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9

Sex and Gender Differences in Responses to Experimentally Induced Pain in Humans

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Sex differences have long interested scientific and medical researchers, and the pain literature is replete with laboratory and clinical studies comparing the reactions of men and women. Often, these studies are based on small samples of convenience, but sufficient evidence has accumulated for us to conclude that males and females often show divergent responses to noxious stimuli. Still, the biological and psychological mechanisms underlying these differences or, for that matter, the experimental conditions giving rise to such differences, are poorly understood.

Several lengthy review and meta-analytic papers have carefully documented the literature on sex differences. Berkley (1997) noted that "when differences are observed under these carefully controlled experimental circumstances, it is often the case that women have lower thresholds, rate similar stimuli as more painful, or have less tolerance for intense stimuli." However, she also indicated that the "differences are inconsistently observed, relatively minor, exist only for certain forms of stimulation, and can be affected by numerous situation variables in daily life such as the presence of disease, the setting of the experiment, the characteristics of the experimenter, and even nutritive status."

Fillingim and Maixner (1995) examined 34 human experimental studies of sex and pain and found sex differences in about two-thirds of them. They concluded that "females exhibit greater sensitivity to laboratory pain compared

to males," that "these gender differences do not appear to be site specific," that "some forms have produced more consistent findings than others (e.g., pressure vs. thermal)," and that "pain responses are characterized by great interindividual variability."

Riley and colleagues (1998) used meta-analytic techniques to extend the evaluation of the studies reviewed by Fillingim and Maixner. They calculated effect sizes for 22 studies of sex differences that had used a variety of stimuli, body sites, measures, sample sizes, populations, and age groups. For pain threshold and pain tolerance, male subjects had higher values than females for all types of noxious stimuli, although the largest effect sizes were obtained when pressure pain was compared across the sexes, followed by electrical pulses and then by thermal stimuli. Statistical analysis suggested that about 40 subjects per group are necessary to provide adequate power to test a sex difference, although only 7 of the 34 studies reviewed by Fillingim and Maixner met this criterion.

In speculating why females are more responsive than males to pain, Riley and colleagues touched on a number of earlier suggestions including sociocultural factors, hormonal influences, body size, and anxiety, concluding that "the conflicting evidence for causal mechanisms only serves to emphasize the complexity of these differences, which, as with most psychological phenomena, are likely to be multidetermined."

Given the ready availability of reviews of the experimental data, this chapter will focus on the mechanisms underlying sex differences in pain responsiveness, paying particular attention to developmental, biological, and psychological factors. Our aim is to bring a broad perspective to the understanding of an issue that is scientifically perplexing and yet highly significant.

Each of these explanatory mechanisms contributes to our understanding of the variables underlying sex differences in pain. Many of the biological data suggest that critical differences arise in early stages of nociceptive processing, while the psychological studies emphasize factors related to pain perception, evaluation, and expression.

DEVELOPMENTAL FACTORS

It would be informative to learn whether there is a particular developmental stage at which sex differences in pain sensitivity begin to appear. An understanding of when biological or psychological correlates of sex differences become operative would allow us to develop more thorough explanatory models. The literature in this area is sparse, yet some experimental

studies have attempted to shed light on this issue. Meier et al. (1999) presented the results of a comprehensive study on a group of children and adolescents (54 girls and 52 boys, ranging in age from 6 to 17 years). The authors measured somatosensory sensitivity to warmth, cold, and vibration and pain sensitivity to heat and cold in the subjects' hands and feet. Even in this relatively large sample, they observed no sex differences in pain sensitivity, although girls had lower thresholds for nonpainful temperatures (warmth and cold) than did boys.

In a study with more clinical content, Bournaki (1997) investigated the responses to venipuncture in 51 girls and 43 boys, ranging in age from 8 to 12 years. Various measures of subjective pain experience as well as heart rate responses failed to reveal a difference between girls and boys. The only difference found was a behavioral measure: girls cried more than boys. Fowler-Kerry and Lander (1991) examined venipuncture pain and anxiety among 90 male and 90 female children and adolescents (aged 5–17 years) and determined that males and females were alike regarding how much they expected the procedure to hurt and how much it did hurt. Overgaard and Knudsen (1999), measuring crying time in neonates during heel prick, also found no sex difference, although Grunau and Craig (1987), for the same procedure, observed that boys were quicker to cry and to display facial expressions of pain.

Particularly interesting is a group of studies that dealt with the pressure pain thresholds of girls and boys, since this experimental pain induction method has yielded especially stable sex differences in adults (Fillingim and Maixner 1995; Berkley 1997; Riley et al. 1998). Hogeweg et al. (1996) used a variable pressure algometer to assess pressure pain thresholds at various body sites in 36 girls and 33 boys, ranging from 6 to 17 years of age. No sex differences were observed, despite findings in the adult literature that male subjects have significantly higher pressure pain thresholds than females (Hogeweg et al. 1992).

Likewise, Pothmann (1993) reported no sex differences in the pressure pain thresholds of 27 children aged 7–15 years, assessed by pressing an algometer against the tip of the index finger. In contrast, Buskila et al. (1993), who determined pressure pain thresholds at various body sites in a sizable sample of schoolchildren (n = 338), found that girls had significantly lower pressure pain thresholds than boys at both fibromyalgia tender points and control sites.

