelles analogiques visuelles (Visual Analog Scales, VAS). En plus, à travers l'expérience, le battement du coeur était contrôlé chaque cinq minutes et l'humeur évaluée une seule fois avant et après l'expérience. Finalement, les sujets ont complétés aussi le questionnaire de douleur de McGill (McGill Pain Questionnaire, MPQ) une seule fois à la fin de chaque session. Les résultats ont révélés que même s'il n'y avait pas statistiquement de différences significatives entre les deux sexes pour l'évaluation de la douleur pendant l'expérience, il y avait un sex * temps d'interaction pour les hommes qui affichent une augmentation d'anxiété à travers le temps avec le bondage du capsaicin sur le visage, alors que, l'anxiété chez les femmes a diminuée à travers le temps avec le

bondage du capsaicin sur le visage (F=1.64, P = 0.02). Aussi, il y avait une tendance pour la déplaisance relative (rapport déplaisance/intensité) sur le visage à travers le temps d'être plus grande pour les hommes que pour les femmes (F= 3.43, P= 0.08). Les hommes et les femmes n'ont pas différés quant au nombre moyen des mots choisis et l'index d'évaluation de la douleur du MPQ pour toutes les catégories. En plus, il n'y avait pas de différences entre les deux sexes en terme de la vitesse de battement du coeur et de l'humeur pour des régions du visage et de la cheville pendant toute l'expérience. Dans l'ensemble, les résultats confirment des conclusions préalables qui stipulent que les hommes peuvent trouver les douleurs de bas niveau plus désagréables que les femmes.

Introduction

Background

Since the beginning of time, humanity has recognized the differences between male and female. Traditionally, the physiological aspects between the sexes have been the most obvious difference. But, even beyond the physiology, numerous differences can be named. In fact, countless books have been written discussing about these differences. Hence, there should be no surprise that differences also exist in the pain perception and pain experience between the genders. Historically, this insight is as ancient as the story of Genesis. For example, in the story of Adam and Eve, Adam felt no pain even when one of his ribs was removed, yet Eve was endowed with the pain of child labour (Genesis 2: 18-24). Even later in time, pain differences between the sexes became even more

apparent. Namely, female pain was simply disregarded (British Medical Journal, 1858 in Morris, 1991). This was because many believed that females were fabricating their illnesses or pain because they were emotionally unstable (Radomsky, 1995). In fact, many of the women who were suffering from pain were simply labelled as hysterics (Radomsky, 1995). However, the truth of the matter is, hysteria provided a convenient way for labelling women whose symptoms did not respond to conventional treatment or if the doctor felt that the women were too emotional (Radomsky, 1995). Actually, this mode of thinking was still present even as late as the seventies of the twentieth century. For example, a 1973 survey of women medical students found their professors often referred to women as "hysterical mothers", "hypochondriacs", and "crocks" whom doctors must manage (Sheridan, 1990).

Within the past ten years, gender differences in pain have been the subject of a few papers. For example, studies have shown that women have a higher prevalence of migraine headaches, arthritis, chronic reproductive organ pain syndromes, temporomandibular disorder, and back pain (Fillingim and Maixner, 1995; Unruh, 1996). In addition, other research reports indicate that men and women respond differently to both pain and pain medications, specifically opioid analgesics (Miaskowski et al., 1997; Robinson et al., 1998; Fillingim and Ness, 2000). Many believe that these variations are due to sex differences in the effects of hormones (Fillingim, 2000) and changes in pain systems at different times of the menstrual cycle (Koutnatji et al., 1998; Giamberdino et al., 1997).

Moreover, though important advances have been made, the reasons for sex differences in pain perception observed in humans are still unclear. In fact, many of the

observed sex differences are highly dependent on the experimental conditions. That is, different types of stimuli may have different reactions for both men and women. For instance, sex differences are apparent when electrical and pressure stimuli are used, but not so with heat pain (Riley et al, 1998; Lautenbacher and Rollman, 1993). In addition, other experimental paradigms have been used in pain studies to clarify the sex differences. These have included pain induction techniques, such as mechanical and cold pressor. Several clinical paradigms have been conducted as well. These have varied from the placement of intraoral implants (Feine et al., 1998; Morin et al., 2000) to arthroscopic anterior cruciate ligament reconstruction (Taenzer et al., 2000). In addition, numerous methods have been used to characterize measurements to assess pain responses, such as threshold and tolerance, visual analogue scales and magnitude matching procedures. However, even with some minor conflicting reports, there is a general agreement that women exhibit an increased sensitivity to acute pain (Riley, 1998) and are likely to report more pain in more regions than men (Berkley, 1997). Furthermore, despite their greater pain burden, women tend to cope with pain more successfully than men do (Unruh et al., 1999).

The aforementioned findings also agree with the results of experiments involving the surgical placement of intra-oral implants. In one of the studies, it was found that the relative unpleasantness (ratio of unpleasantness/intensity) increased significantly with time for males, but not for females. These results suggest that men are more disturbed than women by low levels of pain that last several days (Morin et al., 2000, Chedade et al., 2001). Other clinical studies have found similar results. For example, in a study of 147 arthritic patients, Affleck et al. (1999) found that although women reported higher

levels of daily pain, men were more likely than women to report an increase in negative mood the day after a more painful day. That is, men had a greater "carry-over" effect of intensifying pain on their negative mood the following day. These results indicate that although women may experience more intense pain, they may be able to better limit its emotional consequences than men. In short, taken together, these studies suggest women may be more sensitive to pain but they handle pain better than men. However, Sheffield et al. did not find the same affective response by males using thermal stimuli in an experimental setting (2000).

Literature Review

INTRODUCTION

The present literature review attempts to summarize some of the recent studies on gender differences in pain perception in humans. This review will be separated into two sections, specifically examining the gender variation found in 1) experimental studies and 2) clinical studies. Due to the breadth of current pain research, this review will only highlight some of the more relevant topics to this study. Finally, this review concludes by discussing the pros and cons of both types of pain settings (i.e. clinical vs. experimental).

Experimental Pain Studies

Description

It is important to note that most studies in which sex differences in pain perception are evaluated have employed experimentally-induced pain. These studies have included a variety of pain induction techniques such as: pressure, electrical, thermal, and cold-pressor. These stimuli differ across many dimensions such as site of application, temporal parameters of the stimulation, and the quality of the pain sensation. Thermal pain studies, typically, employ contact thermodes to transmit thermal heat stimuli (Arebdt-Neilsen and Bjerring, 1988). On the other hand, the cold pressor test is usually administered by placing the subject's non-dominant arm (to the elbow) in a plastic cylindrical container filled with ice-water maintained at 0-2 °C (Sternberg et al., 1998). Moreover, pressure pain is usually administered through a constant pressure

device to a specific region of the body, with the dependent variable measured in units of time (Dubreuil and Kohn, 1986). Finally, electrical pain is administered using an apparatus that transmits a constant current, or in some cases, the apparatus is set to deliver currents at a set time interval (Gracely, 1991). Methodologically, these studies are quite diverse, sometimes making interpretations across studies difficult to explain. The majority of studies have attempted to determine if men and women have different levels of pain thresholds, tolerance and intensity. Pain threshold refers to the minimum amount of stimulation that evokes a report of pain in an individual (Miaskowski, 1997). Pain tolerance is defined as the maximally tolerated stimulus intensity that an individual can endure (Miaskowski, 1997), while intensity refers to the actual pain sensation. One of the most common measurement instruments used to characterize pain responses has been the visual analogue scale (VAS). The VAS entails a straight horizontal line (typically 100 mm) on which subjects are asked to mark a vertical line to indicate the level of pain sensation they are feeling. On the extreme ends of the 100 mm line, there are anchor words that indicate either an absolute lack of pain or the worst pain sensation possible. Other more sensitive measurement techniques include the magnitude matching procedure. The magnitude matching procedure consists of the administration of a series of alternating pain and light stimuli of varying intensities of which subjects are asked to rate the intensity on the same numerical scale as the pain. This procedure allows the normalization of ratings from one modality (i.e. pain) using the ratings of intensity from another sensory modality (i.e. light). This normalization reduces the effects of individual differences in use of the rating scale, which results in decreased variability both between and within subjects (Feine et al., 1991).

Results

One of the earlier papers that set out to examine exclusively sex differences in pain perception was conducted by Feine and colleagues (1991). In this study, 40 subjects (20 females, 20 males; mean age 25 yrs) were asked to rate the magnitude of 120 heat stimuli, ranging from 45 C to 50 C. The heat stimulus was administered using a thermode that was applied to different spots of the skin above the subject's upper lip. Then, subjects were asked to rate their pain sensation using the visual analog scale (VAS). The results revealed that females rated heat stimuli as more intense than did males at every temperature point. These results actually reflect the general consensus in most studies to date. In fact, several literature reviews conducted by Fillingim et al. 1995) and Riley et al., (1998) strongly support the notion that females exhibit a greater sensitivity to noxious stimulation than males. Collectively, the studies indicate that females have lower pain thresholds, rate similar stimuli as more painful and have less tolerance to experimental pain stimuli than do men. Although, in general, these results have been reproducible for every type of pain stimuli, the ratings of electrical (Rollman et al., 1987) and pressure (Buchanan et al., 1987, Fischer, 1987) stimuli exhibit greater reliability in observing sex differences than are the ratings of thermal stimuli and cold pressors. For example, one report by Zeichner et al. (2000) did not find sex difference in the cold pressor test. In his study, 42 healthy adults (24 women, 18 men, mean age: 20.8) were administered a cold pressor task, in which the dominant foot was submerged to the top of the ankle in an ice water bath (between 0° and 4 °C) for 2 minutes. Subsequently, the experimenter prompted each subject to rate pain aloud while viewing a vertically

displayed 11- point rating scale of pain descriptors ranging from "no pain at all" to "unbearable pain". The results indicated that there were no statistically significant sex differences for the subjective pain ratings during the cold pressor task, although the mean pain scores for females were greater than their male counterparts.

Moreover, although there are slight discrepancies in terms of the interpretation of the differences, experimental studies suggest overall that women are more sensitive to noxious experimental stimuli than men even though the actual differences demonstrated in each of the individual studies were small (Berkley, 1997). In addition, some have suggested that these small differences in gender ratings may be caused by a lack of willingness to report the pain by males (Berkley, 1995). For example, in study by Nayak et al. (2000), the authors studied the gender effects in pain beliefs and the prediction of pain tolerance. They explored beliefs about appropriate or normative pain responses among 226 college students (aged 18-24yrs) in the US and India. More specifically, they examined differences in pain tolerance and intensity ratings and how the role beliefs play in predicting pain tolerance. Scales to assess beliefs about appropriate pain responses in males and females were completed after the cold pressor test. Results indicated that females believed overt pain expression and the reporting of pain were more appropriate than did males.

More recently, researchers have studied other relevant variables, in addition to the stimulus characteristics, in an attempt to understand how gender differences in pain perception in daily life settings can be explained by differences found in experimental studies. In fact, they have attempted to see how other variables impact differently on the pain perception of males and females. For example, one study investigated the effects of

different attentional strategies (focused vs. avoidance) on how males and females may respond differently to experimentally induced pain (Keogh et al., 2000). In this study, 100 healthy subjects (50 males, 50 females, mean age: 26.4) were told to either focus on the cold pressor sensation or to try not to pay attention to it. Subsequently, measures of pain tolerance, pain threshold and self-report measures of intensity of the pain experience were recorded. The results revealed that males were found to be more tolerant to cold pressor than females and that males reported less pain when they attended toward the pain than when they avoided it. This effect was not found in females. Taken together, these results suggest that men and women may differ with respect to the effect attentional processes have on reported pain. That is, men who were instructed to focus on the pain experience were found to report lower sensory pain compared to men who were told to avoid pain. However, the attentional strategies had no significant role in mediating the sensory reports of women.

Other aspects of sex differences in pain perception include examining the influence of time of day on experimentally induced pain threshold in men and women (Koltyn et al., 1999). In this study 29 volunteers (14 females, 15 males, mean age: 20.5) were randomly assigned sessions between 6.00-8.00 AM and between 6.00 – 8.00 PM with a two day period. Subsequently, pressure (3000 gm force) was applied to the middle digit for 2-min for every subject in their respective time slot. Measurements such as pain threshold and other physiological variables (BP, temp) were then recorded. The results revealed that men had higher systolic blood pressure and pain thresholds than women for both time slots. However, there was not a significant time of day effect for pain threshold.

Another variable that may influence males and females differently involves studying the effects of odour on gender and pain perception (Marchand et al., 2002). For example, in this study, forty healthy subjects (20 women and 20 men, aged 18-25 years) were asked to rate the perception of thermal stimulation every 15 s while their hand was immersed in a hot circulating bath (46-48 °C) for 3 min and while they were continually smelling one of three previously selected odours (most unpleasant, most pleasant and closest to neutral). The results revealed that although there were no sex differences in pain perception, the effect of odour on pain was gender specific, as only females experienced a significant reduction of pain perception during pleasant odors presentation.

In addition, it has also been shown that the presence of other pain conditions can affect experimental pain responses (Edwards et al., 1999). In one study, 46 dental patients (15 male, 31 female, mean age: 35.6) experiencing pain due to acute irreversible pulpitis and 33 healthy controls (13 male, 20 female, mean age: 32.2) were examined for sex differences in thermal pain onset and tolerance. The results indicated that although thermal pain onset and tolerance were lower in control females than in control males, male and female pulpitis patients did not differ in their thermal pain responses. In addition, pulpitis patients also had greater affective distress than controls for the same pain stimuli.

Interestingly enough, other researchers have criticized the use of common experimental pain techniques as futile, since the pain emitted by these pain stimuli are rarely experienced by people during normal daily living (Cook et al., 1998). They cited the importance of examining other pain experiences that are encountered commonly such as muscle pain experienced during exercise. In their study, they investigated whether

males and females exhibited differences in naturally occurring leg muscle during ramped cycle exercise to maximum tolerance. Fifty-two moderately active college students (26 females, 26 males, mean age: 22.6) were matched on weekly energy expenditure and they were required to complete a ramped maximal cycle ergometry test. Subsequently, leg muscle pain threshold, pain intensity ratings as well as perceived exertion were recorded during and after the exercise. The results indicated that, although there were no sex differences in leg muscle pain threshold during cycle ergometry, females reported higher leg muscle pain ratings than males. However, after relativizing peak power output, it was found that the females reported lower pain ratings compared to the males. That is, females rated naturally occurring leg muscle pain as less intense than males when data are relativized to peak power output. The finding of lower pain ratings for females is in contrast to previous research examining pain ratings during painful stimulation. However, the authors admitted that it was difficult to make direct comparisons between this study and previous studies because the analysis in their study has relied upon relativizing the noxious stimuli to each participant's maximal, and this procedure may not always be possible when employing experimental pain procedures such as heat, cold, or electrical stimulation.

