Pain 96 (2002) 163–175

PAIN

www.elsevier.com/locate/pain

Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome ☆

Caroline F. Pukall[a,*], Yitzchak M. Binik[a,b], Samir Khalifé[c,d], Rhonda Amsel[a], Frances V. Abbott[e]

[a]*Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, QC H3A 1B1, Canada*
[b]*Sex and Couple Therapy Service, Department of Psychology, Royal Victoria Hospital, Montreal, Quebec, Canada*
[c]*Faculty of Medicine, McGill University, Montreal, Quebec, Canada*
[d]*Department of Obstetrics and Gynecology, Jewish General Hospital, Montreal, Quebec, Canada*
[e]*Department of Psychiatry, McGill University, Montreal, Quebec, Canada*

Received 16 February 2001; received in revised form 19 September 2001; accepted 8 October 2001

Abstract

Vulvar vestibulitis syndrome (VVS) is a common cause of dyspareunia in pre-menopausal women. Little is known about sensory function in the vulvar vestibule, despite Kinsey's assertion that it is important for sexual sensation. We examined punctate tactile and pain thresholds to modified von Frey filaments in the genital region of women with VVS and age- and contraceptive-matched pain-free controls. Women with VVS had lower tactile and pain thresholds around the vulvar vestibule and on the labium minus than controls, and these results were reliable over time. Women with VVS also had lower tactile, punctate pain, and pressure-pain tolerance over the deltoid muscle on the upper arm, suggesting that generalized systemic hypersensitivity may contribute to VVS in some women. In testing tactile thresholds, 20% of trials were blank, and there was no group difference in the false positive rate, indicating that response bias cannot account for the lower thresholds. Women with VVS reported significantly more catastrophizing thoughts related to intercourse pain, but there was no difference between groups in catastrophizing for unrelated pains. Pain intensity ratings for stimuli above the pain threshold increased in a parallel fashion with log stimulus intensity in both groups, but the ratings of distress were substantially greater in the VVS group than in controls at equivalent levels of pain intensity. The data imply that VVS may reflect a specific pathological process in the vestibular region, superimposed on systemic hypersensitivity to tactile and pain stimuli.

Keywords: Tactile and pain thresholds; Sexual pain disorders; Vulvar vestibulitis syndrome; Vulvodynia; Psychophysics

1. Introduction

Female dyspareunia is defined as recurrent, acute pain experienced primarily during penile–vaginal intercourse. Although it is listed in the 'Classification of chronic pain' (Merskey and Bogduk, 1994), it is almost universally considered to be a sexual dysfunction. However, several recent reviews have examined dyspareunia from the perspective of a pain syndrome. One demonstrated that the pain of dyspareunia is measurable, both qualitatively and quantitatively (Meana et al., 1997a). In addition, it indicated that discriminable subtypes of dyspareunia are characterized by the location and temporal pattern of the pain, rather than the DSM-IV taxa (American Psychiatric Association, 1994) used to describe the sexual dysfunctions (e.g. lifelong vs. acquired; for reviews, see Meana and Binik, 1994; Baggish and Miklos, 1995; Bergeron et al., 1997; Binik et al., 1999; Masheb et al., 2000). Importantly, the pain of dyspareunia was not related to negative sexual experiences or sexual abuse, nor was it limited to sexual intercourse. These findings support conceptualizing and classifying dyspareunia and its subgroups as pain disorders as opposed to sexual dysfunctions.

One subtype of dyspareunia that is clearly distinguishable on the basis of pain characteristics is vulvar vestibulitis syndrome (VVS; Meana et al., 1997b). The vulvar vestibule (see Fig. 1) is located posterior to the glans clitoris between the labia minora, and contains the vaginal and urethral openings and the ducts of the Bartholin's glands (Friedman, 1995). In the sample surveyed by Meana et al. (1997b), VVS was the major cause of dyspareunia in pre-menopausal women. Although this condition was probably described as

☆ Presented in part by C.F.P., the recipient of the Student Research Award at the 25th Annual Meeting of the Society for Sex Therapy and Research (SSTAR), Santa Rosa, CA, March, 2000.

* Corresponding author. Tel.: +1-514-398-5323; fax: +1-514-398-4896.
E-mail address: caroline.pukall@mail.mcgill.ca (C.F. Pukall).

0304-3959/02/$20.00
PII: S0304-3959(01)00442-0

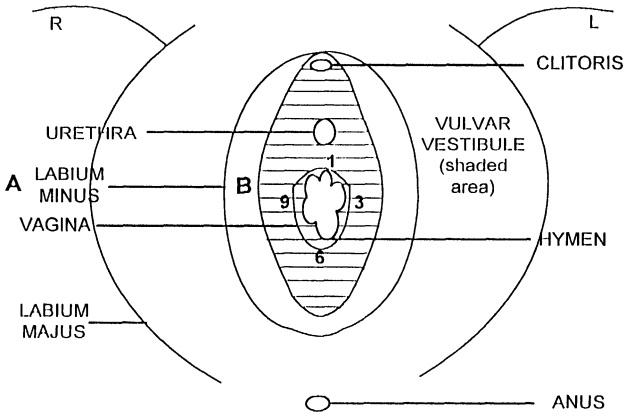

Fig. 1. The female genital region, showing the location of the vulvar vestibule (shaded area) around the vaginal opening between the labia minora and the hymen. Areas tested were the inner medial aspect of the thigh (A) and the midpoint of the labium minus (B) on the participant's dominant side, and four sites around the vulvar vestibule (described in terms of clock positions: 1, 3, 6, and 9 o'clock). R, right side; L, left side.

early as 1880 by the term 'hyperesthesia of the vulva' (Thomas, 1880), only recently have formal diagnostic criteria been proposed. These criteria are: severe pain upon vestibular touch or attempted vaginal entry, exquisite tenderness to cotton-swab palpation of the vulvar vestibule, and, in some women, physical findings limited to vestibular erythema (Friedrich, 1987). VVS is diagnosed by palpating the vulvar vestibule with a cotton swab (Friedrich, 1987), although the application of the swab is not standardized (Eva et al., 1999). For example, the swab may be moistened or dry, and may be applied to variable locations around the vestibule with varying degrees of pressure, and sometimes with an increasing pressure ramp. Over 90% of women with VVS describe experiencing a burning and/or cutting pain during intercourse (Bergeron et al., 2001a). The description of the pain has led some researchers to classify VVS as a subtype of vulvodynia, chronic vulvar discomfort characterized by the patient's complaint of a burning sensation (Wesselmann et al., 1997). However, in VVS, the pain occurs in response to sensory stimulation in the affected area only, while in vulvodynia, the pain is independent of sensory stimulation and not restricted to the vestibular area.

A randomized treatment outcome study (Bergeron et al., 2001b) compared three treatments for VVS: vestibulectomy, group cognitive-behavioral therapy, and pelvic floor muscle exercise using surface electromyographic biofeedback. All three groups reported significant reductions on pain measures post-treatment and at 6 month follow-up, but vestibulectomy was significantly more successful than the other two therapies. These results suggest that local peripheral pathology may be involved in the development and maintenance of VVS. The involvement of peripheral mechanisms is further supported by results of different types of surgery. Resection of the vestibular tissue most often leads to long-term resolution of the pain (e.g. Woodruff and Parmley, 1983; Peckham et al., 1986; Friedrich, 1987; Marinoff and Turner, 1991), while undercutting the tissue which allows regeneration of the innervation and cutaneous vascular bed does not produce long-term pain relief (Bornstein et al., 1995).

Studies of vestibular tissues have produced mixed support for peripheral mechanisms in the etiology of VVS. Studies of inflammation and inflammatory cytokines have produced inconsistent results, depending primarily on the source and availability of appropriately matched control tissue samples (e.g. Pyka et al., 1988; Michlewitz et al., 1989; Furlonge et al., 1991; Friedman, 1995; Prayson et al., 1995; Foster and Hasday, 1997; Lundqvist et al., 1997; Chadha et al., 1998; Slone et al., 1999). In general, these studies suggest that inflammatory infiltrates are common in vulvar tissues whether or not the women have VVS, and thus are not necessarily related to pain. Jeremias et al. (2000) reported that women with VVS were more likely to be homozygous for Allele 2 of the interleukin-1 receptor antagonist gene, which is also associated with other chronic epithelial inflammatory conditions. Two studies have reported increased density of neuropil in the vestibular epithelium in affected women (Bohm-Starke et al., 1998; Weström and Willén, 1998). These findings raise the question of whether VVS is associated with sensory abnormalities, as has been observed in psychophysical studies with other pain disorders, such as fibromyalgia (Kosek et al., 1996) and burning mouth syndrome (Svensson et al., 1993). However, there is very little information about sensory function and none on sensory thresholds in the female genital region, despite the assertion by Kinsey et al. (1953) that the vestibule is "as important a source of erotic stimulation as the clitoris" (p. 579).

