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Does past pain influence current pain: biological and psychosocial models of sex differences

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Abstract

Previous studies have generally indicated sizeable sex differences for both laboratory pain reactivity and clinical pain reports. Numerous biological and psychosocial models have been invoked to account for these findings, but the laboratory and clinical findings have generally been examined in isolation. This paper reviews data which show a relationship between past clinical pain experiences and current responses to experimentally induced pain. Individuals with a greater pain history tend to show lower pain tolerance. Since women often have high pain experience levels and lower pain tolerance, one might ask whether the two factors are related. We review several models, based upon concepts of neonatal differences in pain reactivity, hypervigilance following early pain experiences, and concepts of peripheral and central sensitization or plasticity which might help to bridge the gap between clinical and experimental findings.

Keywords: Sex differences; Gender; Pain history; Pain tolerance; Hypervigilance; Plasticity

1. Sex differences in pain reactivity

There is now a sizable body of literature which indicates that women have significantly lower pain thresholds and tolerance levels than men and rate equally intense stimuli as more painful (Edwards et al., 1999; Ellermeier and Westphal, 1995; Fillingim et al., 1999; Lautenbacher and Rollman, 1993; Maixner and Humphrey, 1993; Riley III et al., 1998; Rollman, 1995; Rollman, 1997; Rollman et al., 2000; Rollman and Harris, 1987). Moreover, there is an equally compelling clinical literature which indicates that women suffer disproportionately from a large number of acute, recurrent, and chronic pain syndromes (Dao and LeResche, 2000; Heitkemper and Jarrett, 2001; Morin et al., 2000; Robinson et al., 1998; Rollman and Lautenbacher, 2001).

Studies of both humans and lower animals provide no single explanation for these findings. Rather, a host of biopsychosocial variables have been implicated as contributing to individual pain responses and, consequently, to some of the striking differences in pain reactivity between males and females. Generally, studies on sex differences have looked at either clinical pain reports or responses to experimentally induced pain, but not to the relationship between the two. If there are common biological or psychosocial factors responsible for the sex differences, one would expect to see a relationship between clinical and experimental variables.

The term "biopsychosocial" could almost have been invented in order to make sense of this complex literature. Certainly, there are important genetic factors which play significant roles both in interindividual and intergroup differences in pain reactivity. Kest et al. (1999) found considerable differences between the responses of male and female mice of some strains in pain reactivity and the analgesic effects of morphine, but no sex differences in others. Jones et al. (1998) reported significant sex and strain differences in the corticosterone response to the stress of repeated restraint. More recently, Karandrea et al. (2002) found sex differences in gene expression and

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HPA axis regulation in the hippocampus following chronic stress. Given the complex relationship between pain and stress (Rivier, 1999), such biological vulnerability may play an important role in helping to account for the disparity in pain reactions between males and females and, more importantly, in developing methods to prevent and manage acute and chronic pain conditions.

Neuroimaging studies also suggest sex differences in the magnitude and direction of brain activation following noxious stimulation, even when stimuli are subjectively matched (Zubieta et al., 2002). Such structural and functional differences between the sexes are also illustrated by disparities in responses to opiate analgesia. Craft (2003) reviewed the growing collection of studies which indicate that agonists which act preferentially at mu receptors (and, often, at κ-receptors) are more powerful in male rodents than female ones but, paradoxically, act in the opposite manner in humans. Likewise, gonadal hormones such as estrogens and androgens modulate prenatal and postnatal functional development and have potent influences on pain threshold in female and male rats (Aloisi, 2003; Liu and Gintzler, 2000). They affect the bioavailability of drugs in humans (Beierle et al., 1999) and may have marked influence on menstrual cycle variability in migraine pain (MacGregor, 1997), temporomandibular disorders (Warren and Fried, 2001), fibromyalgia (Anderberg et al., 1998), and other chronic pain conditions (Meisler, 1999; Riley III et al., 1999).

While arguments regarding the biological underpinnings of sex differences in pain reactivity are persuasive, so, too, are those which emphasize psychosocial factors. A sizeable body of literature, for example, has indicated that there are stereotypical masculine and feminine pain behaviors and that members of both sexes believe that males are less sensitive to pain than are women (Robinson et al., 2001). Wise et al. (2002), for example, had males and females complete a questionnaire which was designed to assess sex-related stereotypic attributions of pain sensitivity, pain endurance, and willingness to report pain. Gender role expectation scores were significant predictors of threshold, tolerance, and pain unpleasantness.