More recently, several researchers have attempted to exploit functional magnetic resonance imaging (fMRI) techniques to map brain regions activated by painful thermal stimuli in men and women. A few studies have already shown through fMRI and positron emission tomography (PET) that painful thermal stimuli activate discrete regions within the brain (Bushnell et al., 1995; Davis et al., 1998; Tracey et al., 2000). In fact, reports indicate through PET imaging that males and females exhibit different brain

responsiveness to painful stimuli (Berman et al., 2000). Other studies using activation of prefrontal cortex have suggested that neuro-processing of noxious stimuli is heightened in women compared with men (Paulson et al. 1998). These works may help clarify and elucidate which physiological mechanism(s) may control the reported differences between the sexes in their response to both clinical and experimental pain.

In short, collectively these studies highlight the complexity of deriving any definitive conclusions with regard to sex differences in pain perception when one considers other interacting variables. With the addition of other situational variables, it is even difficult to compare studies that employ exactly the same pain stimulus. Although, in summary, the studies do seem to support the notion of greater pain sensitivity in women.

Clinical Pain Studies

Description

The literature on clinical pain has been immense. In fact, the issue of sex differences in clinical studies is even more complex. This is due in part to the diversity of conditions examined and the decrease in control over the research settings. For example, studies have investigated clinical pain problems that vary from arthritic to dental pain. Furthermore, sex differences in drug responses have been examined as well. Likewise, the pain measurements used to assess sex differences in pain responses have also varied greatly. Some have measured sex differences in patients' difficulties in performing various activities of daily living (i.e. getting out of bed). For each activity

that is measured, there is a number scale, with high scores indicating high interference. While others have examined gender differences in depressive symptoms, coping strategies and other health-related issues. Moreover, it should be noted that the evidence for sex differences in clinical pain models is not strong as the results found in experimental studies. One possible explanation is that it is not possible to standardize clinical pain, as one can do in experimental studies. Therefore, the variance in data derived from clinical studies is high.

Results

Health statistics routinely report a specific gender distribution for clinical pain problems (Donohoe, 1996). For example, a number of pain conditions affect an uneven number of women. Orofacial pain, fibromyalgia syndrome, rheumatoid arithritis, migraine headaches and temporomandibular disorders are some common examples (Unruh et al., 1996). In addition, findings from several epidemiological studies of common clinical pain problems suggest that women compared to men report greater pain for the same pathology (Warnell, 1991, Koutantji et al., 1998), greater pain with a similar degree of tissue injury (Savedra, 1993) and are more likely to develop a chronic pain syndrome after equivalent trauma (Von Korf M, 1990). A recent report indicated that claims rates for workers' compensation in a large state university and teaching hospital were 1.36-fold higher for women than men (Saleh et al. 2001). The study found that women had higher rates of injury resulting from lifting, falling, noxious exposures, repetitive motion, and carpal tunnel syndrome. Similarly women had significantly higher rates of claims for pain, sprains, bruises, burns, concussion, and inhalation injury, with

lower rates of cuts, ligament injury and jammed joints. Taken together, the body of research suggests that women are more sensitive to painful conditions and that they report pain problems more frequently than men.

In fact, gender differences in pain perception appear to emerge even in infancy. For example, in one study Guinsburg et al. (2000) examined the presence of gender differences in pain expression in pre-term and full-term newborn infants. Sixty-five consecutive neonates (37 female and 28 male) with gestational age between 28-42 wks and with 25-120 hr of life were studied. Subsequently, healthy term neonates were administered a capillary puncture for PKU screening and stable premature infants were given a capillary puncture for glucose dosage. Then, the Neonatal Facial Coding System (NHCS) and the Neonatal Infant Pain Scale (NIPS) were evaluated: at bedside prior to the puncture; when subjects were at rest; during foot heating; during capillary puncture; and at 1,3, and 5 min after heel lancing. The results indicated that recently born female neonates of all gestational ages expressed more facial features of pain than male infants during capillary puncture and 1 min afterwards. Moreover, although this study illustrates greater pain sensitivity for females, it is important to note that gender variations in infancy in response to pain have not been consistent. For example, Grunau et al. (1987) found that boys cried sooner and had more cry cycles than did girls in response to heel lance, but Owens and al. (1984) did not find any gender differences for the same procedure.

Gender variations in the pain experience of adults seem to be more consistent. More recently, aside from the examination of recurrent pains from epidemiological surveys, gender variation in pain intensity and recovery from surgical procedures has also

received some attention. One study examined whether there were differences in pain experience associated with differences in functional outcomes (Taenzer et al., 2000). In this study, patients undergoing arthroscopic anterior cruciate ligament reconstruction (AACLR) were recruited and subsequently measured for any gender-related differences in pain and function. Using a questionnaire, 416 patients (186 females, 230 males, mean age: 27.6) were asked to record pain scores and whether they had the ability to perform a standardized straight leg-raising maneuver on each of the first 5 postoperative days. The results revealed that women reported statistically higher postoperative pain scores and more women were unable to perform the straight leg-raising maneuver. Similar results have also been found in total hip arthroplasty (Holtzman et al., 2002) and osteoarthritis patients (Keefe et al. 2000), in which females demonstrated significantly higher levels of pain and physical disability. However, these results conflict with Ferrari et al. (2001) who found no sex differences in terms of the level of satisfaction with AACLR and Franks et al. (1998), who found in a study involving 758 patients (485 females, 273 males) suffering from leg ulceration that men scored higher in the domains of bodily pain, sleep and social isolation and energy. The difference in the outcomes of these studies may be influenced simply by the fact that different pain procedures or different pain conditions may impact the genders differently. In addition, different pain measurements used to assess sex differences may not permit valid comparisons between studies. Thus, although, it is difficult to make any conclusive statements regarding the issue of sex difference, the majority of papers do tend to support the notion that, following surgical procedures, a greater burden of pain may lie with women.

Although it is obvious that gender differences exist in the experience of pain, less certain is whether these differences are influenced by biological factors and or differences in the meaning and handling of pain.

In fact, there have been relatively few investigations examining the biological mechanisms that may influence the pain experience of males and females. However, some studies have shown that the women's menstrual cycle may have an influence on pain responses, although the results are not necessarily consistent. For example, enhanced perceptual responses to pain have been reported during the premenstrual phase (Fillingim et al., 1997), at the time of ovulation (Goolkasian et al., 1983) and following menses (Giamberdino et al., 1997), but some authors have reported no changes in pain responses across the menstrual cycle (Amodei et al., 1989). In addition, some have suggested that these differences in the hormonal cycle of females may help explain the gender differences in analgesic responses (Fillingim et al., 2000). However, it is important to note that these hormonal influences have not yet been proven in humans (Fillingim et al., 2000). For example, in a recent literature review of studies totalling of 2055 patients, Miaskowski and Levine found that, when a patient-controlled analgesia apparatus was used to administer opioids (1999), certain medications at most doses eased pain in women better and longer than they did in men. In about 56% of these studies, males consumed more opioids immediately postop than did females. Namely, males consumed more diamorphine, fentanyl, and morphine (an average of 2.4 times more), demonstrating that perhaps sexual dimorphism exists in the use of opioids for the management of acute postop pain. Subsequently, the authors concluded that opioids produce better analgesia for women, based largely on findings that males had a slightly

higher opioid consumption postoperatively. However, it is also important to note, that in eight studies, no gender differences were found in the consumption of pethidine, nalbuphine, morphine, or ketobemidone. Although, the authors were uncertain why these studies did not reveal gender differences, they speculated that the small number of patients in the studies did not, in all probability, give sufficient power to detect sex differences.

Sex differences have also been reported in the effectiveness of topical anesthetics. In 1995, Betts and colleagues evaluated sex differences in the effectiveness of topical Lidocaine jelly for reducing pain during the treatment of mandibular third molar extraction sites diagnosed with alveolar osteitis (dry socket) in 30 subjects (18 women, 12 men; mean age: 29 yr). Their analysis indicated that males reported greater pain relief at a 5 min post treatment than females. However, their results may have been confounded by the fact that males presented for treatment reporting higher levels of pain.

In a similar study three years later, investigators carried out a double blind, placebo controlled study using Lidocaine to reduce the perceived pain with stimuli from a pressure algometer. Twenty-one female and twenty-three male adult volunteers (mean age: 26 yr) participated. The results indicated that males rated the stimuli as less painful than the females. Sex differences were not detected for discriminability in the Lidocaine treatment condition. (Robinson et al. 1998)

Likewise, in the March 24th issue of the British Medical Journal (Myles, 2001), it was found that women appear to be less sensitive to the effects of anaesthesia and more prone to its side effects. This study was based on a sample size of 463 men and women undergoing elective procedures such as orthopaedic, plastic and urological surgery. The

results indicated that women opened their eyes about 2 minutes faster and followed commands nearly 3 minutes faster than men did after a surgical procedure.

Women also faced a tougher recovery from surgery. They were more likely to suffer postoperative complications such as nausea, vomiting, headache and backache. These findings support previous reports that three times more women than men have complained of being awake during surgery, and that women wake up almost twice as fast following general anaesthesia (Myles, 2001).

In summary, the results of sex differences in analgesia are unclear and still remain poorly understood. This may be because, in many of the earlier studies in which patient sex was considered, such comparisons were not the primarily focus of the investigation. This results in inadequate controls for confounding variables such as weight, age, and placebo effect, as well as inadequate sample sizes.

On a different note, the influences of familial pain experiences have also been shown to have differential meaning to both sexes. For example, in one study of 212 young adults (122 female, 90 male, mean age: 22), researchers showed that a positive family history of pain was associated with increased pain complaints over the previous month and poorer general health, as well as increased sensitivity to experimental pain (thermal) only among females (Fillingim et al. 2000). Another study indicated that different pain experiences could be interpreted differently between the genders. A study by Pratarelli et al. (1999) investigated gender differences in the perception of estimated pain experienced during execution. A 5-point Likert scale was used with undergraduate students to rate the perceived painfulness of seven methods of execution. These were: shooting, gassing, stoning, electrocution, beheading, lethal injection and hanging. The

results showed that women rated pain significantly higher than men. That is, women provided higher estimates of pain that condemned individuals might experience during their executions than did men.

Gender differences in the presentation of pain in health care settings have also been shown. For example, in one study, researchers investigated whether gender differences exist in the language used when describing angina symptoms (Philport et al., 2001). In this study, 200 (96 females, 104 males) subjects were randomly selected from a list of patients undergoing coronary angiography for chronic stable angina. Written accounts of the symptoms from the patients were recorded. The results revealed that women described more throat, neck or jaw pain than men. Furthermore, women gave more accounts of breathlessness and other symptoms. Other studies have indicated that women will describe their pain in more comparative detail and expressive fashion (Crook, 1982). More importantly, sex differences in the report of pain symptoms for a given diagnosis have led many to believe that it is plausible that gender differences in language use might influence gender differences in the management of their pain. This is because doctors' decisions seem to be influenced by the manner in which symptoms are presented to them. For example, one study (Birdwell et al., 1993) showed that a female actress portraying a patient describing specific cardiac symptoms in a "business like" way was more likely to be diagnosed as having CAD (coronary artery disease) than when the same actress described the same symptoms in an emotional manner. Another study found that doctors tend to ignore emotional issues, preferring to focus on facts during the consultation (Suchman et al. 1997).

Others have suggested that gender differences in language used to describe pain symptoms such as angina may be explained by their lay beliefs about CAD, patterns of co-morbidity and their reporting behaviour. This is because many women still believe that CAD is a male disease and that they are more likely to die from cancer than CAD (Penque et al., 1998). This belief may lead women to describe their symptoms in a way that attributes their health problem to other causes. Compared with men, women tend to have more co-morbidity, report a greater number and variety of symptoms and have greater use of medication and health service consultations (Wingard et al., 1989). One study found that patients with co-morbidity often had difficulty in highlighting their angina symptoms (Gardner et al., 1999). Such factors may serve to mask cardiac symptoms in women, making diagnosis difficult.

Collectively, these studies suggest that gender differences do exist in the meaning and interpretation of pain. However, it is uncertain whether these differences have negative or positive consequences for women and men.

Moreover, sex differences relevant to pain may be related not only to symptom-reporting styles but also to specific active strategies used to cope with pain. For instance, many researchers have demonstrated that men and women cope differently with stressful life events (Hamilton and Fagot, 1988; Ptacek et al., 1992). Studies indicate that women tend to use more "emotion-focused" coping, in particular the expression of emotions and the search for emotional support. In one study of gender differences in daily coping with arthritis pain, researchers showed that women more frequently sought emotional support when trying to contend with a given day's pain, which may have accounted in part for their tendency to use a greater number of pain coping strategies each day (Unruh et al.

1999). A study by Spertus et al. (1999) investigated the relationship between trauma history and emotional functioning in response to a chronic pain condition. The trauma history included events that ranged from sexual and physical abuse to any traumatic events experienced during childhood through adulthood. After administering a series of questionnaires that ranged from the measurement of pain severity to levels of affective distress in 73 chronic pain patients, the results revealed that chronic pain patients with a history of two or more types of trauma showed poorer adjustment to chronic pain than patients without such a history, particularly among men. In addition, results indicated that measures of general negative affect, pain related anxiety and symptoms of depression were related to trauma history only among men. Thus men who have had multiple exposures to traumatic events may not be able to manage stress well, such as chronic pain.

However, in another study of chronic pain patients, Turk et al., (1999) did not find similar results. In their study, 428 (226 females, 202 males, mean age: 42.8) chronic pain patients were evaluated for a wide array of pain conditions that varied from pain severity to depression symptoms. The results revealed that women were more likely to be diagnosed with a depressive disorder and to receive prescription of antidepressants. This may suggest that the emotional impact of pain was significantly greater for women than men. However, in another study, Myers et al., (1984) indicated that women in general are more likely to report depressive symptoms than men. Thus, the differences obtained in depressive conditions in Turk et al., (1999) may simply be a reflection of the differences in reporting depressive symptoms, rather than the specific depressive effect of chronic pain of the patients.