The present study compared women with VVS and matched controls in a series of tests that included the following: (1) thresholds for punctate tactile and pain sensation around the vulvar region, and the stability of these thresholds over time; (2) threshold measurement in non-vulvar areas; (3) pain and distress ratings to sustained pain stimuli in the vestibular region; (4) the tendency for affected women to have exaggerated negative orientation toward painful stimuli (i.e. catastrophizing; Sullivan et al., 1995); and (5) pressure-pain tolerance over the tibia and the deltoid muscle.

2. Methods

The experiment was reviewed and approved by the McGill University Faculty of Medicine Institutional Review Board.

2.1. Participants

Potential subjects were recruited through local media announcements and from gynecologist referrals. After a brief telephone screening, women were interviewed and tested at a participating gynecologist's office, where study

procedures were re-explained and informed consent was obtained. Participants were reimbursed $75 CDN to cover expenses related to their participation in this 3 h study. Most women also returned for a second session to assess threshold stability over time and to test thresholds in additional body sites, and they received an additional $75.

Women with VVS were matched to control women according to age (±3 years) and use of oral contraceptives (yes or no). The inclusion criteria for women with VVS were: (1) pain during intercourse which is/was subjectively distressing, occurs/occurred on most intercourse attempts, and had a minimum duration of 6 months; (2) pain limited to intercourse and other activities involving vestibular pressure (e.g. tampon insertion); and (3) a mean pain rating of at least 4 on a 0 (no pain at all) to 10 (worst pain ever felt) Likert scale during the cotton-swab test (see below). Participants in the control group were included if they reported pain-free intercourse and had an average pain rating of less than 4 on the Likert scale during the cotton-swab test (see below). Exclusion criteria for both groups were pelvic or vaginal pain not clearly linked to intercourse, a history of remitted dyspareunia, major medical and/or psychiatric illness, active vaginal infection, vaginismus, surgical treatment for dyspareunia, or current pregnancy.

2.2. Procedure

2.2.1. Interview

Socio-demographic information, relationship history, and gynecological history were collected from all subjects in a structured interview. Subjects were prompted with a list of body systems and sites, and asked about having any other frequently experienced pain problems not related to intercourse. They were also asked if they had been diagnosed with any other pain disorder. Women with VVS provided a history of their coital pain, while control subjects were asked to describe an occasion during which they had felt pain upon vaginal penetration (e.g. during a gynecological examination). Both groups of women completed the McGill–Melzack Pain Questionnaire (MPQ; Melzack, 1975) with respect to this pain. Both groups also filled out the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) with respect to regularly experienced, non-intercourse-related pain (called 'general' pain, e.g. headache). Additionally, women with VVS were asked to think about their most recent intercourse attempt and answer the PCS with reference to that experience.

2.2.2. Gynecological examination

For the examination by the gynecologist, women lay in the supine position on an examining table with their legs comfortably supported by stirrups that extended from the back of the knee to the foot. The gynecological examination consisted of the following: (1) cotton-swab palpation of six randomly ordered vestibular sites (described in terms of clock positions, with 12 o'clock just below the urethral meatus; see Fig. 1) that were matched within VVS–control subject pairs: 1 o'clock, between 1 and 3 o'clock, between 3 and 6 o'clock, 6 o'clock, between 6 and 9 o'clock, and between 9 and 1 o'clock. This test is commonly referred to as the cotton-swab test and constitutes the main gynecological diagnostic tool for VVS (Friedrich, 1987); and (2) a standard bimanual palpation of the vagina (anterior vaginal wall, pubococcygeal muscle, uterosacral ligament), uterus (cervix and corpus with and without motion), and adnexae (with and without motion). A research assistant recorded the pain ratings on a Likert scale from 0 (no pain at all) to 10 (worst pain ever felt) during the examination. The cotton-swab test was, by definition, painful for women with VVS, but this pain had disappeared in all women before sensory testing began.

2.2.3. Sensory tests

Sensory tests were carried out after the gynecological examination on the same examining table and in the same position by the person who conducted the interview. Because of the very large differences in the responses of women with VVS and controls to any touching in the vestibular region, blind testing was not possible and was, therefore, not attempted. However, blank trials (see Section 2.2.4) constitute a control for bias resulting from interactions between the subject and the tester. Sensory testing took 50–70 min. A rest period was allowed if the woman became uncomfortable in the supine position. Tactile and pain thresholds were measured with graded filaments made from sterile monofilament suture material (Prolene, Ethicon Inc.; Surgilene, Davis and Geck) that varied in length and diameter and were calibrated using an analytical balance (Eliav and Gracely, 1998). These modified von Frey filaments were constructed to include 17 filaments with log-force values ranging from 1.18 (where 1.18 $\log^{-1}/10 =$ 1.51 mg) to 5.07 (11 748.98 mg) covering the lower part of the range of force exerted by the commercially available Semmes-Weinstein filaments, plus three additional filaments which exerted still lower pressures. The filaments were clamped at the appropriate length with small curved hemostatic forceps. A new set of filaments was used for each woman, and the forceps were sterilized before each testing session.

2.2.4. Tactile thresholds

Tactile thresholds were measured using a 2-down 1-up staircase method in which two positive responses (i.e. 'Yes, I felt something') to the same stimulus are required to move to the next lower stimulus value, and one negative response (i.e. 'No, I didn't feel anything') is required to move up to the next higher stimulus value (Fechner, 1860/1966; Cornsweet, 1962). This procedure yields a 71% criterion level, as opposed to a chance level (i.e. 50%) which is obtained when one positive or negative response is sufficient to reverse the procedure (Wetherill and Levitt, 1965). Filaments were applied manually so that they bent to form a semi-circle,

and were held in place for 1.5 s (the standard protocol; Bell-Krotoski, 1990). A research assistant entered the subjects' responses into a computer, and the program then prompted for the application of the next required filament. The inter-stimulus interval was 10 s. The computer randomly inserted blank trials 20% of the time, during which forceps were picked up and held near but without touching the subject. The computer monitor was not visible to the subject. To shorten the testing time, every third filament was applied until the first two positive responses to the same stimulus occurred. After this, the program prompted for the next lower stimulus value until one 'no' response was obtained, then the program prompted for the next higher stimulus value until two 'yes' responses were obtained, and so on. The computer program stopped after five reversals, and the last four of them were averaged to provide the threshold. Upon the first positive response, subjects were asked to describe the sensation by choosing adjectives (e.g. dull, mild, ticklish) from a word list, and responses were recorded by a research assistant.

2.2.5. Pain thresholds

Pain threshold testing started with a filament that approximated the tactile threshold for each vestibular site. Consecutively higher filaments were applied for 1.5 s (Bell-Krotoski, 1990) with an inter-stimulus interval of 15 s until pain was reported. Subjects then rated pain and distress on two Likert scales of 0 (no pain at all, not distressing at all, respectively) to 10 (worst pain ever felt, most distressing ever, respectively) and described the sensation using the MPQ (Melzack, 1975) adjective list. After the pain threshold was identified, three additional consecutive filaments were applied to each area to assess suprathreshold pain, and MPQ descriptors and pain and distress ratings were obtained. The highest filament used for each area was then applied for 40 s, and pain and distress ratings were recorded upon application and at 20 and 40 s.

2.2.6. Body sites tested

Fig. 1 illustrates the regions of the inner thigh, labium minus, and vestibule tested. The inner thigh and labium minus on the dominant side were tested first, and then the four sites around the vestibule (1, 3, 6, and 9 o'clock) were tested in random order, with the same order for each matched subject pair. At the second session, the following sites (in order) were tested for tactile and pain thresholds: the arm over the deltoid muscle, the volar surface of the forearm 4 inches above the wrist, the tibia 5 cm below the knee, the inner thigh, the labium minus, and two counterbalanced vestibular sites (1 and 6 o'clock). All sites except the vestibular sites were on the dominant side. For convenience and comfort in the second session, the deltoid, forearm, and tibia were tested first without removing the underwear, prior to the gynecological examination and sensory tests for the inner thigh, labium minus, and vestibule. The same examiner performed threshold testing in both sessions in order to ensure consistency (Bell-Krotoski and Tomancik, 1987).