In summary, evidence is mixed as to whether sex differences in pain sensitivity occur in childhood and adolescence. Whereas pressure pain induction almost guarantees sex differences in adults, such differences are rarely demonstrated in studies involving children and adolescents. It is

tempting to suggest that at least some important causes of sex differences in pain sensitivity might first become active after puberty.

BIOLOGICAL FACTORS

BLOOD PRESSURE

Given the well-established differences between men and women in many cardiovascular parameters and the documented interaction of blood pressure and reactions to pain, blood pressure regulation must be considered in any attempt to explain sex differences in pain sensitivity (Bruehl et al. 1992; Sheps et al. 1992; McCubbin and Bruehl 1994; Guasti et al. 1999).

Fillingim and Maixner (1996) assessed the impact of resting blood pressure on sex differences in pain reactivity in 23 female and 25 male subjects. They measured pain and tolerance thresholds for contact heat and ischemia and obtained ratings of the intensity and unpleasantness of those stressors. Sex differences occurred only in the ratings of pain intensity for suprathreshold heat stimuli and in ischemic pain tolerance thresholds, with women appearing more sensitive to pain. However, the men had higher blood pressure than the women; the significant differences in male versus female pain reactivity disappeared when blood pressure was used as a covariate. Consequently, blood pressure could be a powerful influence on sex differences in pain sensitivity. A subsequent correlational analysis, however, indicated that blood pressure is inversely related to pain sensitivity only in men, suggesting that this pain-modulatory system may be sex-specific.

To further investigate the hypothesis that higher resting blood pressure does not suppress pain sensitivity in women, Fillingim et al. (1998a) applied contact heat stimuli to the volar forearm and to the face of 21 female subjects. In accordance with the earlier findings, resting blood pressure did not affect pain threshold or pain tolerance threshold. Verbal descriptor pain ratings of suprathreshold stimuli were also unaffected. However, a median split of the blood pressure values indicated that women with higher blood pressure rated thermal pain as less unpleasant than did women whose blood pressure was lower. The relationship between resting blood pressure and pain sensitivity thus appears to depend on the pain dimension under investigation.

A related question concerns whether stress-related changes in blood pressure influence pain sensitivity in a gender-dependent manner. Bragdon et al. (1997) compared 38 men and 36 women for links between stress-evoked cardiovascular responses and changes in pain sensitivity. Contact heat stimuli were administered to the volar forearm to assess pain and toler-

ance thresholds, both before and after recall of a stressful situation. At baseline, no sex differences in thermal pain sensitivity were present. The stressful situation diminished pain sensitivity only in women with a low resting blood pressure, suggesting that an interaction of stress-induced analgesia and resting blood pressure modulates pain reactivity only in women.

Findings of an earlier study by the same research group seemingly contradict these observations. Maixner and Humphrey (1993) assessed both subjective and cardiovascular responses to tonic ischemic pain produced by a submaximal effort tourniquet technique in 33 women and 34 men. There were no sex differences in pain and tolerance thresholds, but ratings of pain intensity and unpleasantness were higher in women than in men. A blood pressure increase was observed among men during pain stimulation, but no comparable trend was apparent in women. The pain-related changes in blood pressure correlated substantially with the degree of pain experienced by men. Bragdon et al. (1997), however, found that situation-related changes in blood pressure influenced pain sensitivity only in women, although these authors assessed blood pressure responses at rest and during a nonpainful stressor, and then correlated those measures with pain sensitivity (finding that both were positively correlated with pain tolerance among women), while Maixner and Humphrey evaluated changes in blood pressure during the painful task itself (observing that pressure was positively related to the amount of pain experienced).

A predisposition for hypertension may be as important as current blood pressure in accounting for the relationship between cardiovascular reactions and pain responsiveness, since normotensive males with a parental history of hypertension were found to have reduced pain sensitivity (Stewart and France 1996). To discover whether this relationship holds for both sexes, al'Absi et al. (1999) investigated 46 women and 82 men either with or without a parental history of hypertension. The responses to cold-pressor pain were assessed by using concurrent numerical ratings and the McGill Pain Questionnaire. Men with a positive parental history of hypertension differed from the other three groups by showing stronger cardiovascular reactions and lower pain responses to the stressor, but these effects were not found for women. However, D'Antono et al. (1999) did find that women with a parental history of hypertension and/or normatively high resting systolic blood pressure experienced significantly less pain during finger pressure and cold-pressor tests compared to normotensive females.

These relationships are clearly complex and are likely to be clarified in coming years. While current blood pressure and a predisposition for hypertension may contribute to the explanation of sex differences in pain sensitivity, they probably do so only to a moderate degree. It is still far from clear

whether the interactions between blood pressure and pain sensitivity, on the one hand, and hypertension risk and pain sensitivity, on the other, are themselves gender-dependent.

BODY SIZE

It has been argued that women are more pain sensitive than men because biological features such as thinner skin, greater density of nociceptive fibers, and shorter length of the afferent pathways accompany their typically smaller body size. Larkin et al. (1986) found that sex differences in electrocutaneous detection and "annoyance" thresholds were eliminated when they covaried the thresholds for body weight or surface area. However, Rollman et al. (1990) found a sex difference in electrical detection, pain, and tolerance thresholds that remained even after statistical correction for body size.