Yet in another study by Turk et al. (1999) no significant sex differences in reports of pain severity and disability were detected in a group of cancer patients (91 men, 52 women, mean age: 57.5). Contrary to previous findings, no significant differences between the sexes in depressive symptoms were found. The authors have suggested that perhaps the seriousness of cancer as a disease may be so great that it cancels out sex differences in the prevalence of depression.

Nevertheless, these studies have demonstrated that the relationship between gender and coping with pain is complex and may be influenced by the type of pain, its severity, frequency, duration and interference with function.

Other areas of clinical pain have also been examined. In one study researchers investigated the inter-relationship between gender, acute pain prediction and memory of the pain experience (Eli et al., 2000). Thirty-seven dental patients (22 female, 15 male, mean age: 33.8) who were scheduled to undergo periodontal were requested to predict the level of pain that they thought they would experience. A week after the surgery, they were asked to rate their memory of surgical pain. The results revealed that men expected to experience more post-operative pain than women but remembered the pain to have been less. These results may be slightly surprising given the fact that several investigations have revealed that women engage in pain catastrophizing to a greater extent than men (Keefe et al., 1989, Sullivan et al., 1995). Catastrophizing has been defined as an individual's tendency to focus on and exaggerate the threat value of painful stimuli (Keefe et al., 1989). For example, researchers found in a sample of patients with musculoskeletal pain that women scored higher than men on the catastrophizing subscale of the Coping Strategies Questionnaire (Jensen et al., 1994).

In short, the results from this review support the notion that clinical pain problems appear to have a specific gender distribution. The findings indicate that there is a trend for women to be more sensitive to painful stimuli than men and that females report pain problems more frequently than males. However, the reasons for these differences are less clear. Some have suggested biological variables, such as hormonal factors, while others believe gender-specific socialization patterns with regard to pain beliefs, expectations, and subsequent behaviours may be a bigger influence on gender differences. However, these accounts are mainly speculative and the uncontrolled nature of the clinical pain conditions further complicates conclusions about differences between the sexes.

CLINICAL VS. EXPERIMENTAL PARADIGMS

Advantages and Disadvantages

Both experimental noxious stimuli and clinical pain models have been proven to be quite useful in investigating gender differences in pain perception and experience. However, both paradigms have their advantages and disadvantages. For example, one major advantage of administering experimental pain is that the pain stimulus is usually given to healthy young human volunteers using a standardized modality (Gawel et al., 1990). Several authors have noted that having young healthy subjects are beneficial for scientific testing because their state of health ensures that they are able to understand the information given, resulting in high degree of compliance (Urquhart, 1994; Norholt, 1998). It should also be noted that the recruitment is usually relatively easy since it often consists of undergraduate students, in a university setting. On the other hand, clinical pain requires subjects with specific pain profiles who may be difficult and costly to

recruit. In addition, clinical studies typically require larger sample sizes for adequate power. Although, recruiting larger samples are more difficult and costly, they also may more accurately reflect societal trends.

In experimental pain, the stimulus can be controlled with respect to intensity, localization and duration (Walker, 1993; Norholt, 1998; Gracely, 1991). However, this same advantage for experimental pain settings can also be a disadvantage. For example, several authors have mentioned that experimentally induced pain in human correlates poorly with pain due to injury or disease (Norholt, 1998, FDA Guidelines, 1992; Gracely, 1991). They cite the fact that the performance of analgesics used in experimental pain studies does not correspond well to pathologic pain caused in clinical settings. Clinical settings are therefore preferred in research protocols, particularly for the development of pain drugs (FDA Guidelines, 1992). However, the variation in the levels of pain experienced even within specific patient groups creates difficulty, as it increases the sample size necessary for adequate power.

Purpose

The overall objective of this investigation was to extend the current literature regarding the relative affective response and pain perception of both men and women. More specifically, this study will attempt to confirm the results of the dental-implant study and to see if those findings are reproducible in an experimental setting. That is, do men find pain over time more disturbing but less intense than females in laboratory settings.

The study will be carried out in two stages. First, healthy subjects will receive a painful stimulus, capsaicin, on their faces. Then, they will be asked to rate their perceived pain intensity (sensory), unpleasantness (affective) and anxiety.

In the second stage, the aforementioned procedure is repeated, except this time, the capsaicin is placed on the ankles of subjects as sensitivity may vary between locations (see Methods). Subsequently, results from males and females will be compared to see if sex differences exist in the pain experienced from the ankle and or the face. In short, this work should help confirm whether females may be better able to limit the emotional consequences of pain than men. Finally, the findings from this study will provide a preliminary analysis of the practicality of using functional magnetic resonance imaging (fMRI) techniques for the detection of sex differences in pain perception. That study may help clarify and elucidate which physiological mechanism(s) may control the reported differences between the sexes in their response to both clinical and experimental pain.

Methods

Subject Characteristics

Twenty French speaking subjects (10 females, 10 males, mean age: 29.8 years), aged from 23 to 46 years were recruited via advertisements on bullentin boards of the Université de Montréal and McGill University (Appendix. 1). Potential subjects were informed that they would be involved in an experiment studying different aspects of pain. Subjects were required to be completely healthy and pain-free on the day of the experiment. Inclusion criteria stipulated that subjects: 1) have never participated in any pain experiments 2) do not experience chronic pain 3) do not get sunburned regularly in the face 4) are not allergic to peppers 5) do not have a pacemaker 6) do not have medical problems 7) are not pregnant 8) are not less than 18 years or greater than 70 years old 9) cannot wear make-up on the day of the experiment. Every subject read and signed a consent form acknowledging that the experimental procedures had been explained and that they could withdraw from the experiment at any time without repercussions (Appendix. 2). All procedures were approved by the Institutional Ethics Committee at McGill University.

Procedures

Upon arrival on the day of the scheduled appointment, subjects were again informed of the experimental procedures. They were warned that they might experience slight redness on the face or ankle for a short period of time (less than 2 hours) after the experiment. In addition, they were told that if they felt pain of any nature (i.e. headaches

etc...) during the day of the experiment, they must reschedule the appointment for another day when they were pain-free. After agreeing to the conditions of the experiment, the different affective and sensory dimensions of pain were explained to the subjects to ensure that they would be able to differentiate between the two. Also, they were given instructions on how VAS ratings scales were to be used for measurements of intensity, unpleasantness, anxiety and mood. To confirm that subjects understood the differences between intensity and unpleasantness, the experimenter applied pressure on the hands of each subject with her index finger. Then, subjects were asked to rate the pressure sensation on the VAS for all measurements. Subjects were informed that if they indicated a number greater than 0 on the VAS for intensity, this would signify that they felt pain from the pressure of the index finger. Likewise, if subjects rated 0 on the VAS for unpleasantness, this would indicate that they were not bothered by the pressure from the investigator. Subjects were also reminded to attend only to the specific sensations in the experiment and not to report other pains one may be feeling (i.e. seat discomfort).

Capsaicin-induced Testing Task

Each subject was instructed to insert the index finger of their non-writing hand (since their writing hand was used to rate the VAS) on a pulse oxymeter that monitored their pulse rate. The pulse was recorded every 5 minutes (from time=0) for 1 hour. Subsequently, subjects were asked to rate once before the application of capsaicin to ensure that only pain experienced by the capsaicin was recorded. That is, at rest, every subject should have a rating of 0 for intensity and unpleasantness since the capsaicin patch had not yet been applied. Then, a solution of capsaicin (Sigma) dissolved in 70% ethanol (0.004 M; 0.3ml) was topically applied on the left facial cheek region of every

subject via a gauze pad (2 x 2 cm). The gauze pad was covered by a self-adhesive plastic film to insure contact and prevent evaporation (Appendix. 3). Subjects were instructed to focus on the pain and begin rating the VAS (31 times for intensity, 31 times for unpleasantness, 31 times for anxiety and once for mood) until the removal of the capsaicin patch over a period of 30 minutes. Hence, subjects rated once every minute for 30 minutes and once for time 0 (when the capsaicin patch was just applied). During the experiment, subjects were reminded that they could terminate the test if they felt that the pain was unbearable. After 30 minutes, the capsaicin patch was removed and then a solution of soap and water was applied to the subject's face to wash away any residues from the capsaicin solution. Then, subjects continued to rate the VAS for intensity, unpleasantness and anxiety for another 31 times. Subjects were instructed to rate once every minute for 30 minutes and once for time 0 (time 0 refers to immediately following the face cleaning). At the end of the experiment, subjects were asked to evaluate pain quality using words from the McGill Pain Questionnaire. In addition, they were asked once again to rate their mood on the VAS. Subjects then completed a receipt to testify the completion of the experiment and subsequently were paid $ 50 CAD. They were also reminded that the redness might be apparent for a few hours.

The experimental procedures were repeated in a second session (a certain number of days later) with the application of capsaicin on the ankle (Flow chart, Appendix.5).

Capsaicin

Background

Capsaicin is the active ingredient found in hot chilli peppers that gives the burning sensation when one consumes spicy food. It elicits massive release of substance P, which in turn mediates the stimulation of polymodal nociceptors of C fibers primary afferent nerves (Helme et al., 1986). Capsaicin is a vanilloid receptor agonist that activates and sensitizes periperal nociceptors, resulting in a burning pain sensation and an enhanced cutaneous sensitivity (Urban et al., 1991). It does not produce permanent skin damage but will cause a burning sensation and reddening of the skin when applied. Moreover, history indicates that capsaicin-containing peppers have been cultivated in South America since 5200 BC (Szolcsanyi, 1993). Since the introduction of capsaicin plants to the Indies in the early 17th Century, the consumption of capsaicin in the form of chilli peppers has become international, particularly in most national cuisines (Szolcsanyi, 1993). Interestingly enough, uses of capsaicin as folk medicine has varied from hair restoration and appetite stimulation, to the treatment of gastric ulcers and rheumatism (Szolcsanyi, 1993). More recently, the anti-inflammatory and analgesic effects of capsaicin have been the subject of some interest, especially in the pharmaceutical industry, as the discovery of the selective actions of capsaicin on peripheral sensory neurons has suggested a possible mechanism for both the therapeutic as well as the pain-inducing actions of this compound (Fusco et al., 1997).

In fact, within the past few years, the application of capsaicin to cutaneous tissue has been used as an experimental model in humans to investigate hyperalgesia and allodynia related to normal tissue damage (Petersen et al., 1999). Many believe the pain and hyperalgesia experienced in the capsaicin model are similar to symptoms in patients

with neuropathic pain and may therefore share some pathophysiological mechanisms (Sang et al., 1996).

Reasons for its Usage

Capsaicin was used as the pain stimulus because it is considered to be safe, and the preparation of the capsaicin solution is relatively easy to fabricate (Appendix. 6). Capsaicin with the same concentration as that used in this experiment has been used in previous studies in both humans and monkeys (Kupers et al., 1997) with no adverse effects. Furthermore, capsaicin induces a *sufficient and tonic* pain sensation. Capsaicin was considered *sufficient* because the levels of pain emitted by this stimulus were painful enough for subjects to classify it as a painful experience, yet not too painful to be unbearable. Secondly, the pain stimulus emitted by capsaicin is considered tonic since the sensation is long-lasting (greater than one hour) and does not have a fast onset. This is pertinent because past studies have demonstrated that gender differences in pain response appear to occur most consistently with pain induction techniques that produce deep, tonic pain sensations, which mimic pain sensations similar to those experienced in real life settings (Fillingim and Maixner, 1995). Finally, capsaicin was chosen as the pain model in this study because it is different from the conventional pain stimulus used in experimental studies. To our knowledge, no studies have employed capsaicin as the pain stimulus to exclusively examine the relationship of gender to pain-related outcomes in healthy adults, even though gender differences in response to capsaicin have been shown from secondary analyses in other studies. For example, Logan et al., (2001) have reported that women in stress conditions indicated greater pain than men in stress

conditions after the administration of capsaicin-induced pain in the form of an injection in the forearm. Also, sex differences have been reported on cough threshold to inhaled capsaicin on 160 non-smoking, healthy subjects (Fujimura et al., 1996). Specifically, the results indicated that cough sensitivity is heightened in females.

Composition of the Pain Recordings

Visual Analogue Scale (VAS)

Subjects rated pain intensity, pain unpleasantness and anxiety on a 100-mm VAS thirty-one times with the capsaicin patch on the face, and thirty-one times without the capsaicin patch on the face. This rating procedure was repeated again for the application of the capsaicin patch on the ankle. In addition, subjects were asked to rate their mood once, immediately following the administration of the capsaicin patch and once, after completion of the experiment. The pain intensity scale was anchored with the phrases "Aucune douleur" (No pain) and "Douleur la plus intense tolerable" (The most intense pain tolerable). The pain unpleasantness scale was described by the phrases "Pas extrèmement désagreable" (Not extremely unpleasant) and "Extrèmement désagreable" (Extremely unpleasant). The anxiety scale included the statements "Pas de tout anxieux" (Not at all anxious) and "La plus anxieux que je pourrais" (the most anxious I can possibly be). Finally, the mood scales were anchored with the statements "La pire que je pourrais être" (The worst I can possibly feel) and "La meilleur que je pourrais être" (The best I can possibly feel).

The VAS has been shown to be a reliable, valid and sensitive method of recording pain (Chapman et al., 1985). Furthermore, the VAS of sensory intensity and affective

magnitude has been validated as a ratio scale measures for chronic and experimental pain (Price et al., 1983). In addition, the VAS places minimal demand on sick patients, and poorly educated patients can usually understand the nature of the scale with little difficulty (Chapman et al., 1985). Finally, patients have been found to prefer the VAS over the procedure of category scaling, the other primary method used in the subjective recording of pain (Chapman et al., 1985).

McGill Pain Questionnaire (MPQ)

The MPQ measures the various qualities of clinical and experimental pain. It divides pain into sensory, affective, evaluative and miscellaneous components (Melzack, 1975). Subjects choose from 20 sets of word descriptors that best describe the pain. Each set compromises 2-6 word descriptors arranged in order of increasing intensity with regard to the component of pain described in the group. Moreover, subjects were instructed to choose only those words that accurately reflected their pain. In addition, they were told that they could choose as many words as they felt best described their pain. Ten of the word groups describe sensory qualities, five are affective descriptors sets, a single set describes the evaluative dimension and the rest are classified as miscellaneous. Subjects were asked to complete the MPQ once after each session (one for the face, and another for the ankle).