2.2.7. Pressure-pain tolerance

At Session 1, the pressure-pain tolerance was measured twice on each side over the deltoid muscle and the tibia 5 cm below the knee using a pressure tolerance meter (Pain Diagnostics and Thermography, New York). Pressure was increased manually until the supine participant said that it was no longer tolerable.

2.2.8. Psychological measures

The MPQ (Melzack, 1975) is a checklist comprised of 78 adjectives to describe pain quality and intensity. The pain rating index is a weighted sum of scaled values of the adjectives and provides a global multidimensional measure of pain. The PCS (Sullivan et al., 1995) consists of 13 statements describing various thoughts and feelings that people may experience when they are in pain (e.g. 'I keep thinking how badly I want the pain to stop', 'There's nothing I can do to stop the intensity of the pain'). Respondents were asked to rank each statement with respect to the degree to which they have these thoughts and feelings when they are in pain according to a five-point scale (0, not at all; 4, all the time).

2.2.9. Data analysis

Differences between and within groups were tested using repeated measures ANOVAs and ANCOVAs (MANOVA; SPSS 9), with the probability level reflecting the Greenhouse–Geisser adjustment for heterogeneous covariances when appropriate. Post-hoc tests of significance were done using Tukey hsd tests and correlations were tested with Pearson's method. For reporting sensory measures, data were converted to mg from log values (see Section 2.2.3) after analysis in order to express thresholds in terms that are intuitively understood. The 95% confidence interval (CI) is given for these values.

3. Results

3.1. Sample characteristics

Twenty-six nulliparous women, 13 suffering from VVS and 13 controls, completed the first test session. There were no significant differences between groups with respect to age (VVS mean 25.85, range 21–44; control mean 26.31, range 21–41), religion, language, relationship status, years of education, income, birth control method, or menstrual cycle status at the time of testing (all $P > 0.05$). All but one of the participants had hymeneal remnants, and all had a vaginal atrophy index of 3, indicating the excellent condition of the vaginal tissue (Leiblum et al., 1983). In addition, all had mobile uteri and adnexae, and none showed evidence of cervical ectropions, cervical polyps, fibroids, or prolapsed uteri. As indicated in Table 1, the groups differed

Table 1
Characteristics of women on relevant variables

	Controls (±SD)	VVS (±SD)
Mean number of non-coital gynecological problems (e.g. STDs)	0.85 ± 0.69	1.15 ± 0.52
Mean number of gynecological interventions (e.g. laparoscopy)	0.39 ± 0.51	0.54 ± 0.52
Mean number of total yeast infections	4.77 ± 5.75	17.08 ± 18.61*[a]
Mean pain ratings during the cotton-swab test (0–10 scale)	1.10 ± 1.42	6.68 ± 1.72***
Mean pain ratings during speculum insertion (0–10 scale)	0.77 ± 1.88	3.31 ± 3.33*
Mean duration of painful intercourse (months)	–	50.08 ± 38.37
Mean number of professionals consulted for VVS pain	–	5.15 ± 3.08
MPQ total scores for penetration pain	9.39 ± 7.30	34.77 ± 12.39***
PCS scores for general pain	12.54 ± 9.43	16.62 ± 12.46
PCS scores for women with VVS (general vs. intercourse pain)	–	27.39 ± 8.53**
Blank trials – mean percent correct (Experiment 1)	95.58 ± 7.77	97.91 ± 2.84
Blank trials – mean percent correct (Experiment 2)	98.46 ± 5.13	98.89 ± 2.26

[a] $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

on variables directly related to VVS. The finding that women with VVS reported more yeast infections than control women has been reported in the literature (e.g. Bergeron et al., 1997).

The interval between the first and second tests ranged from 3 to 12 months (mean 9.2 months). Twenty women, 11 controls and nine VVS, consented to a second session; five were lost to follow-up and one had been successfully treated for VVS. In all, there were seven matched pairs, plus four controls and two women with VVS. There were no significant changes in reports of intercourse pain in the VVS group ($P > 0.05$). One woman with VVS had used local anesthetic cream prior to intercourse, but had ended her relationship and sexual activities more than 4 weeks before testing. Cotton-swab pain ratings from the first and second tests did not differ significantly, and they were highly correlated ($r = 0.78$, $P < 0.001$). Mean pain ratings for the cotton-swab test (±SD) remained significantly different between groups (5.61 ± 1.45 and 0.77 ± 1.35 for VVS and controls, respectively, $P < 0.001$).

3.2. Tactile thresholds

The upper and lower panels of Fig. 2 show the tactile thresholds obtained at the two test sessions. As illustrated in the upper panel, vestibular tactile thresholds were dramatically lower in the VVS group as compared with control women. There was a significant group by site interaction ($F_{(5,120)} = 6.14$, $P < 0.001$). In the control group, tactile thresholds were significantly higher at 1 o'clock than at 6 and 9 o'clock and on the labium minus (all $P < 0.05$); the four vestibular sites were significantly less sensitive than the inner thigh ($P < 0.05$). In the VVS group, tactile thresholds for the vestibular sites and the labium minus were significantly lower than those of the control group (both $P < 0.01$), and there were no differences among these sites. The magnitude of the difference between women with VVS and control women for the vestibular sites is more comprehensible when the data are expressed in mg: the average vestibular thresholds were 95 mg (95% CI 64–146) vs. 371 mg (95% CI 247–567) for the VVS and control groups, respectively. Tactile thresholds for the thigh were similar between groups.

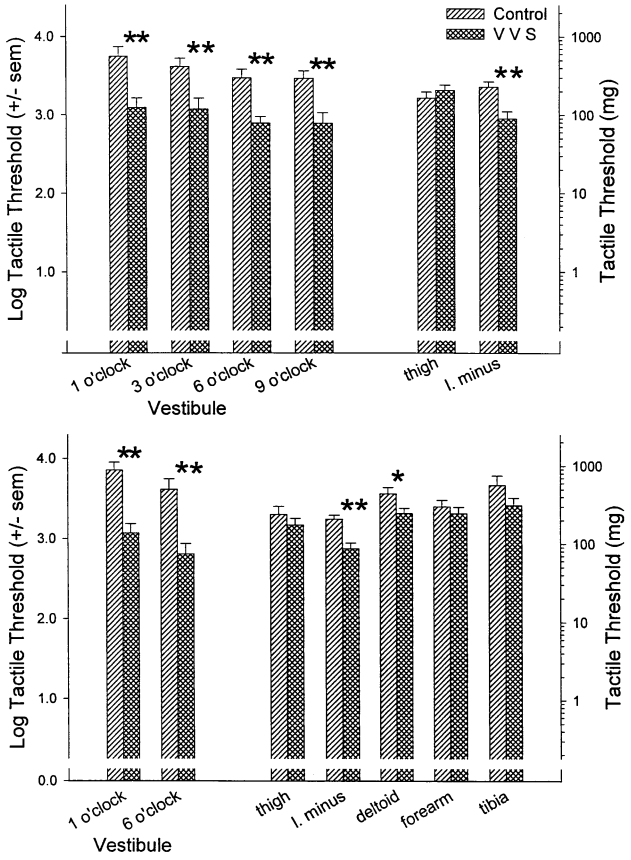

Fig. 2. (Upper) Tactile thresholds (±SEM) at four vestibular sites (1, 3, 6, and 9 o'clock), and the thigh and labium minus on the dominant side of women with VVS ($N = 13$) and controls ($N = 13$) obtained at the first test session. (Lower) Tactile thresholds (±SEM) of two vestibular sites (1 and 6 o'clock), and the thigh, labium minus, deltoid, forearm, and tibia on the dominant side of women with VVS ($N = 9$) and controls ($N = 11$) obtained at the second test session. $*P < 0.05$, $**P < 0.01$.