Analyses based on covariance techniques are potentially very instructive, but they are also prone to misinterpretation. To provide evidence for a relationship between body size and pain responsiveness, substantial correlations between these factors must be uncovered both across and within the two sexes. To this end, Lautenbacher and Strian (1991) investigated warmth, cold, phasic pain, and tonic pain thresholds at the hands and feet of 32 women and 32 men. Sex differences occurred only for warmth thresholds, with women being more sensitive than men. As in the study by Larkin et al. (1986), these differences could be removed by using body height and body weight as covariates. Furthermore, multiple correlations between height, weight, and warmth sensitivity were substantial both within and across genders. Hence, individual differences in body size helped to account for sex differences in warmth sensitivity. However, the correlations between body size and pain thresholds were much lower and were barely significant. The lack of a relationship between pain sensitivity and body size within separate male or female groups was corroborated by two later studies (Lautenbacher and Rollman 1993; Lautenbacher and Strian 1993). Consequently, while some evidence has accumulated to suggest that sex differences in sensitivity to nonpainful somatosensory stimuli can be partially attributed to individual differences in body size, the same has not held true for pain sensitivity.

MENSTRUAL CYCLE

Variation of pain sensitivity during the menstrual cycle is reviewed in Chapter 10 of this volume, but we will present a brief overview here. Knowledge regarding the role of the hormonal milieu can enrich our understanding of

sex differences in two ways: (1) It is possible that women differ from men in pain sensitivity during certain phases of the menstrual cycle but not during others. If so, studies on sex differences should control for the effect of the menstrual cycle and for the use of oral contraceptives. (2) Variations in pain sensitivity during the menstrual cycle would indicate a relationship between pain sensitivity and sexual hormones, with the latter, of course, being inherently different between the two sexes.

Unfortunately, the available data on the associations between pain responsiveness and menstrual phase are far from clear (Riley et al. 1999). The results of the various studies diverge more than they converge, perhaps because of methodological differences such as variations in the sampling procedure, the experimental pain induction technique, and the determination of menstrual phase, as well as the fact that cyclic variations are only a minor source of variance in pain sensitivity (see Chapter 10 for a detailed discussion). Some studies show that pain sensitivity is higher in the luteal or premenstrual phases than in the follicular or postmenstrual phases (Procacci et al. 1974; Goolkasian 1980, 1983; Hapidou and De Catanzaro 1988; Fillingim et al. 1997), but others have shown no effects or another pattern of cyclic changes (Tedford et al. 1977; Veith et al. 1984; Giamberardino et al. 1997; Hapidou and Rollman 1998). Thus, as Riley et al. (1999) concluded, menstrual cycle phase may influence pain responses among females, but these effects are generally moderate and do not completely explain sex differences in pain sensitivity.

TEMPORAL AND SPATIAL SUMMATION

Clear evidence shows that the method of pain induction is of critical relevance in establishing whether sex differences in pain sensitivity occur in the laboratory. For example, whereas women have reliably appeared to be more pain sensitive than men when pressure pain was applied, results have been inconsistent in the case of thermal stimuli (Fillingim and Maixner 1995; Berkley 1997; Riley et al. 1998). Besides the nature of the physical stimulus, pain induction methods also differ with respect to the temporal aspects (frequency and duration) and spatial characteristics (size and location) of the noxious stimulation. An examination of these factors may help to explain the inconsistency of the findings regarding sex differences within a single pain induction method (Lautenbacher and Rollman 1993).

Only recently have a few studies begun to address this issue. Fillingim et al. (1998b) measured temporal summation of heat pain as well as heat pain threshold, heat tolerance threshold, thermal discrimination ability, and magnitude estimation of heat stimuli in 27 female and 22 male subjects. The

women exhibited lower pain thresholds and pain tolerance thresholds than men, but did not differ from men in their discrimination ability or magnitude estimation. Of greatest interest, when tested with a paradigm involving repeated stimulation at noxious temperature levels (designed for measuring temporal summation and "wind-up" of C-fiber-mediated pain; Price et al. 1977), women increased their ratings of pain intensity significantly more than men. This enhancement occurred during the first few trials, suggesting that in women, only a short series of stimuli is required for an augmentation of the pain response.

Fillingim et al. (1998b) suggested that gender differences in thermal pain perception may be more robust for sustained thermal stimuli with a strong C-fiber component, perhaps due to differentially enhanced central wind-up of pain-signaling neurons. Tentative support for this idea came from Fillingim et al. (1999a), who demonstrated that a slow rise time to a painful peak temperature, which also prolongs the time of noxious stimulation, produces slightly greater sex differences in pain threshold than does a fast rise time. Consequently, there is some evidence that women integrate pain signals over time more effectively than men.

A similar hypothesis regarding spatial integration was not supported by the results of a study conducted by Lautenbacher et al. (1999). In 20 women and 20 men, pain thresholds and ratings of suprathreshold stimuli applied to the volar forearm were assessed for four different sizes of thermode ranging from 1 to 10 cm^2. The hypothesis was that women possess a more efficient spatial integration system than men, leading to a robust pain response from smaller areas of stimulation. However, women did not differ from men in any pain measures at any size of thermode. This study indicated that the two sexes have a similar capacity for integrating spatially distinct pain signals.