Data are obtained from the MPQ according to two scoring systems (Melzack, 1975):

- The number of words chosen;

- The pain ratings index (PRI) based on the rank values assigned to the words. In this scoring system, the word in each word set that implies the least pain would be assigned a rank value of 1, the next word is given a value of 2, etc. The values of the words chosen by a subject are then added up to obtain a score for each category.

There has been considerable support for the validity, reliability and sensitivity of the MPQ (Melzack, 1975, Chapman, 1985). In fact, the PRI has been tested in a number of psychometric studies. These studies 1) tracked patients over time following either an intervention to reduce pain or during the natural history of an acute pain experience, 2) examined ratings on different intensities and quantities of nociception and 3) examined the relationship between established scales of affect and scores on the affective subclasses of the PRI (Turk et al., 1985).

Definition and Justification for Selection of Variables

Background

The dependent variables selected for the present study were chosen based on evidence in the literature supporting the presence of gender differences. One variable, pain intensity, has been used extensively for examining the effects of sex differences in pain perception. Less commonly used variables, such as pain unpleasantness, mood, and anxiety, have also been included in studies examining sex differences. The results from

the majority of these variables suggest sex differences. Because a different pain stimulus is being used, it would be interesting to see if gender responses to pain as shown by these variables are reproducible in our experimental setting.

Definition and Differentiation of Intensity and Unpleasantness

In order to ensure that subjects understood exactly what they were rating, the differences between the pain variables of intensity and unpleasantness were explained explicitly to each subject. They were told that pain is generally divided into two main components. The first one is the actual sensation, described in words such as burning, pricking, stinging, aching, throbbing. This component is better known as the intensity of the pain sensation. The second component is the unpleasantness, which reflects how much the sensation bothers or disturbs the subject.

Subsequently, subjects were notified that a stimulus could create a pain sensation without being unpleasant. Likewise, a stimulus can be unpleasant without producing a pain sensation (i.e. dragging an individual's nail along the blackboard is very unpleasant but it is not painful). Another example given to subjects to ensure that they would be able to differentiate between intensity and unpleasantness, was the analogy of the volume on a radio, whereby increases in volume correlated to increases in pain intensity. On the other hand, unpleasantness might be associated with bad music. Although intensity could affect how unpleasant the bad music is, the bad music is unpleasantness even at low volumes.

The literature on sex differences to pain intensity has been extensive. There is a general consensus in both clinical and experimental pain studies that females rate pain as more intense than males for most types of pain (see Literature Review). However, the issue of how pain differentially bothers males and females has received less attention. In a study examining 156 chronic pain patients (66 females, 90 males) at a multidisciplinary clinic, researchers found that men responded to treatment more poorly than women (Burns et al., 1996), alluding to the fact that males may be more bothered by pain than women. Although, further analysis revealed that perhaps this may have been confounded by the fact that men had a greater number of surgeries and thus, had greater pain intensity at baseline. On the other hand, Cook et al. (2001) found in a group of 374 chronic pain patients, that males tended to demonstrate a more "stoic" profile to their pain experiences suggesting that males may be less bothered by pain. Furthermore, in an experimental pain setting, Sheffield et al. (2000) found that women showed a tendency to rate heat stimuli as more unpleasant and more intense than men. However, it may not be valid to compare this study with other clinical studies given the fact that the pain induced by the thermal stimulus may have been too brief for males and females to be sufficiently bothered by the experience. This is because research studies have shown that the affective dimension of pain can be reduced when there is no threat to health or life, as in the case of brief experimental pain (Price et al., 1983).

Mood

Mood is defined as a conscious state of mind or predominant emotion or feeling. Several studies have shown an inverse relationship between pain and emotional well-being (Parker et al., 1988; Salovey et al., 1989; Keefe et al., 1997). In fact, in a study examining patients with osteoarthritis, men were found more likely than women to report an increase in negative mood the day after a more painful day (Affleck et al., 1999). However, in another study using the administration of experimental thermal pain, Marchand et al. (2002) did not find any relationship between mood and pain perception for both genders. However, one may argue that the pain emitted by the thermal stimulus may have been too short to have sufficiently affected the mood.

Pulse

Pulse is defined as the regular throbbing in the arteries caused by the contractions of the heart. In medical settings, vital signs such as pulse and blood pressure are frequently used as an adjunct indicator of distress in patients experiencing acute pain symptoms (Bondenstam et al., 1987). In this experiment, the pulse was monitored in order to assess the physiological distress resulting from the pain associated with the capsaicin patch. Furthermore, previous research has shown that there is an interaction between cardiovascular and pain regulatory systems (Randich et al., 1984). For example, a few studies have shown an association between hypertensive humans and decreased pain sensitivity (Sheffield et al. 2000). Fillingim et al. (1996) found that blood pressure was inversely related to ratings of cold pressor, mechanical and electrical pain. On the other hand, the research on the association between heart rate and pain sensitivity has not

been as extensive and thorough as that of blood pressure. However, a few studies have indicated that women have higher pulse rates than men for the cold pressor task (Koltyn et al. 1999) and pressure pain (Zeichner et al. (2000). On the other hand, Al'Absi et al. (1999) did not find sex differences in the heart rate in a cold-pressor test of 128 healthy subjects (46 females, 82 males, mean age: 27.8).

Anxiety

Anxiety is a normal response to perceived and or actual physical danger (Gorman, 2002). It is often accompanied by physiological signs such as sweating and increased pulse. Anxiety has been known to be linked closely to the sensory, cognitive, and emotional experience of pain (Wall, 1979). Several studies have supported this idea (Dougher et al., 1987; Dworkin et al., 1992; Rhudy et al., 2000). For example, Rollman showed that high levels of anxiety are associated with increased sensitivity to experimental pain and greater experience of clinical pain (Rollman, 1995). Other studies have found interactions between sex and anxiety on pain responses. For example, Edwards et al., (2000) found that anxiety was inversely related to pain thresholds among men but not among women in chronic pain patients. That is, male patients with high pain-related anxiety reported greater pain severity and greater interference of pain than male patients with low anxiety, but this effect was not evident among female patients. Fillingim et al. (1996) also reported similar results in thermal pain sensitivity among male subjects but not among female subjects in a sample of healthy volunteers. However, Eli et al. (2000) found in dental patients undergoing periodontal surgery that women consistently scored higher than men in their state anxiety, but no significant interaction

between gender and the changes occurring in subjects' anxiety over time could be detected. One must note, however, that the scores used in the study by Eli et al. (2000) were based only on subjects' own anticipated anxiety scores and memory of what they recalled. Finally, Koltyn et al. (1999) did not find any sex difference in state anxiety for pressure pain.

Location

Scientific research has shown clearly that different regions of the body have different sensitivity to touch, pain, thermal and mechanical reception (Weinstein, 1968). For example, the "two-point discrimination measurement" indicates that the there is a distinct receptive difference between the facial cheek and the dorsum region of the feet. The two-point threshold measures the minimum distance at which two stimuli are resolved as distinct. A smaller "minimum distance" would indicate a greater sensitivity. The mean two-point discrimination threshold for the human facial cheek is approximately 7mm and 20mm for the dorsum region of the feet, thus indicating a greater sensitivity for touch in the face region (Weinstein, 1968). Likewise, regional differences in pain have also been established. For example, although the homunculus is a somatotopic map in the human cortex, it is however, not necessarily correlated with surface area since innervation density varies according to location (see Ganong for review). Also, in a study of cutaneous sensory receptors in the rat foot indicated that the composition of nociceptor units in nerves supplying different skin locations vary (Leem et al., 1993). More importantly, experimental and clinical studies have indicated gender differences for pain in different locations. Males, for example, tend to have a higher prevalence for chest

pains, while females tend to have a higher prevalence for abdominal (Magni et al., 1992) and facial pain (Von Korff et al., 1988). Though certain diseases are more prevalent in men than women, their sensations of pain are often felt in different areas of the body, and this may or may not be related to gender-specific distributions of nociceptors. In addition, in experimental studies, Zeichner et al. (2000) did not find sex differences in the cold pressor test when it was administered to the dominant foot, while Keogh et al. (2000) found sex differences when the dominant hand was used. However, it may be difficult to truly compare the results of the two papers since there were differences in both the experimental set-ups and objectives.

Data Analysis

Pain Scores: Intensity, Unpleasantness, Anxiety

All statistical analyses were carried out using SPSS 10.0 for Windows. The dependent variables were VAS (100-mm scale) values for pain intensity, unpleasantness, anxiety, mood and pulse rate as recorded in the two experimental sessions. The independent variables were gender (F=female; M=male), time and location of pain stimulus.

As a first step, a screening of the distributions of the responses for each variable was performed. Subsequently, significance of between-group and within subject

differences was determined by a "repeated measures" ANOVA (SPSS 10.0), which was conducted for each of the dependent variables with and without the capsaicin patch.

Ratio of Unpleasantness over Intensity

To determine if the relative unpleasantness of the pain experience was more disturbing for one gender than the other, the unpleasantness/ intensity ratio for each subject was calculated over time with and without the capsaicin patch. A ratio of 1 would indicate that the pain sensation was equally unpleasant and painful, while a ratio greater than 1 would signify that the pain sensation was more unpleasant than painful (Rainville et al., 1992). Differences between the sexes were calculated using repeated measures ANOVA in the same fashion as the raw pain ratings.

Maximal Pain Ratings

Maximal pain ratings were obtained with the use of statistical program (SPSS 10.0) that analyzed the range of scores from each individual subject. An independent samples *t*-test was used to determine if there were any sex differences in the maximal ratings with and without the capsaicin patch. The maximal pain ratings were entered as the "test variable" and gender was entered as the "grouping variable". The maximal ratings for each individual was computed using

Pulse Rates

"Repeated measures" ANOVAs were performed on pulse rates to assess any gender differences, with pulse entered as "within subjects variables", gender as "between subject variable" and time as "within subject factor". In addition, repeated measures were conducted to see if there were any differences in the pulse when compared from the face region to the ankle region for both sexes.

Correlations

The pain ratings and pulse scores were averaged over time for each gender (with the ankle and face scores combined). Correlations were carried out using a Spearman (non parametric) correlation matrix.

Mood

A 2 x 2 ANOVA was performed for comparisons between mood changes "before vs. after" the experiment and for detecting if gender differences were present. The mood scores were entered as the dependent variable and both gender and "before vs. after" were entered as fixed factor(s).

McGill Pain Questionnaire

In order to detect sex differences, a simple independent sample *t*- test was performed for the number of words chosen and the pain ratings indices for each category. These categories are: Sensory, Affective, Evaluative, and Miscellaneous. The number of

words chosen and the pain ratings indices for each category were entered as the "test variable" separately and gender was entered as the "grouping variable".

Results

Pain Scores: Intensity, Unpleasantness and Anxiety

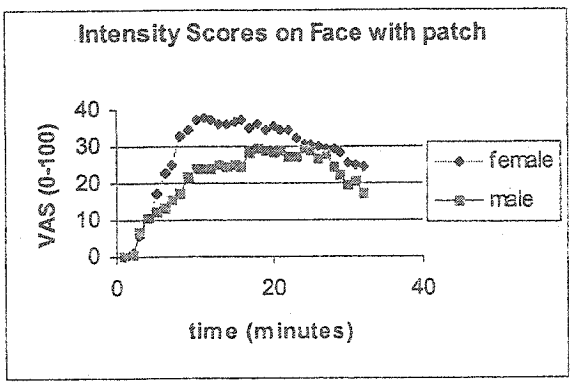
Variances were not normally distributed. Hence, statistical normalization was carried out by expressing every score during the experiment as a percentage of each individual's respective maximum score value. Results revealed that the normalized values were no different from the raw data upon statistical analysis. Therefore, only the raw data values are reported in this thesis.

Fig. 1 shows pain ratings across time for intensity, unpleasantness and anxiety for male and female subjects with the patch on the face. The graphs illustrate that for both intensity and unpleasantness ratings, subjects of both sexes rapidly experienced increasing pain sensation within the first ten minutes and then reached maximal pain ratings around the twentieth minute. Subsequently, the pain scores of both female and male groups began to taper off and drop slowly after the twentieth minute. In fact, there was a time effect on the pain scores for both intensity ($F = 13.1$, $P < 0.001$) (Table 1) and unpleasantness ($F = 7.7$, $P < 0.001$). However, there were no sex differences or sex * time interactions for either pain intensity or unpleasantness with the patch on the face. In contrast, Fig. 1C demonstrates that for anxiety scores with the patch on the face, there was a time * sex interaction ($F = 1.64$, $P = 0.02$), with the male anxiety increasing over time (peaking around the twenty-sixth minute) and the female anxiety decreasing over time (peaking around the tenth minute).

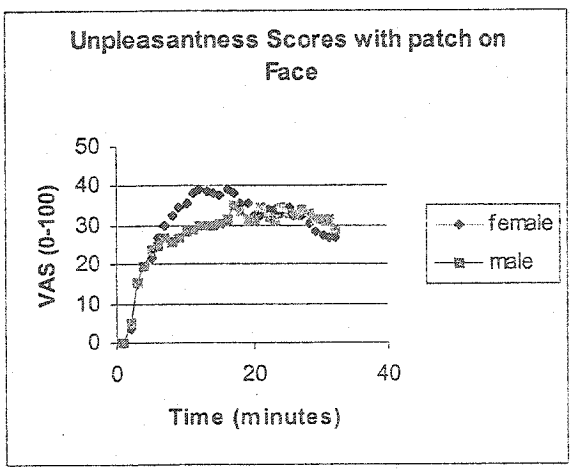
Pain intensity, unpleasantness and anxiety with the patch on the ankle were also examined. Fig. 2 shows that both pain intensity and unpleasantness increased slowly, reaching peaks around the thirtieth minute. In fact, there was a time effect for both

Figure. 1

A



B



C

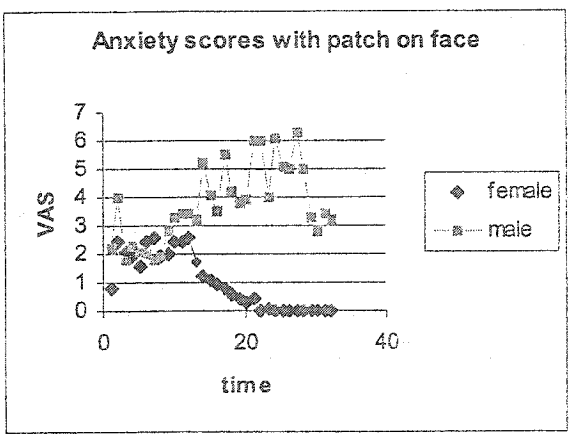
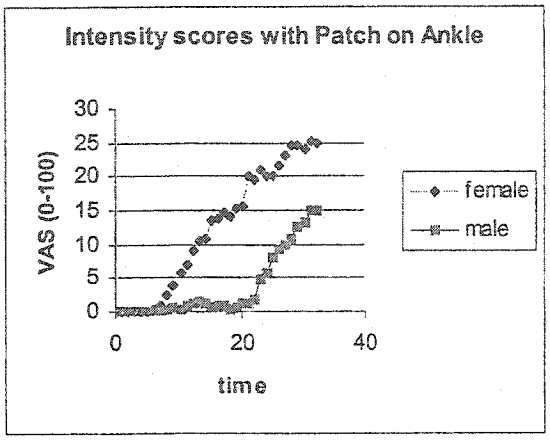


Fig. 1. Pain ratings with patch on face for A)Intensity B) Unpleasantness C) Anxiety

Figure. 2

A.