The lower panel of Fig. 2 shows tactile thresholds obtained in the second session. The average tactile threshold over all sites was 138 mg (95% CI 120–159) and 331 mg (95% CI 263–417) for the VVS and control group, respectively ($P < 0.001$), with a group by site interaction ($F_{(6,108)} = 5.13$, $P = 0.001$). In the control group, vestibular site 1 was the least sensitive site; it was significantly less sensitive than the deltoid, forearm, thigh, and labium minus (all $P < 0.05$). In the VVS group, vestibular site 6 was the most sensitive area, significantly more so than the deltoid, forearm, tibia, and thigh (all $P < 0.05$). Women with VVS had significantly lower tactile thresholds than control women in the following areas: the deltoid ($P < 0.05$), labium minus, and vestibular sites 1 and 6 (all $P < 0.001$). There were no response biases in either group for the first or second tactile threshold sessions as indicated by the mean percent of correct blank trials (see Table 1).

3.3. Stability of tactile thresholds

Tactile thresholds of the thigh, labium minus, and two vestibular sites (1 and 6 o'clock) obtained in the second session were compared with those obtained in the first. All four regions were significantly correlated between studies ($r = 0.46$, 0.66, 0.60, and 0.47 for the four sites, respectively, all $P \leq 0.05$), and there were no significant differences in thresholds between sessions (all $P > 0.05$).

3.4. Pain thresholds

The upper and lower panels of Fig. 3 show the pain thresholds for the vestibular sites, i.e. the value of the filament at the first report of pain. As illustrated in the upper panel, women with VVS had significantly lower pain thresholds around the vestibule than controls (VVS mean 603 mg (95% CI 417–871); control mean 4266 mg (95% CI 3236–5623), $P < 0.001$). This is an underestimate of the actual pain threshold in the control group, because three control women reported no pain, even at the highest stimulus value used (the value of the highest stimulus was used for computing the mean for these cases). There were no threshold differences among the four sites in either group.

There was a significant positive correlation between the tactile and pain thresholds averaged across the four vestibular sites ($r = 0.75$, $P < 0.001$). An ANOVA comparing the averaged pain threshold with the averaged tactile threshold as a covariate indicated that the differences between groups remained significant ($P < 0.001$), with women with VVS reporting significantly lower pain thresholds than control women. The mean pain thresholds adjusted for the covariate were 758 mg for the VVS group and 3388 mg for the control group.

The lower panel of Fig. 3 shows pain thresholds of the sites tested in the second session. Pain thresholds in the VVS group were substantially lower than controls overall, i.e. 2512 mg (95% CI 1445–4365) vs. 7413 mg (95% CI 5370–10233), averaged over all seven sites tested ($P < 0.01$). The group by site interaction ($F_{(6,108)} = 2.56$, $P = 0.05$) indicated differences in the distribution of pain thresholds. In the control group, the pain thresholds were remarkably similar across sites, while in the VVS group the vestibular sites were more sensitive than the other regions, significantly so for the comparisons between vestibular site 1 and the tibia, forearm, deltoid, and thigh (all $P < 0.05$). Most notably, however, the data showed that pain thresholds were significantly lower in the VVS group over most sites.

3.5. Stability of pain thresholds

Pain thresholds of vestibular sites 1 and 6 obtained in the second session were highly correlated with those of the first ($r = 0.81$ and 0.73, respectively, both $P < 0.001$). However, the mean pain thresholds in both groups increased from study 1 to 2 (both $P < 0.05$). The differences were small, with log stimulus value differences between studies of 0.20 (777 mg) and 0.31 (1717 mg) for vestibular sites 1 and 6, respectively. In addition, the change in pain threshold between studies was similar for the VVS and the control groups.

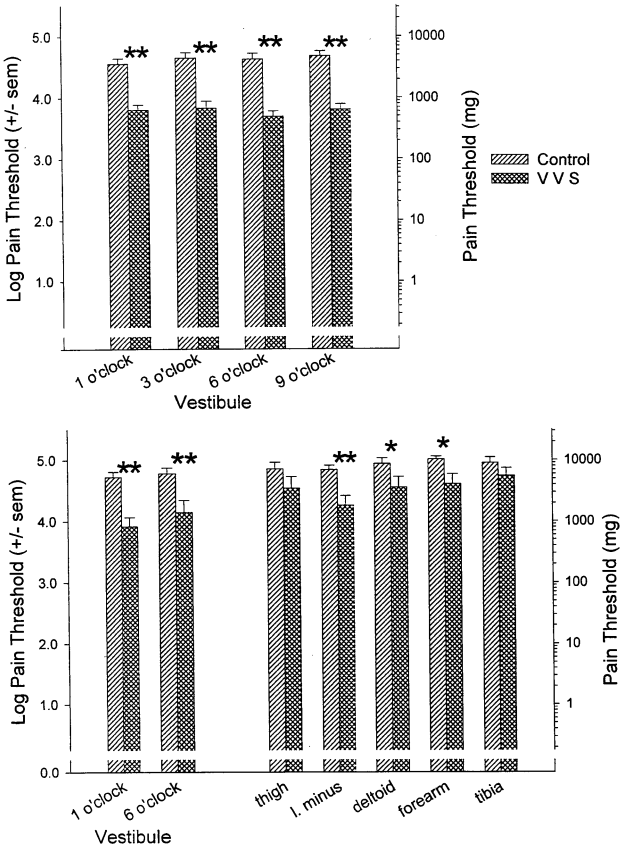

Fig. 3. (Upper) Thresholds (±SEM) for pain produced by punctate stimulation with the filaments of four vestibular sites (1, 3, 6, and 9 o'clock) in the VVS group ($N = 13$) and controls ($N = 13$) obtained at the first test session. (Lower) Pain thresholds (±SEM) of two vestibular sites (1 and 6 o'clock), and the thigh, labium minus, deltoid, forearm, and tibia on the dominant side of women with VVS ($N = 9$) and controls ($N = 11$) obtained in the second test session. *$P < 0.05$, **$P < 0.01$.

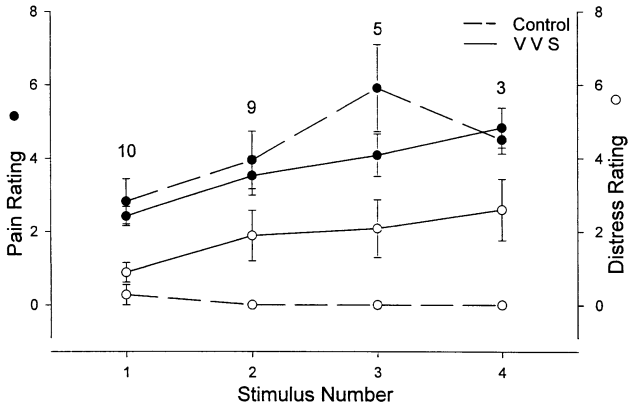

Fig. 4. Mean pain (filled symbols) and distress (open symbols) ratings (±SEM) on the four vestibular sites for consecutive filaments, beginning at the first filament (i.e. stimulus value 1) reported to produce pain – the pain threshold – in women with VVS (solid lines) and controls (dashed lines). The values on the *X*-axis (stimulus values) represent different filaments for each of the two groups. In the control group, three women did not report pain even at the highest filament (stimulus value 4); of the remaining ten subjects, most reported pain at much higher stimulus values than the VVS group. Since control subjects dropped out as they reached the highest stimulus value for all four sites, the number remaining in the control group at each data point is indicated on the graph.

3.6. Pain and distress ratings for suprathreshold pain around the vestibule

When the pain threshold was reached, three further stimuli were applied, and pain and distress ratings were recorded. Fig. 4 shows pain and distress ratings for these stimuli averaged across sites. The actual values of the stimuli for the two groups did not overlap because of the higher pain threshold in the control group, but plotting the ratings by stimulus number emphasizes the response patterns. Both groups' pain ratings increased in a linear fashion with logarithmic increases in stimulus pressure. The pain ratings for the two groups are obviously very similar, with the standard error bars overlapping for most data points. Because of the fact that most of the controls reached the highest stimulus value in three or fewer steps above the pain threshold, the gross inequality of the *N*s precludes statistical analysis. The linear relationship between pain rating and force of the suprathreshold stimuli was computed for each subject if there were at least three measures; this cut-off left 13 VVS subjects and seven controls. The values of the slopes were all positive, and ranged from 0.10 to 0.32 and from 0.09 to 0.32 stimulus number units/unit increase in pain magnitude for the VVS and control groups, respectively. These values are clearly not different ($t = 0.11$, $df = 19$). In contrast to the similarity of the pain ratings for the two groups, distress levels for women with VVS increased systematically with their pain ratings, while women in the control group consistently rated their distress as 0 for all stimuli. Therefore, while distress ratings are parallel to pain ratings within the VVS group, the control group's distress ratings were very low despite their high pain ratings and high stimulus values.