Keogh and Herdenfeldt (2002) considered that if men and women experience pain differentially, they may develop different coping strategies. Having found in an earlier study (Keogh et al., 2000) that there are sex differences in the efficacy of focused and avoidance coping instructions on cold pressor responses (men but not women report less pain when they attend toward the pain), they asked whether women might prefer to focus on the emotional aspects of the pain experience in order to achieve pain relief. The data, however, indicated that emotional focusing seemed to have a detrimental effect on women's ability to withstand cold pressor pain. The results of this and other studies (Keefe et al., 2000; Osman et al., 2000) indicate that negative cognitions, such as catastrophizing, are more common among women and suggest the possible utility of gender-tailored training in effective coping skills.

2. Past pain and present pain

Pain is not experienced in a vacuum. As exemplified by the adaptation level model of pain (Rollman, 1979; Rollman, 1989), pain judgments are often relative rather than absolute. Previous experience with both experimental pain and clinical pain appears capable of resetting anchors or comparison points (Boureau et al., 1991; Daltroy et al., 1999; Dar et al., 1995), so that new pain is judged differently than if the individual had not had the earlier pain experience. If women have a history of greater pain, they, for a variety of biological or psychosocial reasons, are likely to respond to noxious events (in terms of pain threshold or tolerance, pain ratings, and emotional and cognitive responses) very differently than men.

This issue has, to date, received relatively little attention. There is evidence that an individual's pain history and familial models can be useful in predicting and managing post-surgical pain (Bachiocco et al., 1993), that response expectancy among chronic pain patients, influenced by their own history, significantly predicts their tolerance to experimental pain (Cipher and Fernandez, 1997), and that anticipation of pain alters the activity of cortical nociceptive networks in subjects who expected the stimulation of one foot to be painful even in the absence of actual noxious inputs (Porro et al., 2002).

Fillingim et al. (1999) examined thermal pain thresholds and tolerances in a group of young adults and related these levels to the number of pain-related symptoms experienced during the previous month. For women, those with a larger number of pain sites and greater health care utilization exhibited greater pain sensitivity to the thermal stimuli.

We recently explored the relationship between self-evaluated lifetime pain ratings and the response to cold pressor pain, asking 49 undergraduate volunteers to participate in an experiment involving two testing sessions. Visual analog scales (VAS) were used to assess the participants' self-reported general pain tolerance level and the amount of pain they had experienced in their lives from illness and injury. They were then tested with a cold pressor apparatus to determine their tolerance time.

Males ($M = 71.13$, $SD = 16.38$) reported a significantly greater predicted pain tolerance on a hypothetical 100 point scale than females ($M = 56.25$, $SD = 17.04$, $F(1,30) = 11.47$, $p \leqslant 0.01$) and they exhibited a significantly higher pain tolerance time ($M = 107.16$ s, $SD = 63.85$) compared to women ($M = 61.22$, $SD = 54.27$, $F(1,49) = 7.39$, $p \leqslant 0.01$). When asked, "In your life, how much pain do you feel you have had from illness and injury?" women, on average, rated their

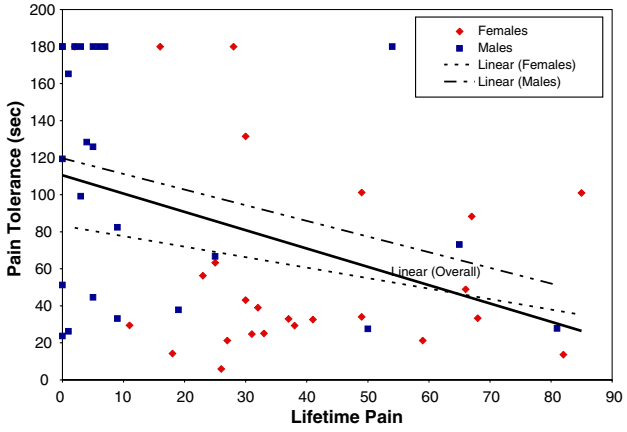

Fig. 1. Scatterplot of pain tolerance (s) as function of lifetime pain score (0–100 scale) for both female and male subjects. Best fitting lines for all subjects combined (overall) and for females and males separately.

lifetime pain level at 38.9 (SD = 21.65) on a 100 point scale, whereas men described their pain history as 14.8 (SD = 23.15), $t(47) = 3.778$, $p \leqslant 0.001$.