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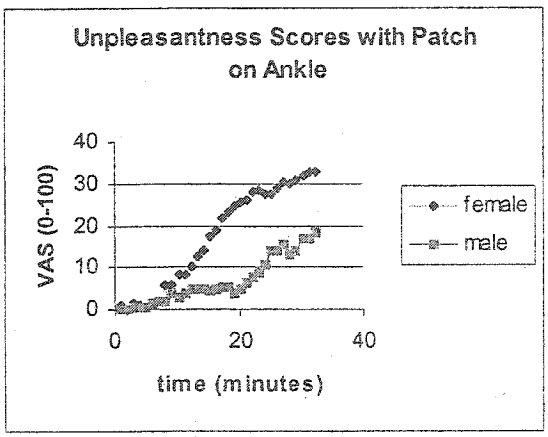


C.

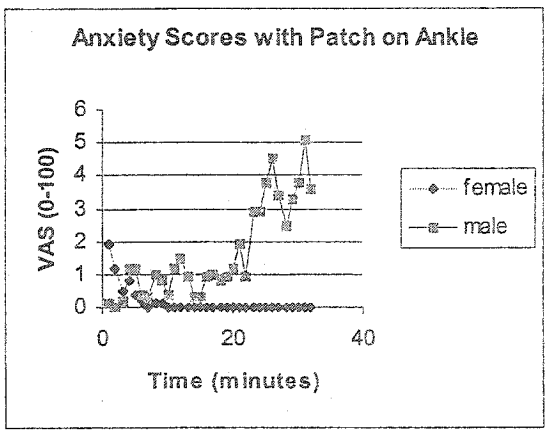


Fig. 2. . Pain ratings with patch on ankle for A) Intensity B) Unpleasantness C) Anxiety

intensity (F = 6.06, P < 0.001) and unpleasantness (F = 8.41, P < 0.001) scores. More importantly, repeated measures ANOVA revealed that there was significant sex difference in the intensity ratings with the patch on the ankle (F = 4.23, P = 0.05), with females showing greater pain sensitivity. In addition, there was a non-significant trend towards a sex difference in unpleasantness ratings with the patch on the ankle (F =3.24, P = 0.09). Also, a sex * time interaction was found for the unpleasantness ratings with the patch on the ankle (F =1.65, P = 0.02). Figure 2B indicates that the unpleasantness sensitivity ratings of females increased faster over time and reached greater maximal pain levels when compared to their male counterparts. This was not the case for the anxiety ratings in which there were neither sex difference (F= 1.23, P = 0.282) nor sex * time interaction (F=1.03, P = 0.42).

Table 1

Summary of Repeated Measures ANOVA for Pain Ratings with Patch: *Comparing Males and Females*

Location	*Pain Measurement*	*Time Effect*	*Sex Difference*	*Time*Sex Interaction*
Face	Intensity	***F =13.12 P <0.001***	*F =0.82 P=0.38*	*F =0.84 P=0.72*
Face	Unpleasantness	***F =7.70 P<0.001***	*F =0.08 P=0.79*	*F =0.51 P=0.99*
Face	Anxiety	*F =0.46 P =0.99*	*F =2.47 P=0.13*	***F =1.64 P=0.02***
Ankle	Intensity	***F =6.06 P<0.001***	***F =4.23 P=0.05***	*F =1.19 P=0.22*
Ankle	Unpleasantness	***F =8.41 P<0.001***	*F =3.24 P=0.09*	***F =1.65 P=0.02***
Ankle	Anxiety	*F =0.70 P=0.89*	*F =1.23 P=0.28*	*F =1.03 P =0.42*

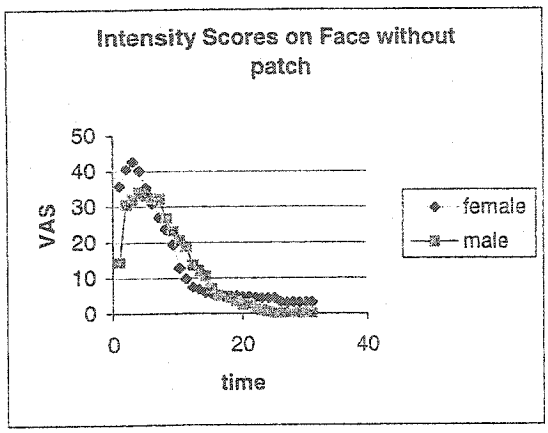
**Bold-faced values indicates statistically significant*

Fig. 3 illustrates the pain and anxiety ratings on the face after the patch has been removed. The graphs show that once again, pain intensity and pain unpleasantness correlate well with each other over time. Fig. 3A and B indicate that after an initial surge in pain sensation (around the fifth minute), there was rapid decrease in the pain scores, reaching a minimum around the thirtieth minute. In fact, there was a time effect for both intensity (F = 20.7, P < 0.001) (Table 2) and unpleasantness (F = 27.196, P < 0.001) scores, with both intensity and unpleasantness scores decreasing with time. No sex difference was found for either intensity (F = 0.047, P =0.83) or unpleasantness (F = 0.68, P = 0.42). Anxiety scores on the face without the patch were also analyzed (Fig. 3C). Repeated measures ANOVA indicated that there was a tendency toward a sex difference in anxiety scores, although not statistically significant (F= 3.213, P = 0.09).

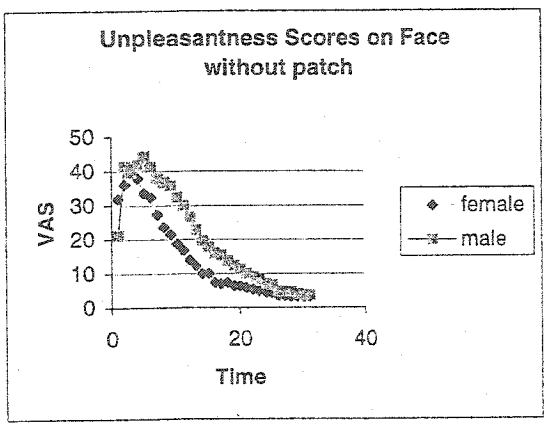
Fig. 4 illustrates the pain and anxiety ratings on the ankle after the patch had been removed. There was a general trend for both intensity and unpleasantness scores to slowly decrease over time, and statistical analyses indicate that there was a time effect for intensity (F =5.52, P < 0.001) and unpleasantness (F = 6.16, P <0.001). In addition, both pain intensity and unpleasantness scores had a sex * time interaction (intensity: F = 2.18, P < 0.001, unpleasantness: F = 2.26, P < 0.001). The graphs indicate that although females experienced more pain initially, they also had a greater decrease in their pain scores over time when compared to males. Males tended to have a moderate linear

Figure. 3.

A



B



C

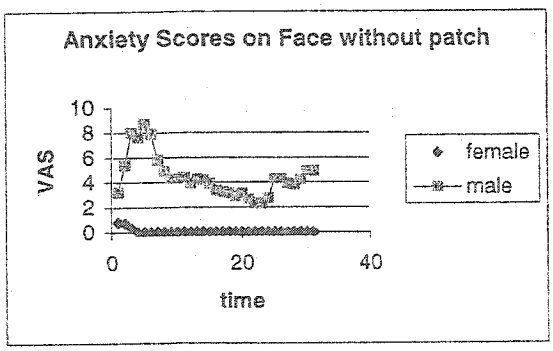
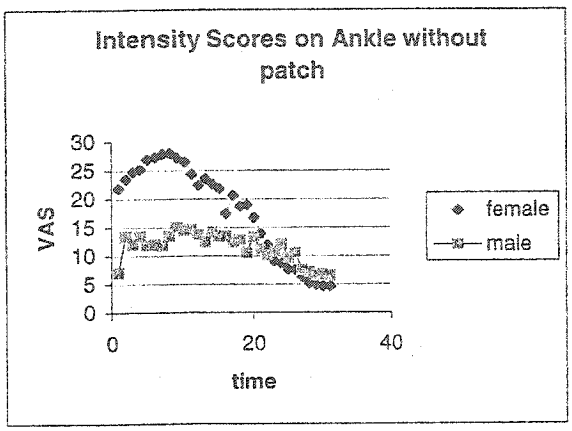


Fig. 3. Pain ratings without patch on face for A) Intensity B) Unpleasantness C) Anxiety

Figure. 4.

A



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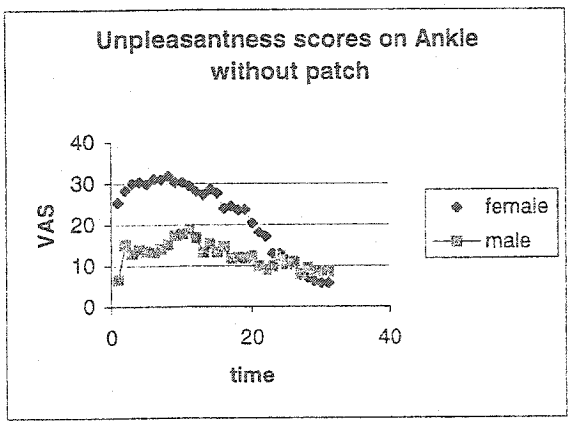

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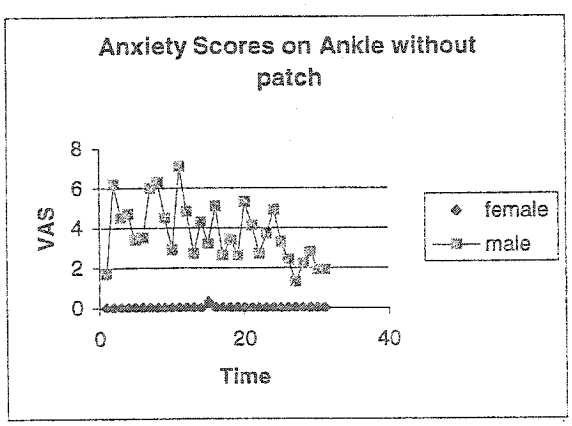


Fig. 4. Pain ratings without patch on ankle for A) Intensity B) Unpleasantness C) Anxiety

decline in response over time. Contrary to the effects for pain ratings, no effect of sex was observed for anxiety ratings ($F = 1.02$, $P = 0.33$).

Table 2

Summary of Repeated Measures ANOVA for Pain Ratings without Patch: *Comparing Males and Females*

Location	*Pain Measurement*	*Time Effect*	*Sex Difference*	*Time*Sex Interaction*
Face	Intensity	***F =20.70 P <0.001***	*F =0.05 P =0.83*	*F =1.13 P =0.29*
Face	Unpleasantness	***F =27.19 P <0.001***	*F =0.68 P =0.42*	*F =1.23 P =0.19*
Face	Anxiety	*F =1.33 P =0.11*	*F =3.213 P =0.09*	*F =1.28 P =0.15*
Ankle	Intensity	***F =5.51 P <0.001***	*F =0.41 P =0.53*	***F =2.18 P <0.001***
Ankle	Unpleasantness	***F =6.16 P <0.001***	*F =0.80 P =0.38*	***F =2.26 P <0.001***
Ankle	Anxiety	*F =0.99 P =0.48*	*F =1.02 P =0.33*	*F =1.03 P =0.47*

**Bold-faced values indicates statistically significant*

Ratio of Unpleasantness over Intensity examining for sex difference

Unpleasantness/intensity ratios were calculated with and without the patch. Repeated measures ANOVA revealed that there were no sex differences in the ratios with the patch on either the face ($F = 1.54$, $P = 0.23$) or the ankle ($F = 0.04$, $P = 0.84$) (Table

3). A similar result was found for the ratio on the ankle without the patch ($F = 0.82$, $P = 0.38$). However, examination of the ratio on the face without the patch indicated that there was a tendency toward a sex difference in the relative unpleasantness over intensity ($F = 3.43$, $P = 0.08$) with males having a greater relative unpleasantness, although it was not statistically significant. Also, it is interesting to note that there was a time effect for the face without the patch ($F = 3.04$, $P < 0.001$) and on the ankle with the patch ($F = 1.72$, $P = 0.01$). Fig. 5 illustrates that the relative unpleasantness on the ankle with the patch increases over time. On the other hand, the relative unpleasantness decreases over time for the face without the patch.