3.7. Pain and distress ratings in response to sustained pressure

The highest filament used, i.e. three steps above the pain threshold, was applied to the vestibular sites for 40 s. Fig. 5 illustrates pain (upper panel) and distress (lower panel) ratings in response to sustained pressure for both groups. With respect to pain ratings, there was a significant main effect of time ($P < 0.001$), but no significant group effect or group by time interaction. Planned comparisons indicated that the groups differed at 40 s ($P < 0.05$), with women in the VVS group reporting significantly higher pain ratings (mean 2.23) than controls (mean 0.98).

Distress ratings were significantly higher in the VVS group as compared with the control group ($P < 0.05$). There was a significant main effect of time ($P < 0.001$), with distress ratings upon application (mean 1.78) differing significantly from those at 20 (mean 1.22) and at 40 (mean 0.77) s. Planned comparisons indicated that the distress ratings of the VVS group were significantly higher than the controls at 20 and 40 s (both $P \leq 0.05$).

Since averaged pain and distress ratings at each time period were significantly correlated, a 2 (group) × 3 (distress ratings at each time period) ANCOVA was performed with pain ratings treated as a covariate. There

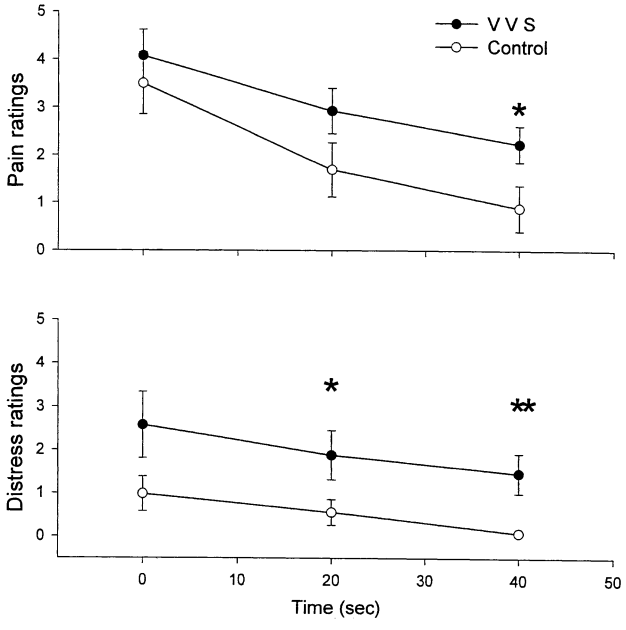

Fig. 5. (Upper) Pain intensity ratings (±SEM) by women with VVS (filled symbols; $N = 13$) and controls (open symbols; $N = 13$) in response to sustained pressure with the filament three steps above the pain threshold, averaged over the four vestibular sites (1, 3, 6, and 9 o'clock). Subjects were asked to rate the pain at the time of application, and 20 and 40 s later. (Lower) Average distress ratings (±SEM) reported at the same time as the pain intensity ratings were made for VVS (filled symbols; $N = 13$) and control (open symbols; $N = 13$) women. $^*P < 0.05$, $^{**}P < 0.01$.

were no significant group differences and no interaction. Planned comparisons on adjusted distress ratings at 40 s remained significant ($P < 0.05$), with women in the VVS group reporting significantly higher distress ratings than control women.

3.8. Pressure-pain tolerance

Pressure-pain tolerance was measured on all subjects over the deltoid muscle, but two women in the VVS group had recent injuries to their knees (surgery in one case, a fall in the other), so the tibial measures were not made on them. As shown in Fig. 6, women with VVS tolerated less pressure in both areas than controls ($F_{(1,22)} = 5.21$, $P < 0.05$). Planned comparisons showed that women with VVS tolerated significantly less pressure over the deltoid muscle ($F_{(1,22)} = 7.98$, $P = 0.01$) but not over the tibia ($F_{(1,22)} = 2.08$, $P > 0.05$) as compared with controls.

3.9. Verbal descriptors of tactile and pain sensation

Words used more than 10% of the time to describe the quality of the sensations are listed in Table 2. Words chosen for tactile sensation were variable, with mild, tingling, and ticklish dominating. Pricking and pinching were somewhat more consistently used to describe pain, in contrast to the burning and incisive qualities typically reported for intercourse pain and the cotton-swab test.

3.10. MPQ and PCS scores

MPQ and PCS scores are shown in Table 1. There were no correlations between MPQ scores for recalled penetration pain with cotton-swab pain ratings, or with tactile or pain thresholds within the groups. PCS scores for general pain were similar for the two groups. However, within the VVS group, PCS scores were significantly higher for intercourse pain than for general pain (see Table 1). PCS scores did not correlate with tactile or pain thresholds, with cotton-swab pain ratings, or with total MPQ scores, either within groups, or overall.

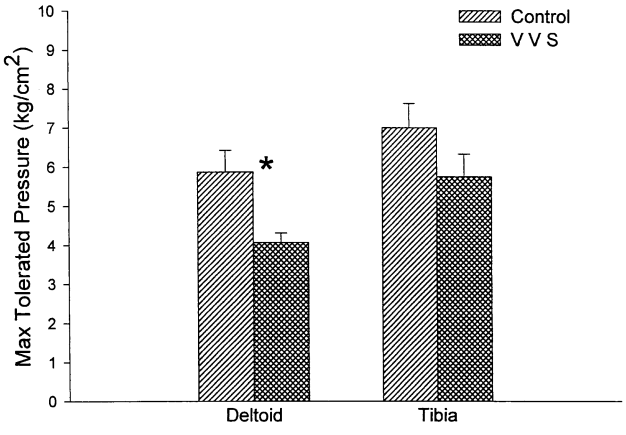

Fig. 6. Maximum tolerated pressure (kg/cm^2; ±SEM) over the deltoid muscle and tibia of controls ($N = 13$) and women with VVS ($N = 13$). Data are averaged across two measures on each side. *$P < 0.05$.

Table 2
Verbal descriptors of vestibular tactile and pain sensation

Words (French translation)	Control (%)	VVS (%)
Tactile sensation		
Experiment 1		
Ticklish (chatouilleuse)	15	14
Mild (légère)	15	11
Prickling (picotante)	14	–
Tingling (picotement)	12	–
Brushing (effleurement)	–	16
Dull (émoussée)	–	10
Experiment 2		
Brushing (effleurement)	10	24
Tingling (picotement)	17	12
Mild (légère)	27	12
Prickling (picotante)	13	–
Ticklish (chatouilleuse)	10	–
Pain sensation		
Experiment 1		
Pricking (qui pique)	32	20
Pinching (qui pince)	12	10
Experiment 2		
Pricking (qui pique)	40	24
Annoying (agaçante)	13	–
Boring (qui perce)	–	14

3.11. Other pains

Despite the similarity in the PCS scores for general pain for the two groups, women with VVS reported suffering from pain in more non-genital sites in the body (Fig. 7; $\chi^2(1, N = 26) = 4.25$, median split point = 2, $P < 0.05$, one tail) than controls. None of the subjects reported having a previous diagnosis of any other pain syndrome.

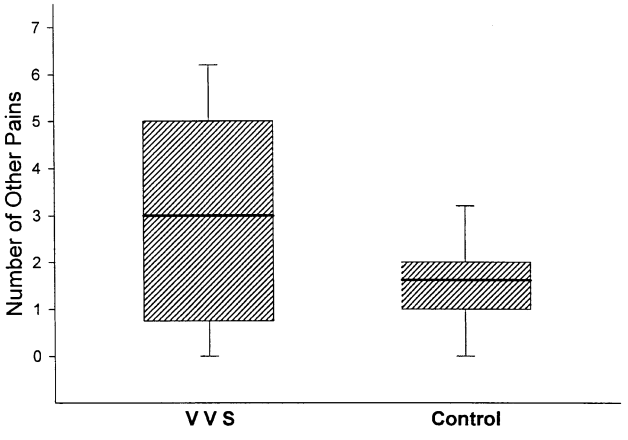

Fig. 7. Box and whisker plots of the numbers of other, non-intercourse related pains reported by women with VVS ($N = 13$) and controls ($N = 13$). The mean and 75th and 25th percentiles are indicated on the plots, with the error bars representing the 5th and 95th percentiles.