Of particular interest to us was whether expectations and previous pain experience predicted current pain response. Both showed strong relationships to pain tolerance. For the entire sample, the VAS self-reported pain tolerance rating was highly predictive ($r = 0.36$, $p \leqslant 0.05$) of the laboratory pain tolerance time. Notably, the VAS amount of lifetime pain due to illness or injury was found to show a significant negative correlation ($r = -0.40$, $p \leqslant 0.005$) with the laboratory pain tolerance measurement. Individuals with greater lifetime pain were more reactive to the induced experimental pain.

This relationship is depicted in Fig. 1. Shown there, as well, are linear functions for females and males separately. The relationships between pain tolerance and lifetime pain ratings were both in the same direction ($r = -0.23$ for females and $r = -0.31$ for males), but, probably because of sample size, were non-significant.

3. Mechanisms of pain response: biological and psychosocial models

Women in our study, as has often been shown before, demonstrated a significantly lower tolerance time than men. When asked to rate the level of perceived pain at tolerance, both groups reported that it was "slightly intense," indicating that although they likely did not reach true tolerance times in this voluntary exposure, the differences were not due to differential willingness to endure discomfort.

Prior to tolerance testing, participants were asked to predict their pain tolerance. Women chose a significantly lower level to describe their capacity to withstand pain than men. While one could suggest that this indicates the psychophysical performance illustrates a self-fulfilling prophesy, it could also indicate that women know, correctly, that they have a lower endurance level for pain.

While the data are intriguing, there are a number of quite different models that could account for such findings. One important discovery was that our sample of young women reported significantly greater lifetime pain levels, from illness and injury, than men. This finding supports other indications (e.g., Berkley, 1997; Unruh, 1996) that adult women have a significantly higher prevalence of pain complaints than men. These clinical reports, coupled with the pervasive sex differences in laboratory performance, could indicate that women have greater sensitivity to pain from birth (Fuller, 2002; Guinsburg et al., 2000) or shortly thereafter (Fearon et al., 1996; Fowler-Kerry and Lander, 1991; Goodenough et al., 1999; Hodgins and Lander, 1997; Perquin et al., 2000) and, as a consequence, continually experience more pain than men due to general environmental interactions and medical procedures.

A second model relates to the concept of hypervigilance: a perceptual tendency to focus attention on threatening stimulation (Chang et al., 2000; Grisart et al., 2002; Lautenbacher and Rollman, 1999; McDermid and Rollman, 1999; Peters et al., 2000; Rollman and Lautenbacher, 1993). Women's early pain experience may make them more vigilant than men for pain and other internal experiences (Aldrich et al., 2000; Crombez et al., 1999; Stenberg and Wall, 1995).

The studies cited above indicate girls do find a variety of childhood aches and pains to be more intense and troubling than do boys. Then, following menarche, young women experience a new and often intense source of monthly pain (Schroeder and Sanfilippo, 1999) plus a greater prevalence of abdominal pain (Mollitt and Dokler, 1997), headache (Leonardsson-Hellgren et al., 2001; Passchier and Orlebeke, 1985; Sillanpaa and Aro, 2000), temporomandibular disorders (Krogstad et al., 1992), and other forms of acute and chronic pain (Merlijn et al., 2003).

Consequentially, they might be expected to engage in greater bodily monitoring (Pennebaker, 1994), attribute internal events to a physical disorder rather than a stress-related or environmental cause (Robbins and Kirmayer, 1991), exhibit heightened anxiety (Asmundson and Taylor, 1996; Barsky et al., 2001; Edwards et al., 2000; Jones and Zachariae, 2002), and respond to symptoms with maladaptive coping strategies (Osman et al., 2000; Sullivan et al., 2001). These characteristics of hypervigilance (Lautenbacher and Rollman, 1999; McDermid et al., 1996; McDermid and Rollman, 1999) would be expressed in terms of increased clinical pain reports and treatment seeking (Buckelew et al., 1990; de Leeuw et al., 1994; Epker and Gatchel, 2000; Robinson et al., 1998; Von Korff et al., 1988), low expectations

about ability to withstand pain (Robinson et al., 2001; Wise et al., 2002), and low tolerance for experimentally induced pain (Riley III et al., 1998).