DIFFUSE NOXIOUS INHIBITORY CONTROLS (DNIC)

"Diffuse noxious inhibitory controls" (DNIC) is the term applied to the finding, first identified in animal-based neurophysiological studies conducted by Le Bars et al. (1979), that noxious stimulation produces antinociceptive effects in an anatomically heterotopic fashion even in far-removed sites. Put more simply, painful stimulation at one body site can suppress pain at more distant loci. DNIC effects are believed to be caused by a descending inhibitory control system that includes supraspinal links in the brainstem. The associated phenomena have also been repeatedly observed in humans (Willer et al. 1984, 1990).

Since the experimental paradigms developed for studying DNIC use two concurrently applied pain stimuli, one for eliciting pain inhibition (the

conditioning stimulus) and one for assessing pain inhibition (the test stimulus), the bulk of the laboratory findings on sex differences obtained in single-stimulus procedures cannot be explained by DNIC-like mechanisms. Nevertheless, it is of great interest to determine whether women differ from men in this endogenous pain-inhibitory system.

France and Suchowiecki (1999) investigated sex differences in DNIC effects among 44 women and 39 men. They used ischemic pain on the forearm, produced by a modification of the submaximal effort tourniquet test, as the conditioning stimulus, which activated DNIC and evoked pain inhibition. The inhibitory effect was tested by assessing the amplitude of the R-III nocifensive reflex before and during concurrent ischemic forearm pain. In both males and females, the reflex amplitude was reduced by the concurrent ischemic pain stimulation without any indication of a sex difference. As such, DNIC appeared to be similarly effective in both sexes.

S. Lautenbacher and G.B. Rollman (unpublished data) used a very different methodological approach. We presented concurrent tonic (contact heat to the thigh) and phasic (electrical current to the forearm) pain stimuli at levels above and below pain threshold. The perceptual interaction between the two pain types was assessed in 20 women and 20 men by asking them for combined visual analogue scale ratings of the two pains. Our findings demonstrated, in accord with a DNIC-like phenomenon, that tonic painful heat suppresses the perceived intensity of the phasic stimulus, but that tonic nonpainful heat does not. However, there were no differences between women and men in this respect. Hence, it appears unlikely that DNIC can account for sex differences in pain processing.

PSYCHOLOGICAL FACTORS

ANXIETY

Lautenbacher and Rollman (1993), testing a single group of men and women, found no sex differences in heat pain thresholds, but significant sex differences in pain and tolerance thresholds for electrical pulses applied to the skin (with lower thresholds in women). Likewise, magnitude estimates were similar in women and men for thermal stimuli, but women rated electrical stimuli from 2.5 mA on as more intense than did men. A biological interpretation might suggest that the difference is due to differential activation in men and women of receptors, afferent fibers, spinal pathways, or central regions. It is also plausible to suggest that the differential activation of anxiety could play an important role.

Perhaps women are less familiar with certain noxious stimuli such as electrical pulses or are more likely to catastrophize about dreadful outcomes. In the Lautenbacher and Rollman (1993) study, women had higher state anxiety scores than men (although the differences did not achieve statistical significance). Rollman et al. (1990), however, did find a significant sex difference in anxiety about electrical pulses. So, too, did Robin et al. (1987), who also found a significant correlation between anxiety scores and pain tolerance threshold.

Much has been published on the relationship between anxiety and pain. Cornwall and Donderi (1988) found that anxiety-evoking instructions increased pain ratings, stress intensity ratings, and heart rate compared to standard control instructions when painful pressure was applied to the skin. von Graffenried et al. (1978) indicated that anxiety had a marked effect on experimental pain thresholds.

Women show greater dental anxiety (Liddell and Locker 1997) and greater fear of stimuli associated with dental care (e.g., "feeling the drill in the mouth") (Holtzman et al. 1997). Women have more fear than men of coronary angiography (Heikkila et al. 1999), and girls have more fear than boys about medical procedures (Aho and Erickson 1985). Girls give higher fear ratings for lightning, enclosed spaces, darkness, flying, heights, spiders, snakes, injections, dentists, and injuries (Fredrikson et al. 1996), and they generally report significantly higher levels of fearfulness of objects and situations than do boys (Gullone and King 1993).

Rollman (1995) reviewed a series of studies in which anxiety enhanced pain responsivity and disrupted self-control strategies for dealing with pain. He cited a number of animal studies in which female rats or mice showed more defensive behaviors to threat, had lower levels of analgesia mediated by endogenous opioids after exposure to a predator, and exhibited significantly less opioid and non-opioid stress-induced analgesia than did males. Detailed information about animal studies is found in Chapters 3 and 5 of this volume and in recent articles (e.g., Cicero et al. 1997, 2000; Craft et al. 1999; Kest et al. 1999).

Anxiety sensitivity (fear of anxiety-related bodily sensations) predicts pain sensitivity and anxiety in the cold-pressor task (Schmidt and Cook 1999). Keogh and Birkby (1999) recently reported, for the same test, that high anxiety sensitivity was associated with enhanced pain sensitivity in females, but not males. Asmundson and Taylor (1996) suggested that anxiety sensitivity may act as a risk factor for chronic pain. Indeed, women are at greater risk for a multitude of pain syndromes (Unruh 1996), and interference due to pain has a greater impact on threat appraisal of pain for women and leads to greater health care utilization (Unruh et al. 1999). Clearly, the

findings obtained from laboratory studies with induced pain provide provocative proposals regarding clinical pain perception and coping patterns in men and women.