Table 3

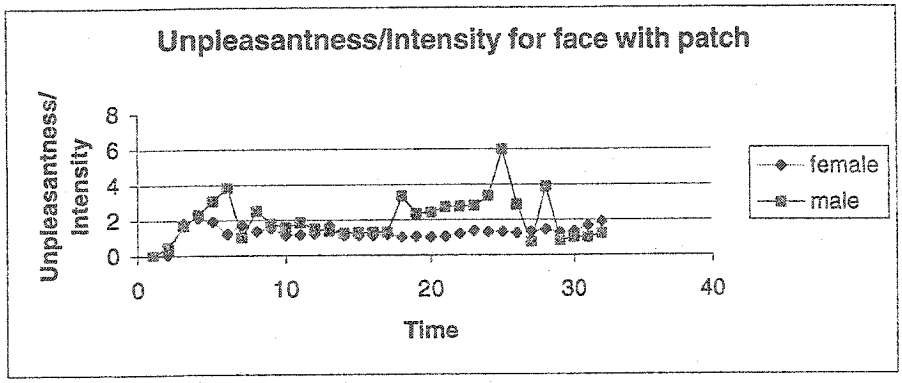
Summary of Repeated Measures ANOVA for Relative Unpleasantness Pain Ratings with and without Patch: *Comparing Males and Females*

Location	*Capsaicin Status*	*Sex Difference*	*Time Effect*	*Time*Sex Interaction*
Face	With patch	*F =1.54* *P =0.23*	*F =1.32* *P =0.12*	*F =1.20* *P =0.21*
Ankle	With patch	*F =0.04* *P =0.84*	***F =1.72*** ***P =0.01***	*F =0.95* *P =0.54*
Face	After patch	*F =3.43* *P =0.08*	***F =3.04*** ***P <0.001***	*F =0.62* *P =0.95*
Ankle	After patch	*F =0.82* *P =0.38*	*F =1.15* *P =0.27*	*F =0.78* *P <0.79*

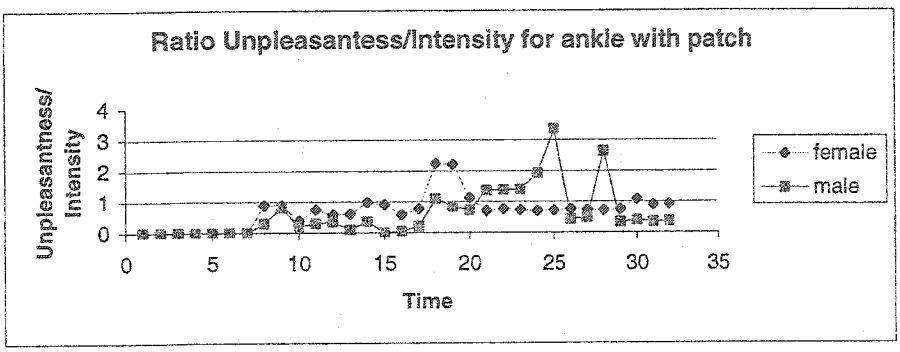
**Bold-faced values indicates statistically significant*

Figure. 5.

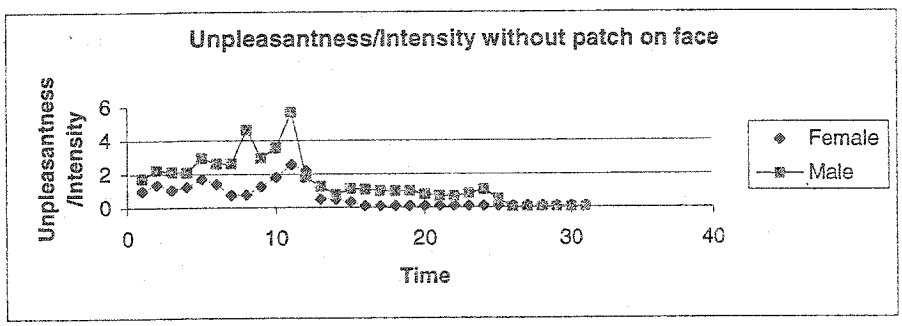
A.



B.



C.



D.

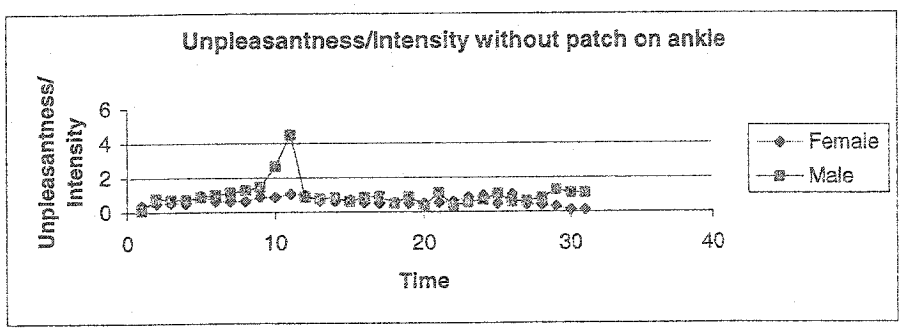


Fig. 5. Ratio of Unpleasantness over Intensity for A) face with patch B) ankle with patch C) face without patch D) ankle without patch

Maximal Pain Rating Scores

The maximum pain measurement values for each subject were recorded and analyzed. Independent sample T-test analysis revealed that there was a sex difference in the maximal anxiety scores on the face without the patch (t = -2.17, P =0.04) (Table 4). However, there were no significant differences between sexes for every other pain measurement category (Table 4).

Table 4

Summary of Independent Samples T-test Analysis: *Comparing Maximum Pain Scores between Males and Females*

Location	Capsaicin Status	Maximum Intensity	Maximum Unpleasantness	Maximum Anxiety
Face	With patch	*t = 0.70* *P =0.49*	*t = -0.34* *P =0.74*	*t = -1.63* *P =0.12*
Ankle	With patch	*t = 1.22* *P =0.24*	*t =1.35* *P =0.20*	*t = -0.81* *P =0.44*
Face	After patch	*t =0.36* *P =0.72*	*t =-0.64* *P =0.53*	***t = -2.17*** ***P =0.04***
Ankle	After patch	*t =0.85* *P =0.41*	*t =0.97* *P =0.34*	*t =-1.00* *P =0.33*

**Bold-faced values indicates statistically significant*

Table 5 summarises the mean scores and standard deviations for the maximal pain scores for both males and females.

Table 5

Summary of Mean Scores and Standard Deviations: *Comparing Maximum Pain Scores between Males and Females*

Location	Capsaicin Status	Maximum Intensity *(Mean Scores; SD)*	Maximum Unpleasantness *(Mean Scores; SD)*	Maximum Anxiety *(Mean Scores; SD)*
Face	With patch	Females: 47.2; 25.1 Males: 39.0; 27.3	Females: 47.7; 27.8 Males: 51.6; 22.6	Females: 3.8; 5.8 Males: 11.2; 13.1
Ankle	With patch	Females: 32.1; 34.5 Males: 16.1; 22.9	Females: 38.6; 36.9 Males: 19.8; 24.2	Females: 1.9; 6.0 Males: 6.1; 15.3
Face	After patch	Females: 45.7; 29.9 Males: 41.1; 26.7	Females: 42.7; 29.6 Males: 49.9; 19.9	Females: 1.0; 2.5 Males: 11.6; 15.2
Ankle	After patch	Females: 31.4; 36.3 Males: 19.7; 24.1	Females: 36.8; 37.7 Males: 22.7; 25.9	Females: 0.3; 0.9 Males: 7.3; 22.0

Pulse Rate

Pulse rates during and after stimulation of the capsaicin on the face and ankle regions were analyzed. Fig. 6 illustrates the changes in the pulse for both males and females during the experiment. Repeated measures ANOVA revealed that there were neither location ($F = 0.00$, $P = 0.98$) nor gender differences ($F = 0.05$, $P = 0.82$) (Table

6) for pulse rates during the experiment. In addition, there was a time effect for the pulse rate, with the rate gradually decreasing over time. Moreover, there was a time*sex interaction ($F = 3.2$, $P < 0.001$) with females having a greater decrease in pulse rates over time. Also, there was a time * location interaction ($F = 2.39$, $P = 0.003$) with the pulse having a more rapid decrease on the face.

Table 6

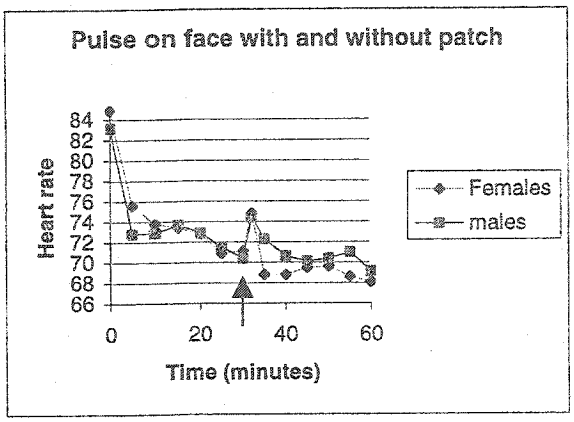
***Summary of Repeated Measures ANOVA:* Comparing Gender and Location Differences in Pulse Rates**

	F-Ratio	*P-Value*
Sex Difference	0.05	0.82
Location Difference	0.00	0.98
Time Effect	44.3	**<0.001**
*Sex * Location Interaction*	0.02	0.89
*Time*Sex Interaction*	**3.2**	**<0.001**
*Time*Location Interaction*	**2.39**	**0.003**
*Time * Sex * Location Interaction*	0.57	0.89

**Bold-faced values indicates statistically significant*

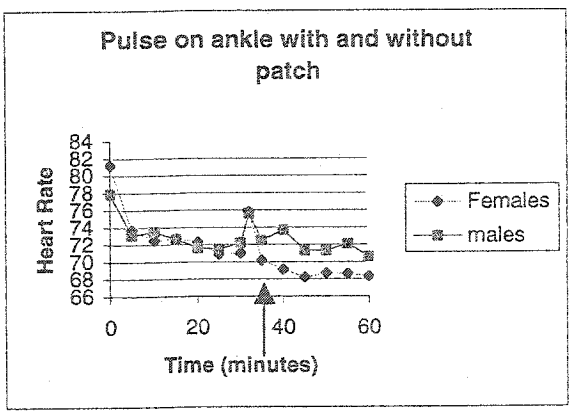
Figure. 6

A.



* ↑ *indicates removal of patch*

B.



* ↑ *indicates removal of patch*

Fig. 6. Graphs of pulse for males and females on A) face B) ankle

Spearman Correlation Analysis

Table 7 illustrates that for females, unpleasantness and intensity scores were highly correlated with each other r=0.96 (p<0.001) (Table 7). Furthermore, the pulse rates of females were highly linked with their anxiety scores r=0.79 (p<0.001).

Table 7

Spearman Correlation Analysis: ***Female's Pain Ratings and Pulse Scores (with and without patch combined)***

	Intensity	Unpleasantness	Anxiety	Pulse rates
Intensity	1	**r =0.96** **p <0.001**	r =-0.32 p =0.25	r =0.22 p =0.43
Unpleasantness	**r =0.96** **p <0.001**	1	r =-3.63 p =0.18	r =0.15 p =0.60
Anxiety	r =-0.32 p =0.25	r =-3.63 p =0.18	1	**r =0.79** **p <0.001**
Pulse rates	r =0.22 p =0.43	r =0.15 p =0.60	**r =0.79** **p <0.001**	1

**Bold-faced values indicates statistically significant*

Table 8 shows that for males intensity scores were highly correlated with unpleasantness r=0.99 (p<0.001) and anxiety scores r= 0.67 (p=0.01). However, pulse rates were not related to any pain measurements (Table 8).

Table 8

Spearman Correlation Analysis: *Male's Pain Ratings and Pulse Scores (with and without patch combined)*

	Intensity	Unpleasantness	Anxiety	Pulse rates
Intensity	1	**r =0.99 p <0.001**	**r =0.67 p =0.01**	r =0.08 p =0.78
Unpleasantness	**r =0.99 p <0.001**	1	**r =0.69 p =0.01**	r =0.25 p =0.93
Anxiety	**r =0.67 p =0.01**	**r =0.69 p =0.01**	1	r =-0.48 p =0.07
Pulse rates	r =0.08 p =0.78	r =0.25 p =0.93	r =-0.48 p =0.07	1

**Bold-faced values indicates statistically significant*

Mood

The mood before and after each experiment was examined for both sexes. A 2 x 2 ANOVA revealed that there was neither sex differences (F = 0.254, P = 0.62) nor before vs. after experiment differences in mood (F = 0.003, P = 0.96) (Table 9). In addition, there was no before vs. after * sex interaction (F = 0.092, P =0.77). Table 10 illustrates the mean mood scores and standard deviations before and after the experiment for both males and females.

Table 9

***Summary of 2 x 2 ANOVA:* Comparing Gender and Before vs. After Experiment Differences in Mood**

	F-Ratio	*P-Value*
Sex Difference	0.003	0.96
Before vs. After Difference	0.254	0.62
*Sex * Before vs. After Interaction*	0.092	0.76

**Bold-faced values indicates statistically significant*

Table 10

Mean Gender Mood Scores Before and After Experiment

Capsaicin Status	*Mean Scores; Standard Deviation*
Before	*Females: 65.1; 21.7* *Males: 63.7; 14.8*
After	*Females: 65.9; 20.2* *Males: 66.9; 12.6*

McGill Pain Questionnaire

Fig. 7 illustrates the mean number of words chosen for both sexes. Independent sample t-tests revealed that there were no statistically significant sex differences in any category of the McGill Pain Questionnaire for either the ankle or the face region (Table 11).

Table 11

Summary of Independent Samples T-test Analysis: *Sex Differences in the Mean Number of Words Chosen*

Location	Sensory	Affective	Evaluative	Miscellaneous
Face	*t = -0.07* *P =0.94*	*t = -0.40* *P =0.70*	*t = 0.80* *P =0.44*	*t = -1.17* *P =0.26*
Ankle	*t = 1.38* *P =0.18*	*t = -1.00* *P =0.33*	*t = 0.58* *P =0.57*	*t = -0.16* *P =0.88*

Likewise, the mean pain rating indices also had similar results to the mean number of words chosen from the McGill Pain Questionnaire (Fig. 8). Statistical analyses revealed that there were no sex differences in pain rating indices for all categories of the McGill Pain Questionnaire for both regions (Table11).

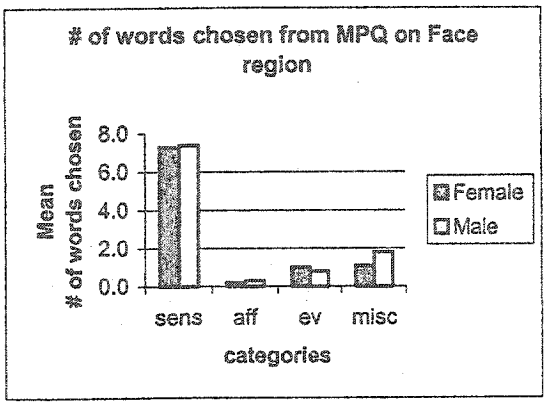
Table 11

Summary of Independent Samples T-test Analysis: *Sex Differences in Mean Pain Rating Index*

Location	Sensory	Affective	Evaluative	Miscellaneous
Face	*t = -0.15* *P =0.88*	*t = -0.60* *P =0.56*	*t = 0.87* *P =0.40*	*t = -1.03* *P =0.32*
Ankle	*t = 1.51* *P =0.15*	*t = -1.00* *P =0.33*	*t = 0.90* *P =0.38*	*t = 0.15* *P =0.88*

Figure. 7.