4. Discussion

The present study is the first to determine sensory thresholds in female vestibular tissue. The data indicate that the vulvar vestibule is relatively insensitive to punctate tactile stimuli compared to sites on the hairy skin of the arms and legs in the control women. The latter sites are themselves relatively insensitive regions of the body, compared to the face and hands (Weinstein, 1968). Interestingly, the labium minus was the most sensitive of all areas tested for punctate tactile sensitivity. In contrast to the high variability across body regions for tactile sensitivity, the thresholds for pain produced by punctate stimuli were remarkably similar across all body regions tested in control women. This emphasizes the protective role of the pain threshold under normal conditions. None of the regions we tested were on thickened horny skin, in which higher pain thresholds might be expected.

In women suffering from VVS, the thresholds for both tactile and pain sensation in the vulvar vestibule were dramatically lower than in control women. These differences are striking; vestibular pain thresholds of women with VVS were closer to the vestibular tactile thresholds of control women than to their pain thresholds. Thus, stimuli that evoked vestibular tactile sensations in control women produced pain in women with VVS. In addition, women with VVS reported tactile sensations at stimulus levels imperceptible to control women. These findings cannot be explained by the hypothesis that women with VVS anticipated sensation in the vestibular area during tactile testing, because there were no differences in the false positive rate between groups. Moreover, women in both groups described both non-painful and painful sensations with similar descriptors, implying that the sensations had similar qualities despite the differences in sensitivity. The data indicate that the sensory pathology in VVS is not limited to pain, but extends to other somatosensory modalities as well.

In addition to higher sensitivity to tactile and pain stimuli in the vulvar vestibule, women with VVS had lower thresholds on the adjacent labium minus. This is consistent with the finding by Bergeron et al. (2001a) that some women with VVS reported pain in this area during cotton-swab palpation. However, the low tactile and pain thresholds were not limited to the genital region. Women suffering from VVS had significantly lower tactile thresholds than controls on the arm over the deltoid muscle, and trends for lower thresholds over most other sites tested. The pain thresholds for punctate stimuli also tended to be lower over most of the sites tested, again significantly so over deltoid muscle and the volar surface of the forearm. Taken together with the lower thresholds for pressure pain over the deltoid and the tibia, the data suggest that VVS involves a generalized sensory abnormality that is not restricted to the vulvar region or to pain.

Tactile thresholds were virtually identical in the two sessions. However, vestibular pain thresholds increased from the first to the second test session in both groups. Since tactile thresholds were reliable over time, the differences in pain thresholds are unlikely to be due to inaccuracy or changes in the methods. In addition, both groups showed similar increases over time. The most likely explanation for the increased pain thresholds at the second test is that familiarity with the procedure reduced anxiety focused on the testing. This explanation would be consistent with the findings by Rhudy and Meagher (2000) that anxiety lowered pain thresholds, whereas fear focused away from the pain stimulus increased pain thresholds.

4.1. Psychological responses to and descriptions of vestibular pain

Women with VVS and controls reported virtually identical ratings of the sensory intensity of pain for stimuli at and above the pain threshold, i.e. the function relating stimulus intensity to perceived pain intensity was not different for the two groups despite the differences in the pain threshold itself. However, women with VVS reported much higher levels of distress in relation to the sensory intensity of pain. This pattern is typical of chronic pain patients (Price and Harkins, 1992), and it provides an indicator of the significance of pain in the lives of the women suffering from VVS. In the present study, the differences between the VVS group and the controls were increased because most of the controls denied any distress from the suprathreshold stimuli. It is possible that the control group was not typical of 'average normal' women in this regard, because they were selected for never having had pain related to intercourse and very low scores on the cotton-swab test. Nevertheless, the data support the notion that the extensive experience of pain that interferes with function changes the relationship between the sensory experience of pain and the emotional response to pain, even when the pain is episodic. It is probable that it is this aspect of pain that is most influenced by cognitive behavior therapy (e.g. Turner and Clancy, 1986; Turk and Rudy, 1992; Basler et al., 1997).

Women with VVS also had a greater tendency toward catastrophizing about their intercourse pain than about general pain. These results are not surprising since many women suffering from VVS had endured the pain for many years either without treatment or after having undergone several unsuccessful treatments. The intimate and emotionally loaded aspects of this pain syndrome may also contribute to the higher PCS scores. However, the tendency of women with VVS to catastrophize was limited to intercourse pain, and when asked to think about other types of pain, their PCS scores did not differ from those of the control group. This suggests that VVS is not associated with a generalized change in how pain is evaluated, despite the finding of the present study that women with VVS report more non-genital pains, and have been found to disclose more frequent bodily symptoms and complaints (Danielsson et al., 2000), than controls. From the perspective of cognitive behavioral inter-

ventions, this indicates that therapy needs to be focused on the specific problem, and that the issue of responses to pain in general is not particularly relevant.

The tendency for catastrophizing to be specific for the pathological pain problem is also interesting in regard to the catastrophizing questionnaire itself. It has been proposed that catastrophizing assesses a general characteristic in chronic pain patients (Sullivan et al., 1995). The present data suggest that catastrophizing may not be a general characteristic of pain patients, and that the scale should be applied with reference to more than one kind of pain. Note that when the scale is administered without any specific instructions, it is probable that patients assume it must refer to the presenting chronic pain problem.

The words chosen by both groups to describe both tactile sensations and pain in the vestibular region were rather variable, but the two groups chose similar words (Table 2). The variability may relate to the fact that there is rarely any social discussion of the qualities of sensory experience in the genital region, and there is unlikely to be culturally influenced naming and classification of the sensations. The punctate pain sensations produced in the present study were, however, clearly different from the pain evoked by intercourse in that the descriptors 'burning' and 'cutting' were not chosen frequently by either group. One likely reason is that a very small area was stimulated without motion, a very different experience from a penetrative sexual encounter where the whole vestibular area is stretched and exposed to repetitive friction.

4.2. Comparison of results with existing literature

The tactile thresholds in the present study are about one log unit higher than those given by Weinstein (1968) for comparable sites. One reason for the higher values is that sensory sensitivity declines with age (Stevens and Choo, 1996) and the mean age of Weinstein's female subjects was 3 years lower, and the age range was not as great. More importantly, the number of determinations of the thresholds was lower because of the position necessary to expose the vulvar vestibule for testing, and there would be expected to be more emotional arousal and muscle tension, both of which would be expected to increase thresholds (e.g. Pertovaara et al., 1992). Thresholds obtained also vary according to the contact duration (van Vliet et al., 1993) which may have varied between studies. The thresholds in the present study are very similar to those obtained in other clinical settings. For example, for the two sites innervated by the cervical nerves (volar forearm and over the deltoid), our thresholds were very close to those reported by Voerman et al. (1999) for the cervical dermatomes in normal subjects. In addition, tactile thresholds at the sites that we tested twice 3–12 months apart were very similar, the difference between sessions averaging 54 mg for controls and 17 mg for women with VVS.

The relative insensitivity of the vulvar region to tactile stimuli is consistent with the small amount of data that exists on other mucocutaneous regions such as the areola and nipple in human females (Benediktsson et al., 1997) and the glans penis in male humans and animals (cf. Johnson and Kitchell, 1987). In addition, the sensitivity of the genital region to vibration, which also involves rapidly adapting afferent neurons, is also low compared to other parts of the body (Helström and Lundberg, 1992; Greenspan and LaMotte, 1993). The data imply that, despite the importance of sensory input from the genitals for sexual behavior, the sensory innervation is much less sensitive than other body parts, such as the face and hands.