The issue of differential engagement of neural mechanisms associated with emotion and pain appraisal is made all the more germane by the results of a neuroimaging study conducted by Paulson et al. (1998). The authors used positron emission tomography to detect increases in regional cerebral blood flow in normal male and female subjects as they discriminated differences in the intensity of innocuous and noxious heat stimuli applied to the forearm. Females rated the 50°C stimuli as significantly more intense than did males and had significantly greater activation of the contralateral prefrontal cortex, a region seen as particularly salient in encoding anxiety (Wedzony et al. 1996; Kimbrell et al. 1999).

We still have much to learn about the relation between anxiety and pain. Recently, Rhudy and Meagher (2000) examined the effects of experimentally induced fear and anxiety on radiant heat pain thresholds. Fear was induced by exposure to three brief shocks and anxiety by the threat of shock. While fear resulted in decreased pain reactivity, anxiety had the opposite effect. It would be interesting to see whether there are interactions among the nature of the affective stimulus, pain responsiveness, and sex. We also need to look carefully at measures of pain-specific anxiety and fear that are focused on the experimental stressors rather than simply assessing the more wide-ranging state anxiety.

STRESS RESPONSES

Curiously, while the animal literature contains much evidence of sex differences in stress reactions, little is known about stress as a candidate for accounting in sex differences in human pain responsiveness. Among mice, a sexual dimorphism in the pituitary-adrenal function is evidenced by higher corticosterone levels in females (Gaillard and Spinedi 1998). Exposure to mild electrofoot shocks caused female rats to secrete significantly more adrenocorticotropic hormone, a stress hormone, than did male animals (Rivier 1999). Romero and Bodnar (1986) discovered that female rats show significantly less stress-induced analgesia than males following both continuous cold-water (non-opioid) and intermittent cold-water (opioid) swims, and others have demonstrated sex-dependent alterations in the neurochemical mediation of stress and pain in mice and rats (e.g., Mogil and Belknap 1997; Aloisi et al. 1998; Sternberg 1999).

Jones et al. (1997) showed that women who suffer temporomandibular dysfunction (TMD) (a disorder in which the prevalence rate for women is

much greater than that for men) showed a significantly higher cortisol response to experimental stress than did a control group. The patient data indicated the presence of two subgroups, one of which was particularly reactive to stress. The findings suggest a biological predisposition to TMD; the epidemiologic data (e.g., LeResche 1997), suggest a differential effect on women. Given the overrepresentation of women in other disorders such as fibromyalgia and chronic fatigue syndrome, researchers ought to conduct more laboratory-based studies of sex differences in stress perception, stress response, stress-induced analgesia, and the elicitation of hormones and neuropeptides. Derangements in the stress axis and accompanying neuroendocrine modifications may render women particularly vulnerable to numerous complex pain syndromes (Rollman and Lautenbacher 1993; Clauw 1995; Clauw and Chrousos 1997; Demitrack 1997).

The literature on the relationship between stress and the organism's sex has largely looked at stress-induced analgesia elicited by environmental stressors. Both animal and human studies are needed that carefully examine sex differences in the behavioral and neuroendocrinological correlates of the stress induced by exposure to the pain laboratory itself (Dworkin and Chen 1982) and to the trial-by-trial discomfort of various noxious stimuli. We must explore the implications of any resulting differences in accounting for disproportionate incidence of chronic pain disorders (Winfield 1999).

CRITERION EFFECTS

Perhaps because of anxiety, perhaps because of greater wisdom, women may choose not to play the same game as men. That is, women and men may perceive experimentally induced pain to be equally painful, but women prefer not to go to higher levels. Some data might counter that argument. In studies using electrical pulses (Rollman and Harris 1987; Rollman et al. 1990; Lautenbacher and Rollman 1993), women had a significantly lower detection threshold than men (even in experiments that used forced-choice adaptive techniques that eliminated response bias). Also, compared to men, women gave higher pain ratings to equally intense stimuli, for both thermal pulses (Feine et al. 1991) and electrical pulses (Lautenbacher and Rollman 1993).

Still, data indicate that at least part of the sex difference in pain responsiveness is related to willingness rather than ability to endure discomfort. Rollman (1995) describes an experiment in which male and female observers were tested for pain threshold and tolerance with three different noxious stimuli: electric shock, cold-pressor pain, and a constant-pressure algometer. When subjects felt that they had reached the appropriate level, they

were asked to use a 10-point scale to describe the painfulness of their experience. There were interesting differences across induction methods (the mean rating when subjects had reached the maximum level they were willing to endure was 5.9 for shock but 7.9 for cold and 7.1 for pressure). Moreover, women stopped the presentation of electrical pulses at a level of about 5 (moderate), whereas men went to nearly 7. It appears that women knew that this was not truly their tolerance; rather, they preferred to call a halt at a level far below maximum tolerance. The same tendency was observed for cold and pressure, but the difference was considerably smaller. Rollman (1995) suggested that the sex difference in self-described tolerance, particularly for electrical shock, was due to differential anxiety to the stimuli, an interpretation supported by the results of an experiment in which electrical pain tolerance levels increased over repeated testing sessions for women but remained constant for men.