A



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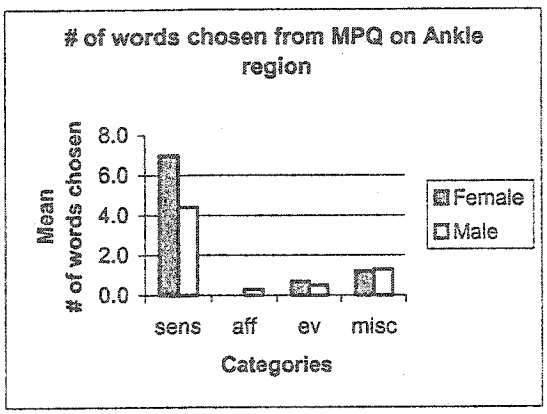
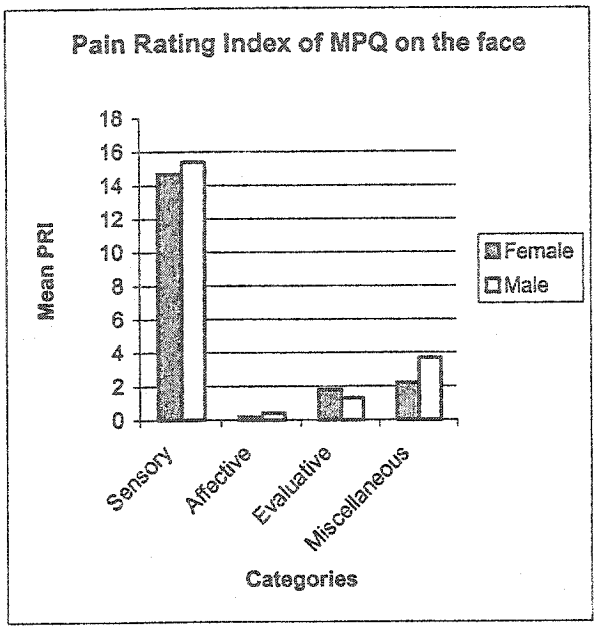


Fig. 7 The mean number of words chosen from MPQ on A) Face B) Ankle region

Figure. 8.

A



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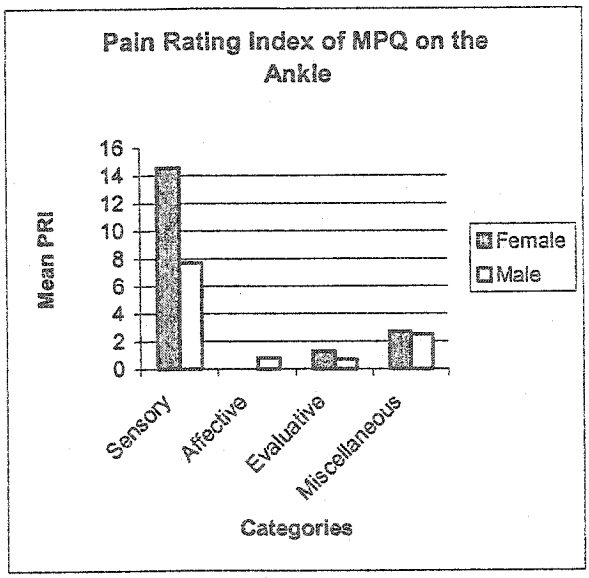

Fig. 8. The mean Pain Rating Index of the MPQ on A) Face B) Ankle region

Discussion

Description

Pain Ratings: Intensity, Unpleasantness and Anxiety

Although on the surface the results of this study do not seem to replicate previous findings supporting a greater disturbance of pain for men, a closer examination would indicate that this is not the case. For example, one sees that there was a sex * time interaction for anxiety ratings on the face with the patch, indicating that the anxiety of males increased over time, while the anxiety of females decreased over time. Based on personal experience, one would notice that anxiety is typically a normal response to unpleasant thoughts. In fact, the words associated with unpleasantness and anxiety are very similar. For instance, an individual who is experiencing an unpleasant situation would usually be stressed and worried. These same words can also be applied to describe an individual who is in an anxious state. More importantly, anxious responses to pain typically reflect, in part, a manifestation of difficulties managing negative emotional responses to stress or pain (Spertus et al., 1999). Thus, one can see that this study does, to some degree, confirm the idea that men may be more bothered by pain over time than women when the pain is on the face. This interpretation is congruent with recent findings in clinical studies, which have indicated that females are less disturbed by pain than males are (Affleck et al., 1999, Spertus et al., 1999, Morin et al., 2000, Chedade et al., 2001

Another interesting finding that emerged was that females exhibited greater sensitivity and unpleasantness scores than their male counterparts on the ankle. Similar

results were found after the capsaicin patch was removed (meaning after the first 30 minutes of the experiment). The findings of greater unpleasantness and intensity scores are consistent with another experimental study involving the use of thermal pain on healthy subjects (Sheffield et al. 2000), although it may be difficult to compare the results of these studies given the differences inherent in the pain stimulus. For example, capsaicin stimulates C-fibers whereas thermal pain can stimulate Aδ or C-fibers, depending on location and rise-time rate (see Ganong for review). In addition, the pain induced by the thermal apparatus is considered acute (the thermal stimulus was placed on the volar foramen for only a couple seconds) and completely different from the type of pain emitted by capsaicin, which is considered tonic in experimental settings. On the other hand, the lack of sex differences in intensity and unpleasantness scores on the face agrees with another study which found no sex difference in thermal pain threshold and tolerance using heat stimuli (Lautenbaucher et al.,1993) and cold pressor (Zeichner et al., 2000). Unfortunately, these results do not agree with the findings of most studies, which have reported that women have greater pain sensitivity than men (Feine et al., 1991, Fillingim et al. 1996, Berkley, 1997). The lack of statistically significant sex differences in pain ratings in this study may be partly due to the large variability in score values that existed within a given sex. The large variability and lack of significant sex differences in pain scores is consistent with prior related research (Fillingim et al., 1995, Maxiner et al., 1993).

Finally, as expected there was a time effect for intensity and unpleasantness scores with and without the patch on both the ankle and face regions. That is, during the initial 30 minutes of the experiment, when the capsaicin patch was on the subjects (for

both ankle and face), the intensity and unpleasantness scores gradually increased over time before reaching a plateau (more pronounced on the face). On the other hand, during the last 30 minutes of the experiment, when the capsaicin patch was removed from the subjects (for both ankle and face), the intensity and unpleasantness scores gradually decreased over time. These effects were not found for anxiety scores with and without the patch since the anxiety values were extremely low throughout the experiment. One could speculate that the anxiety values were low since subjects were informed prior to the commencement of the experiment that it was completely safe and hence, there would be no danger in the participation.

Ratio of Unpleasantness / Intensity

Comparisons of the relative unpleasantness (unpleasantness/ intensity ratios) did reveal difference between the sexes. Although there were no statistically significant differences from the analysis, there was a tendency for males to have a greater relative unpleasantness over time on the face without the patch (the last 30 minutes of the experiment). These results support another study involving the use of dental intra-oral implants, which indicated that the ratio of unpleasantness over intensity increased significantly with time (over days) for males but not for females (Morin et al., 2000). Taken together, these results confirm the notion that men are more disturbed than women by low levels of pain that persist over time.

Maximal Pain Ratings

In our study, we also failed to observe sex differences in maximal pain intensity, unpleasantness and anxiety. However, consistent with the analyses of mean ratings, there was a tendency for males to rate pain anxiety higher than females. The lack of sex effects on maximal pain ratings has been shown in another study involving dental intra-oral implants (Morin et al., 2000). It is interesting to note, that in both studies the maximal pain levels varied only between low to moderate levels for intensity and unpleasantness. One can speculate that perhaps at low to moderate levels of pain, sex differences may not be noticeable in the maximal pain levels since the stimulus may not have been painful enough.

Pulse Rate

Another interesting finding from this paper was that neither males nor females showed pain-related changes in heart rate throughout the experiment. Fillingim et al., (1996) also found similar results in healthy volunteers. However, this finding contrasts with the results of other studies. For example, women have been found to display higher pulse rates than men for the cold pressor task (Zeichner et al., 2000) and pressure pain (Koltyn et al., 1999). However, one must note that the experimental pain stimuli were different from the one used in this study, hence, it may be difficult to make comparisons. Strangely enough, it was discovered that only the pulse rates of females were positively correlated with anxiety scores. It may be difficult to make any interpretation from this finding due to the relatively scarce research in this specific field. On the other hand,

several studies have shown that blood pressure was inversely related to pain sensitivity among males and not females (Fillingim et al., 1996, Sheffield et al., 2000).

Correlations of Pain Scores

While it was revealed that the unpleasantness and intensity ratings were highly correlated for both males and females, only males had anxiety scores that were correlated with both pain ratings. Several papers have indicated a relationship between anxiety and pain ratings (Eli et al., 2000). In fact, typically, when anxiety exists the perception of painful experiences are increased (Robin et al., 1987). More importantly, the finding that only the anxiety ratings of males were correlated with pain scores is in agreement with both experimental and clinical studies. For example, in experimental settings, Fillingim et al. (1996) reported anxiety was positively related to thermal pain sensitivity for men only. Also, in clinical studies, it was shown in a study of chronic pain patients, that anxiety was inversely proportional to pain threshold only for men (Edwards et al., 2000). Researchers have suggested that there are several possible mechanisms by which pain-related anxiety potentiates the experience of pain, including increased attentional focus (Arntz et al. 1993) and passive or avoidant coping strategies (Asmundson et al., 1997).

Mood

Our results did not reveal either gender or "before vs. after experiment" differences in the mood during the entire experiment. These results agree with Marchand et al. (2002) which also found no correlation between mood and pain perception.

However, this may be surprising given the fact that there is much evidence indicating an inverse relationship between pain and emotional well-being (Parker et al., 1988; Salovey et al., 1989; Keefe et al., 1997). In addition, in another study examining patients with osteoarthritis, men were found more likely than women to report an increase in negative mood the day after a more painful day (Affleck et al. (1999). However, one should note that most of the studies that have indicated a correlation between mood and pain experiences have involved long-lasting chronic pain conditions. In our experiment, the pain induced by capsaicin typically lasted only a couple of hours. Hence, the brief overall pain experience may not have been sufficient to instill significant changes in mood.

McGill Pain Questionnaire

Finally, the analysis from our study revealed that there were no sex differences in either the pain rating index or the number of words chosen in the McGill Pain Questionnaire. The results from our finding may not be difficult to explain given the fact the McGill Pain Questionnaire is typically used in clinical studies which involve pain conditions that are chronic and perhaps more painful. More importantly, the pain experienced from the capsaicin stimulus may not have been long enough in duration or maybe not painful enough for sex differences to emerge in the McGill Pain Questionnaire.

Limitations

Several limitations of this research should be acknowledged. First, the small sample size (N=20) of this study may not have been adequate to detect sex differences in the ratings of pain unpleasantness, intensity, anxiety and mood. In addition, this sample consisted of healthy young adults who were all to some degree university-educated and wanted to participate in a pain study (i.e. they were not randomly selected from the university), which may not realistically represent the population in society. Hence, the results of this study may not necessarily be generalizable to clinical populations. Second, only one experimental pain modality was used. Since only one painful stimulus was used, there may be a possibility that different patterns of results may have emerged with other painful stimuli. More specifically, the slow onset and tonic duration of pain induced by capsaicin may have caused some subjects to be slightly distracted, while others may have become gradually more accustomed to the pain over time. This in turn may have caused the wide variations in the pain ratings among subjects. Typically, in experimental settings, the pain provoked from the pain stimuli is immediate and short-lived. Although the pain provoked from capsaicin is considered tonic in experimental studies, it is certainly not considered chronic in clinical studies. In fact, compared to chronic clinical pain the pain induced from capsaicin would be regarded as extremely acute. Third, perhaps more sensitive measurement techniques should have been employed. The magnitude matching procedure would have been a good example. This technique consists of presenting stimuli from another modality, such as visual stimuli, in addition to the pain stimuli (Duncan et al., 1988). Subjects are asked

to rate the intensity of both types of stimuli on the same numerical scale. This procedure allows the normalization of ratings from one modality (i.e. pain) using the ratings of intensity from the other sensory modality (i.e. light). The normalization minimizes the effects of individual differences in the use of the rating scales, which ultimately results in decreased variability both between and within subjects. Fourth, the weather may have also affected the results of this study. For example, the cold and dry temperatures of the winter season during which the experiments were conducted may have caused some subjects to have dry skin. Our female subjects may or may not treat their skin with lotion and ointments during the winter making their skin more or less supple than males (same situation for males). These subjects may in turn, have a slightly decreased sensitivity to pain perception although, to my knowledge there has been no reports on this matter. Fifth, subjects may have felt slightly embarrassed or uncomfortable by having a painful patch (capsaicin) on their face in the presence of a stranger (the investigator of the experiment). This notion of embarrassment may be more relevant in the session involving the administration of capsaicin on the ankle in which subjects were asked to remove their socks. More importantly, the embarrassment may have caused some subjects to be distracted and hence, less than accurate in their ratings of the pain measurements.

Areas of Future Research

Future investigations could examine whether there are any physiological differences in the brain using functional magnetic resonance imaging (fMRI) between the sexes when the capsaicin pain stimulus is applied. fMRI will measure the relationship

between activity in the anterior cingulate cortex and the primary somatosensory cortex. PET and MRI studies in normal humans have reported that pain activates three cortical areas: S1, S2 and the cingulated gyrus on the opposite of the stimulus (see Ganong for review). In addition, a recent study has revealed that the emotional component of pain is due to the activation of the anterior cingulate cortex (Rainville et al., 1997). More importantly, the results from the fMRI could be compared between the male and female subjects. This work could help elucidate which physiological mechanism(s) may explain the reported differences between the sexes in their response to both clinical and experimental pain. In addition, future work should also address issues relating to psychological characteristics and coping styles utilized during exposure to painful stimuli that may differentially influence pain perception between the genders.