4.3. Etiological perspectives of VVS

Etiological theories of VVS have focused on two possibilities that are not mutually exclusive. Researchers who classify VVS as a subtype of vulvodynia suggest that treatment include medications that are typically used to treat neuropathic pain (Wesselmann and Reich, 1996). Indeed, the allodynia and hyperpathic or burning quality of VVS pain is consistent with the clinical description of pain associated with peripheral neuropathies, and may be indicative of common processes. However, neuropathic pain is thought to result from damage to, and subsequent loss of, peripheral afferent elements, leading to changes in the central nervous system (CNS) (Bennett, 1994). Damage to afferent neurons would be expected to be associated with impairment of sensory function, as has been observed in postherpetic neuralgia and diabetic neuropathy (Moriwaki and Yuge, 1999; Gottrup et al., 1998). In contrast, the present data suggest that the pathology underlying VVS leads to an increase in sensory sensitivity.

The second proposal for the etiological basis of VVS is that it involves chronic inflammation of the vestibular tissues, with consequent sensitization of primary afferents by inflammatory peptides, prostaglandins, and cytokines (e.g. Pyka et al., 1988; Cox, 1995; Bohm-Starke et al., 1998). A natural extension of this theory is that inflammation leads to sensitization in the spinal cord, with facilitation of nociceptive transmission in the CNS, and development of secondary hyperalgesia around the primary hyperalgesic region (e.g. LaMotte et al., 1991; Woolf, 1993; Sandkuhler, 2000). Allodynia to light touch in the vestibular region and the hyperalgesia on the adjacent labium minus is readily explained by this hypothesis. However, some histopathological studies suggest that inflammatory infiltrates may be relatively common in vestibular tissue, and are not necessarily related to pain (Lundqvist et al., 1997; Slone et al., 1999; but see, for example, Foster and Hasday, 1997; Chadha et al., 1998). It is possible that prolonged inflammation in susceptible individuals leads to changes that are more complex. Two studies have reported increased density of neuropil in vulvar biopsy tissues (Bohm-Starke et al., 1998; Weström and Willén, 1998) of women with VVS, and Bohm-Starke et al. (1999) reported high levels of calci-

tonin gene-related peptide (CGRP) staining. The finding that VVS is associated with allele 2 of the gene encoding the interleukin-1 receptor antagonist further suggests that there are genetic factors that may confer vulnerability to this pain syndrome (Jeremias et al., 2000), and supports the notion of an inflammatory basis for VVS.

The present study indicates that in addition to the hyperesthesia and hyperalgesia in the genital region, women affected by VVS have decreased tactile and pain thresholds on distant body sites. The implication is that VVS involves a generalized alteration of cutaneous sensory sensitivity. This is not to deny that there is also some specific pathology in the vulvar region, since the relative decrease in thresholds in the vestibular region was much greater than for other sites on the body, and the evidence discussed above points to a local inflammatory process. However, the data raise the question as to whether generalized changes in somatosensory function play an important role in VVS.

Generalized changes in pain thresholds have been observed in other chronic pain conditions. Burstein et al. (2000a,b) found that migraine sufferers experience hyperalgesia and allodynia both inside and outside the areas of referred head pain during a fully developed migraine attack, and Okifuji et al. (1997) found that 40% of chronic headache patients reported pain or tenderness at many body locations that are associated with fibromyalgia. Further support comes from studies examining nerve sural reflex in migraineurs (Micieli et al., 1989) and movement-related pain in osteoarthritis patients (Farrell et al., 2000).

Taken together with the current data, these studies imply that there may be a subset of chronic pain patients, including women with VVS, whose primary problem may be either causally related to, or exacerbated by, a generalized disorder of sensory modulation. However, the results from the treatment outcome study by Bergeron et al. (2001b) do not support this idea since the surgery was the most successful treatment. Nonetheless, the findings from the present study support the notion that the pain of VVS may be associated with widespread pain and tenderness, and they have important implications. If pain related to intercourse is the most salient feature of a systemic pain problem, then searching for the etiology in and around the genitals may be misleading. The presence or absence of generalized pain and tenderness may have implications for treatment as well. One possibility is that the response to different kinds of treatments is determined by the extent to which the underlying pathology is restricted to the vestibular region. It is also possible that patients who are referred to specialty pain clinics, i.e. the complicated and refractory cases, are more likely to have coital pain that is superimposed on generalized sensory disregulation, while less severe VVS is a fundamentally different problem.

4.4. Future directions

Further research is needed in order to more fully explain the peripheral and central mechanisms involved in the development and maintenance of VVS. It is important to test women before and after various therapies. The data suggest that thresholds may be useful to assess the progress and nature of effects of therapies such as physiotherapy, psychotherapy, or vestibulectomy, in so far as whether thresholds in surrounding tissues remain the same. Also, testing other somatosensory modalities in the genital region, such as vestibular temperature sensitivity and thresholds to static vs. dynamic touch, will aid in determining what peripheral fibers underlie the pain of VVS. In addition, imaging this pain with fMRI technology will allow us to compare neural activation between women with VVS and chronic pain patients. These types of valuable information which we are currently collecting will provide further definitive proof that VVS is better conceptualized as a pain disorder. The shift in perspective from examining VVS as a sexual dysfunction to studying it as a pain syndrome is more than a semantic one. It will affect: (1) how and which scientists go about studying pain; (2) how and which health professionals treat it; (3) how individuals and their significant others react to the pain; and (4) the way in which larger social institutions address the problem (Hanson and Gerber, 1990).

Acknowledgements

This study was supported by Health Canada, NHRDP Grant #6605-4381-503, Medical Research Council of Canada Grant #21466, and a grant by Pfizer Canada, Inc. to Y.M.B. C.F.P. was supported by a fellowship from Fonds pour la Formation et l'Aide à la Recherche (FCAR). This paper stands in partial fulfillment of C.F.P.'s PhD requirements. We would like to thank Frances Wilkinson for her help with the computer program, Karen Berkley, Cathy Bushnell, Michael J. Roberts, and Ursula Wesselmann for their comments on the manuscript, and Janet Bradley, Alina Kao, Marie-Andrée Lahaie, and Monica Oala for their assistance in collecting data.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.

Baggish MS, Miklos JR. Vulvar pain syndrome: a review. Obstet Gynecol Surv 1995;50:618–627.

Basler H-D, Jaekle C, Kroener-Herwig B. Incorporation of cognitive-behavioral treatment into the medical care of chronic low back patients: a controlled randomized study in German pain treatment centers. Patient Educ Couns 1997;31:113–124.

Bell-Krotoski JA. Light touch-deep pressure testing using Semmes-Weinstein monofilaments. In: Hunter JM, Schneider LH, Mackin EJ, Callahan AD, editors. Rehabilitation of the hand: surgery and therapy, 3rd ed. St. Louis, MO: CV Mosby, 1990. pp. 585–593.

Bell-Krotoski JA, Tomancik E. The repeatability of testing with Semmes-Weinstein monofilaments. J Hand Surg 1987;12A:155–161.

Benediktsson KP, Perbeck L, Geigant E, Solders G. Touch sensibility in the breast after subcutaneous mastectomy and immediate reconstruction with a prosthesis. Br J Plast Surg 1997;50:443–449.

Bennett GJ. Neuropathic pain. In: Wall PD, Melzack R, editors. Textbook of pain, 3rd ed. Edinburgh: Churchill Livingstone, 1994. pp. 494–510.

Bergeron S, Binik YM, Khalifé S, Pagidas K. Vulvar vestibulitis syndrome: a critical review. Clin J Pain 1997;13:27–42.

Bergeron S, Binik YM, Khalifé S, Pagidas K, Glazer HI. Reliability and validity of the diagnosis of vulvar vestibulitis syndrome. Obstet Gynecol 2001a;98:45–51.

Bergeron S, Binik YM, Khalifé S, Pagidas K, Glazer HI, Meana M, Amsel R. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic feedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain 2001b;91:297–306.

Binik YM, Meana M, Berkley K, Khalifé S. The sexual pain disorders: is the pain sexual or is the sex painful? Annu Rev Sex Res 1999;10:210–235.

Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Increased epithelial innervation in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest 1998;46:256–260.

Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest 1999;48:270–275.

Bornstein J, Zarfati D, Goldik Z, Abramovici H. Perineoplasty compared with vestibuloplasty for severe vulvar vestibulitis. Br J Obstet Gynaecol 1995;102:652–655.

Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 2000a;123:1703–1709.

Burstein R, Yarnitsky D, Goor-Aryeh F, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol 2000b;47:614–624.

Chadha S, Gianotten WL, Drogendjik AC, Weijmar Schultz WC, Blindeman LA, van der Meijen WI. Histopathologic features of vulvar vestibulitis. Int J Gynecol Pathol 1998;17:7–11.