A more recent study by Rollman and Hervieux (1999) had a somewhat different outcome. Recognizing that numerous earlier studies that looked at the scaling of noxious stimuli at different intensities were obliged to drop potential subjects who were unable to tolerate the stimuli at the upper end of the range (thereby obtaining a nonrepresentative sample of women), Rollman and Hervieux measured each subject's pain threshold and tolerance for electrical shocks and tailored the range for the scaling experiment to span that range. Large sex differences in pain threshold and tolerance were found. The power functions that related perceived intensity or unpleasantness to current were essentially parallel, with those for women shifted to the left of those for men. Moreover, although members of both sexes reached tolerance at a self-admittedly low level of pain, the average ratings for threshold and tolerance were much the same across sexes. These data suggest that an important biological component may underlie the sex difference in electrically induced pain. A corresponding study with thermal heat stimuli is in progress (G.B. Rollman and L. Parlea, unpublished data).

Related evidence for a low-level contribution to sex differences comes from a study by Ellermeier and Westphal (1995) on responses to tonic finger pressure. Female subjects reported greater pain than males at high levels of stimulation and showed greater pupil dilations. Since pupil response is seen as an autonomic indicator of pain that is beyond voluntary control, these sex differences should reflect fundamental sensory or affective components of pain. The R-III reflex, a spinal nociceptive reflex recorded from the biceps femoris and typically considered to be outside conscious control, also occurs at a lower level of electrical stimulation for females relative to males (France and Suchowiecki 1999).

Signal detection theory methods have been proposed as a way to learn about criterion effects in pain. While there are questions about the unambiguous interpretation of the resulting data (Rollman 1977), Clark and Mehl (1971) stated that women had a lower criterion than men for reporting pain. Likewise, Ellermeier (1997), in a re-analysis of scaling data (Ellermeier and Westphal 1995) showing that women rate various levels of pressure on the finger as more painful than men, suggested that the two sexes are equal in sensory discrimination but that women have a greater bias to assign higher ratings, particularly as stimulus intensity approaches tolerance.

HYPERVIGILANCE

Numerous disorders (e.g., fibromyalgia, temporomandibular disorders, irritable bowel syndrome) have a large preponderance of women among the patients (Dworkin et al. 1990; Wolfe et al. 1995; Toner and Akman 2000). In these syndromes, patients generally have lower pain thresholds and tolerance levels than do pain-free controls (e.g., Scudds et al. 1987; Rollman 1989; Gibson et al. 1994; Lautenbacher et al. 1994; Maixner et al. 1995; Fillingim et al. 1996; Naliboff et al. 1997; Kashima et al. 1999). Might these factors be related?

Gender imbalance in prevalence for painful disorders and enhanced pain sensitivity may be linked through the concept of hypervigilance (Rollman and Lautenbacher 1993). Hypervigilance reflects a generalized pattern of hyper-responsiveness to internal and external discomfort which, because it is also seen for response to other sensory inputs such as noise (McDermid et al. 1996), extends beyond the traditional pain domain. The hyper-responsiveness in fibromyalgia patients may account for their report of a wide range of bodily symptoms and complaints including headache, irritable bowel, dysmenorrhea, light sensitivity, temporomandibular dysfunction, and paresthesias (Yunus et al. 1991; Waylonis and Heck 1992). Even certain forms of the DNIC paradigm, discussed above, may reflect an attentional disorder in which individuals concentrate on all noxious inputs while others channel their attentional capacity to the longest and most intense input.

Further research must determine whether the heightened responsiveness seen in these patients, and perhaps more generally in women, reflects a widespread disturbance of sensory processing (Dohrenbusch et al. 1997), a localized or generalized hyperalgesia (Okifuji et al. 1999), a neural sensitization (Bell et al. 1998), or a more comprehensive alteration in pain detection, interpretation, and response.

Rollman and Lautenbacher have proposed that hypervigilance is a more focused hypothesis than hypochondriasis, emphasizing perceptual and cogni-

tive processes rather than psychopathological ones (Rollman and Lautenbacher 1993; Lautenbacher and Rollman 1999). As applied to sex differences, the concept goes beyond differences in sensory transduction and transmission to include a series of affective and cognitive states (Rollman 1998). Women may be more likely than men to monitor internal and external events (Miller 1987), to attribute bodily signs to physiological causes rather than to environmental or psychological factors (Robbins and Kirmayer 1991; van Wijk and Kolk 1997), to demonstrate a maladaptive pattern of coping in attempting to deal with their situation (Unruh et al. 1999), and to react to negative events and cognitions with increased pain responsiveness. Additionally, women may respond to noxious events with one or more bodily reactions such as localized or widespread muscle tension, altered gastric motility, and marked autonomic or cardiovascular function.

van Wijk and Kolk (1997) noted that health surveys, studies on symptom reporting, and examination of medical records all reveal consistent sex differences in the description of physical symptoms, with women having higher rates independent of morbidity. The authors' symptom perception model, an expansion of the symptom sensitivity hypothesis (Gijsbers van Wijk et al. 1991), emphasizes sex differences in selection of information about one's body, attribution of somatic sensations, and the personality factors of somatization and negative affectivity.

Further research is needed to relate individual differences in symptom perception, symptom appraisal, symptom reporting, illness behavior, and negative mood (e.g., Verbrugge 1980; van Vliet et al. 1994; Katon and Walker 1998; Almeida et al. 1999; Gijsbers van Wijk et al. 1999; Wolfe and Hawley 1999). Corresponding differences in the sensory, affective, and cognitive response to experimentally induced pain (e.g., Fillingim et al. 1999b) must be investigated, with particular attention paid to the role of sex.