Why Study Sex Differences in Pain Perception?

Although, this experiment will not lead directly to any changes to society, the findings from this study may have important implications for the management of pain. First, clinicians need to recognize that there may be important gender differences in the experience of pain. Specifically, males may be more anxious about their experience of pain than females. Perhaps, new behavioural interventions tailored for men should be implemented so as to help them better address dealing with the emotional aspects of pain. Furthermore, men should be encouraged to seek out advice from others when dealing with pain, as opposed to coping on their own. Overall, more customized treatments for both genders will lead to better outcomes in the advancement of chronic pain management and subsequent improvements in the health care system.

Conclusion

Results from this study suggest that men and women may be differentially responsive to pain. More specifically, males may be more disturbed by low levels of pain that lasts over time. This may not be the case for females. These conclusions are interpreted from the finding that men had tendencies for higher anxieties over time than females. These findings correlate well with other clinical studies that have generally found that although females may be more sensitive to pain, they may be better able to cope with pain than males do (Affleck et al., 1999, Spertus et al., 1999, Morin et al., 2000, Chedade et al., 2001). On the other hand, the results of the current study may conflict with Sheffield et al. (2000), who found that females had higher unpleasantness ratings for thermal pain. Similarly, the lack of sex differences in maximal pain ratings, heart rate, McGill Pain Questionnaire and mood do not support the results of some studies, which have suggested the presence of gender differences. These findings emphasize the limitation from generalizing from one type of noxious stimulus to others with regard to sex differences in pain ratings. On the other hand, the finding that only males have anxiety scores that are correlated with pain ratings fits well with other studies (Fillingim et al., 1996, Edwards et al., 2000). Taken together, the overall results of this paper highlight the fact that, at times, the interpretations are difficult to explain and understand. Typically, the nature of this field indicates that there are usually more

questions than answers. Clearly, more research is needed to elucidate sex-specific relationships between reporting of pain and the subjective experience of pain.

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APPENDIX. 1

ADVERTISMENT FOR CAPSAICIN PROJECT

SUBJECTS NEEDED

The Anesthesia Research Unit is looking for healthy subjects to participate in a pain study.

If you are interested and/or have questions please email:

RECHERCHE SUJETS

Le laboratoire de Recherche en Anesthesie de l'Universite McGill recherche des sujets volontaires sains pour participer a une etude sur la douleur.

Contactez Alanna Smith par e-mail :

Merci

APPENDIX. 2

CONSENT FORM

QUANTITATIVE SENSORY TESTING CONSENT FORM

Title of the project: **Neural Correlates of Peripheral and Central Neuropathic Pain Syndromes Evaluated by Psychophysical Testing and fMRI.**

Investigators: M.C. Bushnell, J. Persson, A. Genge, A.V. Smith, F. Carli

Reason for the study

The purpose of this study is to try to understand how experimental and clinical pain is processed in the brain. We will perform physical examinations to carefully characterize your responses to painful stimuli.

Procedures

Your participation in this study will involve 1 to 3 sensory testing sessions, each lasting less than two hours. In consultation with your physician, we will discuss with you the possibility of discontinuing use of some or all of your pain medication for a period of 24 hours to 1 week before each testing session, with the specific period being based on the nature of the medication you are taking. The discontinuation of your medication is not a requirement of the study. If you choose to do so, you will be free to begin taking your medication at any time.

During the sensory testing sessions, you will be presented hot, cold, pressure, brushing, capsaicin (active ingredient of hot chili peppers) and/or vibratory stimuli on the skin of various parts of your body. We will present a range of weak and strong intensities and ask you to rate how these feel, using rating scales and/or questionnaires. Although some of the stimuli we will present may be uncomfortable or painful, none will damage your skin. Also, you can withdraw from and terminate any stimulus at any time that you feel it is too uncomfortable. In some cases, we may ask you to just relax and rate the pain you spontaneously feel.

Contraindications

The following are contraindications for this study:

- Pregnancy or breastfeeding
- Regular use of alcohol or drugs
- Serious Cardiovascular disease
- Less than 18 or greater than 70 years of age

Advantages of the proposed study

There is no immediate advantage to you in participating in this study. However, it is hoped that the information obtained in this study will help researchers in understanding some of the mechanisms of chronic pain.

Disadvantages of the proposed study

The hot, cold, pressure stimuli or capsaicin may cause some pain and/or discomfort and/or temporary reddening of the skin. However, these stimuli will not damage or burn your skin.

Effects of participation in this study on your treatment

Sensory testing does not interfere with any treatment or other diagnostic tests. Your decision whether or not to participate will not affect any current or future treatments.

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

Incidental findings
Any incidental findings regarding your own health will be communicated to you or to your physician at your request.

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

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

Compensation
After you have completed the screening/training session, you will receive a sum of 50 dollars. After each testing session, you will receive a sum of 100 dollars.

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

SUBJECT'S DECLARATION OF CONSENT

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

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

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

Subject

Print Name	Signature	Date	Phone

Investigator

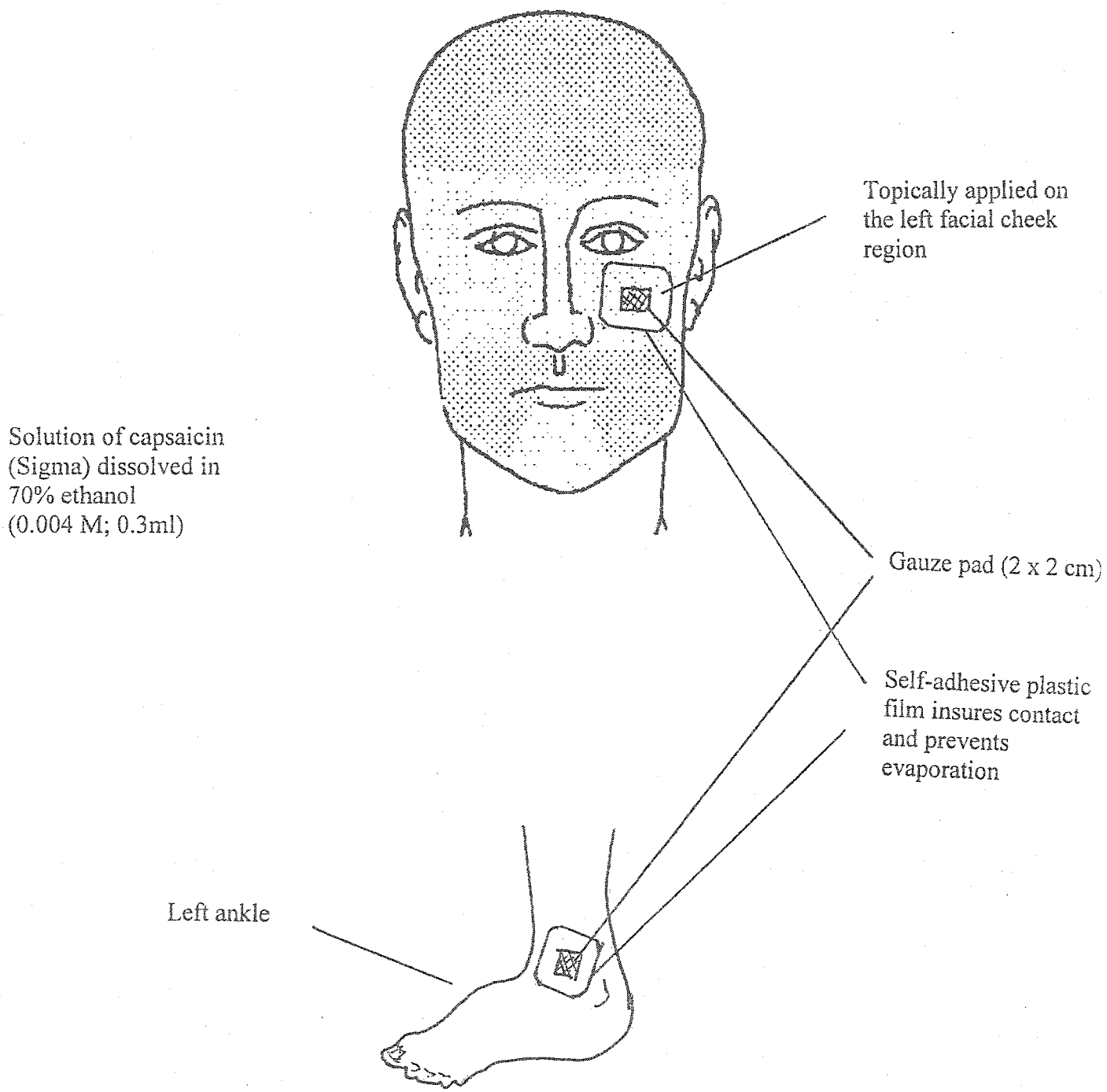
Print Name	Signature	Date	Phone

Witness

Print Name	Signature	Date	Phone

APPENDIX. 3

THE APPLICATION OF THE CAPSAICIN PATCH ON THE FACE AND ANKLE OF THE SUBJECT



APPENDIX. 4.

THE VAS RATING SCALES FOR INTENISTY, UNPLEASANTNESS, ANXIETY AND MOOD

Subject :

PAIN INTENSITY

No pain — Most intense pain tolerable

0 — 50 — 100

UNPLEASANTNESS

Not at all Unpleasant — Extremely Unpleasant

0 — 50 — 100

ANXIETY

Not at all Anxious — Extremely Anxious

0 — 50 — 100

MOOD

Extremely Bad — Neutral — Extremely Good

0 — 50 — 100

PAIN INTENSITY

No pain — Most intense pain tolerable

0 — 50 — 100

UNPLEASANTNESS

Not at all Unpleasant — Extremely Unpleasant

0 — 50 — 100

ANXIETY

Not at all Anxious — Extremely Anxious

0 — 50 — 100

APPENDIX. 5.

FLOW CHART OF THE CAPSAICIN EXPERIMENT

BEFORE APPLICATION OF THE CAPSAICIN PATCH

Subjects rated once for all VAS measurements of Intensity, Unpleasantness, Anxiety and Mood

↓

Time 0-30 minutes

APPLICATION OF CAPSAICIN PATCH ON FACE OR ANKLE

Subjects rated once/min on the VAS for Intensity, Unpleasantness, and Anxiety

↓

Time 30-60 minutes

REMOVAL OF CAPSAICIN PATCH ON FACE OR ANKLE

Subjects rated once/min on the VAS for Intensity, Unpleasantness, and Anxiety

↓

After 60 minutes

Subjects rated once for mood and the McGill Pain Questionnaire

Preparing Capsaicin Solution

Preparing 2 5 ml of ~~0.2 M~~ 0.04 sol'n

Background to determine how many grams of capsaicin we need to measure: M = mol/liter. We want 0.005 liter of 0.2 mol/liter. Therefore we need 0.001 mol. The molecular weight of capsaicin is 305.42 g/mol. 0.001 mol x 305.42 g/mol = 0.3 g of capsaicin powder.

Ingredients: 0.3 g of capsaicin powder
2 5 ml of ethyl alcohol 70% (not isopropyl alcohol)

Method: Wearing lab coat , gloves and mask, measure capsaicin and put in amber glass container. Add 3 ml of ethyl alcohol 70%, close container and shake to dissolve. Add the remaining 2 ml of ethanol.

Preparing 5 ml of 0.004 M sol'n

This is the solution that we use on the skin

Background to determine how much 0.2 M sol'n capsaicin we need to measure: $C_1V_1=C_2V_2$ (C=concentration, V=volume, 1=sol'n 1 and 2=sol'n 2). We want 0.005 liter of 0.004 mol/liter starting from a concentration of 0.2 mol/liter. 0.2 M x ? = 0.004 M x 0.005 liter. ? = 0.0001 liter or 0.1 ml.

Ingredients: 0.1 ml of 0.2 M capsaicin sol'n
5 ml of ethyl alcohol 70% (not isopropyl alcohol)

Method: Wearing lab coat and gloves, measure 0.1 ml of 0.2 M sol'n and put in amber glass container. Add 5 ml of ethyl alcohol 70%, close container and shake to mix.

Using capsaicin solution

You will need:

1. 2 transparent dressing without pad (Tegaderm 3M).
2. 2 2x2 cm gauze
3. 2 1cc syringes fitted with needles (to measure capsaicin and ethanol)
4. 0.5 ml of 0.004 M capsaicin sol'n
5. 0.5 ml of ethanol 70% (not isopropyl alcohol)

Procedure:

1. Wearing gloves, prepare the capsaicin and vehicle patches
2. Apply to the skin leaving at least 8 cm between center of patches
3. Leave for 20 minutes
4. Wearing gloves, remove patches
5. Wash skin with soapy water taking care not to contaminate vehicle area with capsaicin area.
6. Wait a minimum of 30 minutes before stimulating the skin with mechanical or thermal stimuli. SPONTANEOUS PAIN MUST HAVE DISAPPEARED. If after 30 minutes spontaneous pain is still present, wait until it has completely disappeared.

N.B. If subject finds the application of capsaicin too uncomfortable, remove the patches, wash the skin with soap and water and abort experiment.

APPENDIX. 7

MCGILL PAIN QUESTIONNAIRE

Some of the words below describe how pain can de experienced. In each grouping of words underline only those words that best describe your pain. Leave out any group that is not suitable.

1	2	3	4	5
flickering	jumping	pricking	sharp	pinching
quivering	flashing	boring	cutting	pressing
pulsing	shooting	drilling	lacerating	gnawing
throbbing		stabbing		cramping
beating		lancinating		crushing
pounding				

6	7	8	9	10
tugging	hot	tingling	dull	tender
pulling	burning	itchy	sore	taut
wrenching	scalding	smarting	hurting	rasping
	searing	stinging	aching	splitting
			heavy	

11	12	13	14	15
tiring	sickening	fearful	punishing	wretched
exhausting	suffocating	frightful	grueling	blinding
		terrifying	cruel	
			vicious	
			killing	

16	17	18	19	20
annoying	spreading	tight	cool	nagging
troublesome	radiating	numb	cold	nauseating
miserable	penetrating	drawing	freezing	agonizing
intense	piercing	squeezing		dreadful
unbearable		tearing		torturing