Cornsweet TN. The staircase-method in psychophysics. Am J Psychol 1962;75:485–491.

Cox JT. Deconstructing vulval pain. Lancet 1995;345:53.

Danielsson I, Sjöberg I, Wikman M. Vulvar vestibulitis: medical, psychosexual and psychosocial aspects, a case-control study. Acta Obstet Gynecol Scand 2000;79:872–878.

Eliav E, Gracely RH. Sensory changes in the territory of the lingual and inferior alveolar nerves following lower third molar extraction. Pain 1998;77:191–199.

Eva LJ, Reid WMN, MacLean AB, Morrison GD. Assessment of response to treatment in vulvar vestibulitis syndrome by means of the vulvar algesiometer. Am J Obstet Gynecol 1999;181:99–102.

Farrell M, Gibson S, McMeeken J, Helme R. Pain and hyperalgesia in osteoarthritis of the hands. J Rheumatol 2000;27:441–447.

Fechner GT. Elements of psychophysics, New York: Holt, Rinehart, & Winston, 1860/1966.

Foster DC, Hasday JD. Elevated tissue levels of interleukin-1 beta and tumor necrosis factor-alpha in vulvar vestibulitis. Obstet Gynecol 1997;89:291–296.

Friedman M. Understanding vaginal vestibulum dyspareunia syndrome. The Cerv Lower Female Genital Tract 1995;13:135–140.

Friedrich Jr. EG. Vulvar vestibulitis syndrome. J Reprod Med 1987;32:110–114.

Furlonge CB, Thin RN, Evans BE, McKee PH. Vulvar vestibulitis syndrome: a clinico-pathological study. Br J Obstet Gynaecol 1991;98:703–706.

Gottrup H, Nielsen J, Arendt-Nielsen L, Jensen TS. The relationship between sensory thresholds and mechanical hyperalgesia in nerve injury. Pain 1998;75:321–329.

Greenspan JD, LaMotte RH. Cutaneous mechanoreceptors of the hand: experimental studies and their implications for clinical testing of tactile sensation. J Hand Ther 1993;6:75–82.

Hanson RW, Gerber KE. Coping with chronic pain: a guide to patient self-management, New York: Guilford Press, 1990.

Helström L, Lundberg PO. Vibratory perception thresholds in the female genital region. Acta Neurol Scand 1992;86:635–637.

Jeremias J, Ledger WJ, Witkin SS. Interleukin 1 receptor antagonist gene polymorphism in women with vulvar vestibulitis. Am J Obstet Gynecol 2000;182:283–285.

Johnson RD, Kitchell RL. Mechanoreceptor response to mechanical and thermal stimuli in the glans penis of the dog. J Neurophysiol 1987;57:1813–1836.

Kinsey AC, Pomeroy WB, Martin CE, Gebhard PH. Sexual behavior in the human female, Philadelphia, PA: W.B. Saunders, 1953.

Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 1996;68:375–383.

LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190–211.

Leiblum SR, Bachmann GA, Kemmann E, Colburn DW, Swartzman L. Vaginal atrophy in the postmenopausal woman. J Am Med Assoc 1983;249:2195–2198.

Lundqvist EN, Hofer PA, Olofsson JI, Sjoberg I. Is vulvar vestibulitis an inflammatory condition? A comparison of histological findings in affected and healthy women. Acta Derm Venereol 1997;77:319–322.

Marinoff SC, Turner ML. Vulvar vestibulitis syndrome: an overview. Am J Obstet Gynecol 1991;165:1228–1233.

Masheb RM, Nash JM, Brondolo E, Kerns RD. Vulvodynia: an introduction and critical review of a chronic pain condition. Pain 2000;86:3–10.

Meana M, Binik YM. Painful coitus: a review of female dyspareunia. J Nerv Ment Dis 1994;182:264–272.

Meana M, Binik YM, Khalifé S, Cohen D. Dyspareunia: sexual dysfunction or pain syndrome? Pain 1997a;71:211–212.

Meana M, Binik YM, Khalifé S, Cohen D. Biopsychosocial profile of women with dyspareunia. Obstet Gynecol 1997b;90:583–589.

Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–299.

Merskey H, Bogduk N. Classification of chronic pain, 2nd ed. Washington, DC: IASP Press, 1994.

Michlewitz H, Kennison RD, Turksoy RN, Fertitta LC. Vulvar vestibulitis – subgroup with Bartholin gland duct inflammation. Obstet Gynecol 1989;73:410–413.

Micieli G, Tassorelli C, Magri M, Sandrini G, Cavallini A, Nappi G. Vegetative imbalance in migraine: a dynamic TV pupillometric evaluation. Funct Neurol 1989;4:105–111.

Moriwaki K, Yuge O. Topographical features of cutaneous tactile hypoesthetic and hyperesthetic abnormalities in chronic pain. Pain 1999;81:1–6.

Okifuji A, Turk DC, Sinclair JD, Starz TW, Marcus DA. A standardized manual tender point survey. I. Development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome. J Rheumatol 1997;24:377–383.

Peckham BM, Maki DG, Patterson JJ, Hafez GR. Focal vulvitis: a characteristic syndrome and cause of dyspareunia – features, natural history, and management. Am J Obstet Gynecol 1986;154:855–864.

Pertovaara A, Kemppainen P, Leppanen H. Lowered cutaneous sensitivity to nonpainful electrical stimulation during isometric exercise in humans. Exp Brain Res 1992;89:447–452.

Prayson RA, Stoler MH, Hart WR. Vulvar vestibulitis: a histopathologic study of 36 cases, including human papillomavirus in situ hybridization analysis. Am J Surg Pathol 1995;19:154–160.

Price DD, Harkins SW. Psychophysical approaches to pain measurement and assessment. In: Turk DC, Melzack R, editors. Handbook of pain assessment, New York: Guilford Press, 1992. pp. 111–134.

Pyka RE, Wilkinson EJ, Friedrich Jr. EG, Croker BP. The histopathology of vulvar vestibulitis syndrome. Int J Gynecol Pathol 1988;7:249–257.

Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain 2000;84:65–75.

Sandkuhler J. Learning and memory in pain pathways. Pain 2000;88:113–118.

Slone S, Reynolds L, Gall S, Peiper S, Martin A, Ackermann D, O'Connor D. Localization of chromogranin, synaptophysin, serotonin, and CXCR2 in neuroendocrine cells of the minor vestibular glands: an immunohistochemical study. Int J Gynecol Pathol 1999;18:360–365.

Stevens JC, Choo KK. Spatial acuity of the body surface over the life span. Somatosens Mot Res 1996;13:153–166.

Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995;7:524–532.

Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S. Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. Clin J Pain 1993:207–215.

Thomas TG. A practical treatise on the diseases of women, . Philadelphia, PA: Henry C. Lea, 1880.

Turk DC, Rudy TE. Cognitive factors and persistent pain: a glimpse into Pandora's box. Cognitive Ther Res 1992;16:99–122.

Turner JA, Clancy S. Strategies for coping with chronic low back pain: relationship to pain and disability. Pain 1986;24:355–364.

van Vliet D, Novak CB, Mackinnon SE. Duration of contact time alters cutaneous pressure threshold measurements. Ann Plast Surg 1993;31:335–339.

Voerman VF, van Egmond J, Crul BJP. Normal values for sensory thresholds in the cervical dermatomes. Am J Phys Med Rehabil 1999;78:24–29.

Weinstein S. Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In: Kenshalo DR, editor. The skin senses, Springfield, IL: Charles C. Thomas, 1968. pp. 195–218.

Wesselmann U, Reich SG. The dynias. Semin Neurol 1996;16:63–74.

Wesselmann U, Burnett AL, Heinberg LJ. The urogenital and rectal pain syndromes. Pain 1997;73:269–294.

Weström LV, Willén R. Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome. Obstet Gynecol 1998;91:572–576.

Wetherill GB, Levitt H. Sequential estimation of points on a psychometric function. Br J Math Stat Psychol 1965;18:1–10.

Woodruff JD, Parmley TH. Infection of the minor vestibular gland. Obstet Gynecol 1983;62:609–612.

Woolf CJ. The pathophysiology of peripheral neuropathic pain – abnormal peripheral input and abnormal central processing. Acta Neurochir Suppl 1993;58:125–130.