PSYCHOSOCIAL INFLUENCES

Thoughts, attitudes, and behaviors are all generated within a social context (Jacklin 1989). Individuals are likely to think about and react to painful events in a manner consistent with socially accepted, gender-based expectations. However, the influence of gender on the sensory, affective, and cognitive components of pain has only recently begun to be explored.

Gender has been defined as "a scheme for the social categorization of individuals" (Sherif 1982), and has been proposed as a term that allows us to distinguish between the biological and social components of sex (Unger 1979). As opposed to the study of more biologically oriented sex differences, research on gender seeks to view differences between men and women

through a culturally defined lens, one that provides an image of appropriate traits and behaviors for men and women. Gender (or sex) roles have been characterized as scripts that men and women follow in specific situations; they contain information relating to socially expected and encouraged patterns of masculine or feminine behavior (Bem 1981).

Gender-based psychosocial factors may predispose men and women to respond to pain in different ways. For instance, several studies have demonstrated that sex differences in health behavior can be partially explained by role obligations (Verbrugge 1985; Unruh 1996). By means of cognitive appraisal, men and women may come to develop different interpretations of the meaning of a painful experience.

Unruh (1996) argues that some pain experienced by women is associated with normal biological events related to the reproductive cycle; women must therefore make more distinctions than men between the kinds of pain that originate from normal and abnormal processes. Other authors have noted that the consequences of pain, especially in its more chronic manifestations, are linked to gender-based self-perceptions. In a study looking at women with musculoskeletal pain, Johansson et al. (1999) found that many described such discomfort as having negative consequences for their everyday life, challenging their self-perceptions as women. These findings highlight the corollaries of pain that operate on social and interpersonal levels.

The role of sex in pain-coping strategies figured prominently in a recent paper by Affleck et al. (1999). Patients with osteoarthritis or rheumatoid arthritis completed daily diaries, over a 30-day period, rating their pain, mood, and ability to cope. The average pain of women patients was 72% greater than that of men; women tended to emphasize emotion-focused strategies (venting emotions, redefinition, seeking spiritual comfort, and seeking emotional support) rather than problem-focused coping (attempted pain reduction, relaxation, and distraction).

Several studies have determined that the choice of coping strategies is mediated not only by sex but also by gender-role orientation (Evans 1982; Nezu and Nezu 1987; Long 1989). Bendelow (1993) postulated that while women may be expected to possess superior capacities for coping with pain because it is linked to their biological and reproductive systems, cultural role expectations and socialization processes undermine these potential strengths because both women and men are taught that high tolerance of pain is a "masculine" trait. Women tend to be more worried and irritated about pain (Bendelow 1993), and men to be more embarrassed by lapses of stoicism (Klonoff and Landrine 1992).

Research suggests that male and female reactions to stressors relate to whether the situations elicit an appraisal process based on perceived

sex-role expectations. Lash et al. (1991) found that sex differences in cardiovascular reactivity to a stressor were strongly related to the participants' cognitive appraisals of the stressor as involving masculine or feminine components. When confronted with a cold-pressor task, men showed greater cardiovascular response when they had been given instructions that were framed in a masculine way (emphasizing perseverance or endurance) as opposed to a gender-neutral manner. Wright et al. (1997) found that physiological responsivity in a stressful task was linked to expectations about differential sex-linked performance. However, further research is needed to determine the extent to which such attributions and beliefs underlie the experimental pain experience.

As discussed in detail above (see "Criterion Effects" section), Rollman (1995) noted that women called for the cessation of aversive electrical shock when it had reached only a moderate degree of painfulness, whereas men waited until the stimulus train was more painful before they stopped the trial. In essence, the women were aware that their true tolerance levels were higher than those they reported. Perhaps these results can be ascribed to the influence of gender-role expectations regarding the pain experience.

Some evidence supports this claim. Otto and Dougher (1985) uncovered a significant interaction between masculinity-femininity scores and sex for pain thresholds. High masculinity scores on the Bem Sex Role Inventory (Bem 1974) were linked to higher pain threshold and tolerance, indicating that men and women may base their perceptions of the appropriateness of a particular pain response on their affiliation with traditional masculine or feminine roles.

A recent study by Jones and Rollman (1999) attempted to determine the relative influence of gender role and gender-based appraisal on the pain experience. Significant sex differences existed for a number of traditionally gender-based variables (e.g., masculinity-femininity, instrumentality-expressiveness, attitudes toward women), but their ability to predict pain responsivity in a cold-pressor task was overshadowed by the influence of sex as a predictor variable in subsequent regression analyses. The relationship between sex and pain, on the one hand, and sex and gender identity, on the other, are each so strong that it is fruitless to try to argue for a purely biological or purely psychosocial explanation of male-female differences in pain response.

Higher scores on the Bem femininity subscale were linked with lower pain threshold scores in female participants, while a negligible relationship was observed between these variables for the male group. Additional results indicated that increased femininity scores were associated with higher pain intensity ratings in women, while increased masculinity scores were associated with lower pain ratings in men. This tendency may directly reflect

differences in early socialization practices relating to pain behavior. Bendelow (1993) found that men indicated that as boys they already felt an obligation, when faced with pain, to display stoicism, while women reported that as children they were permitted to be much more expressive. Fearon et al. (1996) found no sex differences among a group of 3- to 7-year-old children in the incidence of everyday pain from mishaps such as bumps, cuts, and scrapes, but that girls engaged more often in distress responses and received more physical comfort from adult caregivers.