Other psychosocial variables, which undoubtedly overlap with each other and with the hypervigilance model, could also be invoked in explaining these data. These stress the importance of such factors as self-efficacy (Piira et al., 2002), anxiety sensitivity (Asmundson et al., 1999; Keogh and Birkby, 1999; Keogh and Cochrane, 2002; Keogh and Mansoor, 2001), fear avoidance (Vlaeyen and Linton, 2000), gender-role expectations (Sanford et al., 2002; Wise et al., 2002), threat appraisal (Sanford et al., 2002; Unruh et al., 1999), and somatization (Neitzert et al., 1997; Pankhurst, 1997; Raphael et al., 2000; Rief et al., 2001; Walker et al., 1991).

A biological plasticity hypothesis is also compatible with these findings. Such a model might indicate that women's early pain experiences (Taddio et al., 1997), which these and other self-reports indicate are greater than those of men, influence their later neuronal responses to noxious internal or external stimuli. A process of peripheral sensitization may alter the activity of primary sensory or dorsal horn neurons (Craig and Andrew, 2002; Woolf and Salter, 2000) and, subsequently, create central sensitization or neuroplasticity (Coderre et al., 1993; Melzack et al., 2001).

This leads to such powerful neural and behavioral effects as expansion of receptive fields (Jinks and Carstens, 1999; Suzuki et al., 2000), enhancement of flexion reflexes (Dahl et al., 1992; France et al., 2002), allodynia and hyperalgesia (Finnerup et al., 2003; Price and Verne, 2002), wind-up (Arendt-Nielsen and Petersen-Felix, 1995), altered temporal summation (Arendt-Nielsen et al., 1997; Staud et al., 2003a), changes in diffuse noxious inhibitory controls (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Staud et al., 2003b), and modified cerebral blood flow (Bushnell et al., 2002).

Such biological alterations have been reported for a variety of pain disorders: fibromyalgia (Lautenbacher and Rollman, 1997; Mountz et al., 1995; Staud et al., 2001; Staud et al., 2003b), irritable bowel syndrome (Naliboff et al., 1997; Verne and Price, 2002; Whitehead et al., 2002), temporomandibular disorder (Fillingim et al., 1998; Maixner et al., 1998; Svensson et al., 2001; Svensson and Graven-Nielsen, 2001), headache (Bendtsen, 2000; Bendtsen, 2002; de Tommaso et al., 2002), neuropathic pain (Attal and Bouhassira, 1999; Jorum et al., 2003) and rheumatoid arthritis (Bradley and McKendree-Smith, 2002; Niissalo et al., 2002).

This plasticity model predicts that greater early pain occurrences in women (possibly combined with their enhanced pain or stress reactivity) could sensitize them, neurally and behaviorally, for later intensification of experienced pain. The greater prevalence of women among those suffering from many of the chronic and recurrent pain disorders listed above may be a consequence of a series of sex-related characteristics: differential genotypes (Mogil et al., 2000; Mogil et al., 2003) contributing to neonatal sex differences in pain reactivity (Gibbins et al., 2002; Guinsburg et al., 2000), disparity in the operation of gonadal hormones and opioid-activated endogenous pain modulating circuits (Aloisi et al., 1998; Craft et al., 1999; Craft and Bernal, 2001; Gear et al., 1996), and to a series of critical postnatal changes in the peripheral and central mechanisms of pain transmission and modulation.

One important proviso needs to be noted. Most studies of sex differences, whether biological or psychosocial, show considerable overlap in the data obtained from male and female subjects. We predict that individuals of either sex who report a history of high pain and a low pain tolerance are at considerably greater risk for developing chronic pain conditions later in life. Large-scale prospective studies will be needed to test this prediction and, if supported, to look for appropriate preventative and ameliorative treatments and procedures.

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