Jones and Rollman (1999) found that male participants, when asked to report their own pain tolerance on a 0–100 scale, gave a significantly higher value than that given by females. The majority of both male and female participants endorsed the notion that the laboratory pain tolerance of men is higher than that of women. Interestingly, the women's concession that men were more tolerant of experimental pain did not necessarily imply that they believed men were less sensitive to pain in general.

These various cognitive-evaluative judgments relating to expectations and beliefs concerning pain demonstrate gender differences along several interesting lines. Further investigation into the pain-related beliefs of men and women would help to determine which factors influence the formation of such beliefs and how they are implicated in interpretations of and coping reactions to pain. Research must determine whether gender-based beliefs and attributions (Unruh et al. 1999) apply equally to experimentally induced and clinical pain, since the former is brief and voluntary while the latter is often extended and outside the individual's control. As Morris (1999) noted, pain is infused with meaning, and our beliefs concerning pain (its cause, control, and duration) are determinants of our reactions to it. The relationship between gender-dependent beliefs concerning sex differences in pain and responses to both experimental and clinical pain situations is an area worthy of further investigation.

CONCLUDING REMARKS

Psychologists are fond of saying that behavior is multiply determined. Perhaps nowhere is that as evident as in the literature on sex differences in pain. An argument can be made for the importance of each of the factors reviewed in this chapter and for many more. None of them alone can explain sex differences. Research on sex differences, whether in the laboratory or in the clinic, validates the biopsychosocial model with respect to all aspects of pain: etiology, pathogenesis, suffering, and management.

This chapter has illustrated the interplay of developmental, biological, and psychological variables in accounting for pain behavior. While some may question the validity of studies conducted in the pain laboratory, the robust findings reported here suggest that such experiments have direct and immediate applicability to our understanding of "real world" pain experiences. Clearly, there are differences in the outcomes of seemingly similar experiments. Investigators are faced with the need to carefully identify the stimulus, situational, and response variables that distinguish those studies and to develop models that permit us to specify, with greater precision, the role of direct and moderating influences.

To take just one example, that of experimental pain induction, the evidence suggests that mechanical, electrical, thermal, and chemical stimulation techniques differ in terms of neural mechanisms, central integration, affective responses, and cognitive evaluations. Given that sex differences are seen most often when pressure is used as the noxious input (Fillingim and Maixner 1995; Berkley 1997; Riley et al. 1998), and given the clinical relevance of that form of stimulation, efforts should be made to develop and use precisely controlled mechanical stimuli in explanatory studies.

Even simple situational variables deserve more attention. Researchers rarely ask subjects about recent nicotine consumption, yet Jamner et al. (1998) demonstrated in 44 female and 30 male smokers that nicotine increased the pain threshold and tolerance ratings for electrocutaneous stimuli in men but had no effect on the pain parameters of women. Similarly, the consumption of high-sugar snacks, a frequent behavior that differs across the sexes (e.g., Millen et al. 1996; Hoglund et al. 1998) is largely overlooked in pain research, yet women were more likely than men to exhibit a decrease of pain sensitivity after consuming sugar (Mercer and Holder 1997). Accordingly, common behaviors that affect pain sensitivity in a gender-dependent manner and are likely to take place shortly before laboratory experiments need to be considered in the design of future studies.

Electrophysiological and brain imaging studies indicate that sex differences occur at many stages of pain processing (Paulson et al. 1998; Chapman et al. 1999). Numerous biological factors are candidates to account for sex differences in pain sensitivity, including blood pressure, body size, menstrual cycle, temporal and spatial summation, and dysregulation of central nervous system structures involved in pain inhibition and stress responses. These reports indicate that the variables associated with sex differences start with the onset of nociceptive processing and extend to late affective and cognitive components of pain. Given that men and women differ in many biological and psychological domains, the next step is to develop a

scientific framework for understanding these differences and for generating accurate predictions about sex differences that have not yet been fully uncovered.

The influence of gender roles, attitudes, and self-beliefs concerning the ability of men and women to withstand experimental pain situations requires further investigation. Since any sex differences are likely to be tightly intertwined with being male or female, the ability to successfully define such influences will ultimately depend on the nature of the empirical questions asked and the strength of the associated research designs. Indeed, as argued by Spence and Buckner (1995), the notion of gender includes within it a huge collection of characteristics. Future research should attempt to delineate the specific traits, tendencies, or beliefs more commonly associated with one gender versus the other that help to determine how men and women perceive, feel, and react in a pain situation.

This need was summarized concisely by Leventhal (1994), who stated that as the various factors that distinguish men and women are identified, incorporated, and sequenced in a multifactorial model of gender and health, the confusion created by the often divergent responses made by men and women will vanish. Instead, these differences will come to be seen as consequences of diverse antecedent factors, driving mechanisms that are somewhat overlapping and somewhat independent.

People endow many objects and events with gender significance (Spence and Buckner 1995). Pre-existing beliefs concerning sex differences in pain may largely result from the differential socialization of males and females into masculine and feminine roles. Given the need for rehabilitative strategies that target the different behaviors and strengths exhibited by men and women in response to pain, research focusing on the effects of sex and gender on reactions to pain is both scientifically justified and clinically relevant. While the measurement of gender-based differences may tap into only one of the complex multidimensional components involved in the human experience of pain, it represents a quest that continues to be both timely and appropriate.

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