Altered Central Sensitization in Subgroups of Women With Vulvodynia

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Objective: To investigate the clinical correlates of central nervous system alterations among women with vulvodynia. Altered central sensitization has been linked to dysfunction in central nervous system-inhibitory pathways (eg, γ-aminobutyric acidergic), and metrics of sensory adaptation, a centrally mediated process that is sensitive to this dysfunction, could potentially be used to identify women at risk of treatment failure using conventional approaches.

Methods: Twelve women with vulvodynia and 20 age-matched controls participated in this study, which was conducted by sensory testing of the right hand's index and middle fingers. The following sensory precepts were assessed: (1) vibrotactile detection threshold; (2) amplitude discrimination capacity (defined as the ability to detect differences in intensity of simultaneously delivered stimuli to 2 fingers); and (3) a metric of adaptation (determined by the impact that applying conditioning stimuli have on amplitude discriminative capacity).

Results: Participants did not differ on key demographic variables, vibrotactile detection threshold, and amplitude discrimination capacity. However, we found significant differences from controls in adaptation metrics in 1 subgroup of vulvodynia patients. Compared with healthy controls and women with a shorter history of pain [n = 5; duration (y) = 3.4 ± 1.3], those with a longer history [n = 7; duration (y) = 9.3 ± 1.4)] were found to be less likely to have adaptation metrics similar to control values.

Discussion: Chronic pain is thought to lead to altered central sensitization, and adaptation is a centrally mediated process that is sensitive to this condition. This report suggests that similar alterations exist in a subgroup of vulvodynia patients.

Key Words: vulvodynia, central sensitization, adaptation

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Vulvodynia is a heterogeneous family of idiopathic pain disorders affecting upward of 16% of reproductive age women in the US.[1] It is characterized by both provoked and unprovoked pain in and surrounding vulvar skin, mucosa, and underlying musculature. Clinically, vulvodynia is classified into subgroups based on anatomic location (vulvar mucosa vs. hairy/nonhairy epithelium) and temporal characteristics as provoked versus unprovoked. Although a given patient may experience both provoked and unprovoked pain, the most common symptom is that of provoked pain on contact, precipitated by tampon use or intercourse. Unlike unprovoked pain, where the clinical examination is nonspecific, the majority of women with provoked pain have localized tenderness in vulvar mucosa (ie, vestibule).[2] In addition, women with provoked vulvodynia tend to be younger, and in most instances unaware of their condition until coital debut or the first attempt at using a tampon.

Although both peripheral and central abnormalities have been implicated in vulvodynia, the extent to which peripheral versus central factors contribute to the pain state in an individual patient remains unknown. A substantial portion of women with vulvodynia show hypersensitivity at extragenital sites (eg, arms and feet); this nonspecific hypersensitivity has conventionally been attributed to changes in "central sensitization" caused by the chronic pain state. To date, clinical signs and symptoms associated with central dysregulation in subgroups of women with vulvodynia remains unknown. Thus, understanding of the mechanistic (central vs. peripheral) implication of clinical signs and symptoms in vulvodynia is a necessary first step toward individualized, symptom-based treatment approach.

Current literature[1,3,4] suggests that symptoms of vulvodynia are likely to be triggered by peripheral factors in the skin and underlying musculature. With time (and chronicity), varying degrees of central dysregulation may develop. In this setting, patients may experience superimposed unprovoked (spontaneous) pain in otherwise unaffected tissue. Thus, investigating clinical correlates of central involvement in vulvodynia (eg, how sensory information processing is altered) may provide us with a unique opportunity to investigate the mechanisms of clinically similar disorders (eg, localized pain at the vulvar vestibule vs. generalized vulvar pain). Once the fundamental mechanisms of the centrally versus peripherally mediated vulvar pain is understood, this knowledge will enable the development of robust research and clinical tools that could improve diagnosis and lead to informed therapeutic options.

In this study, we investigated sensory information processing in subgroups of patients with vulvodynia and healthy controls. The quantitative sensory testing methodology used in this study has been shown to be sensitive to systemic cortical alteration,[5–7] and in pilot studies, has been shown to return to normative values with treatment (Tommerdahl; personal communication, 2010). In this study, we hypothesized that women who had experienced a longer time course with pain or had unprovoked symptoms are more likely to have measures consistent with altered central sensitization when compared with healthy controls or those participants who had experienced a shorter duration of provoked pain.

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MATERIALS AND METHODS

In this study, a convenience sample of 12 women with vulvodynia and 20 healthy controls without gynecologic pain were recruited from the University of North Carolina, Pelvic Pain Clinic and the surrounding community, respectively. The groups did not differ in basic demographic characteristics. All the participants were naive both to the study design and issue under investigation. The study was performed in accordance with the Declaration of Helsinki, all participants gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Experimental sessions were conducted with the patients seated comfortably in a chair with the right arm resting on an arm rest attached to the head unit of a portable 4-site vibrotactile stimulator (Fig. 1; CM4; Cortical Metrics, LLC). Vibrotactile stimulation was conducted through 5-mm probes that come in contact with patient's digit 2 (index finger) and digit 3 (middle finger). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for 2 reasons: (1) to allow the convenience of access and comfort of the patient, and (2) because of the wealth of neurophysiologic information that exists for the corresponding somatotopic regions of cortex in primates. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz, Hz) and amplitudes (measured in micrometers, μm). Stimulus parameters are specified by test algorithms that are based on specific protocols and patients' responses during those protocols.

Participants viewed a computer monitor that provided continuous visual cueing during the experimental session. Specifically, an onscreen light panel indicated to the participant when the stimulus was on and when the participant was to respond. Practice trials were performed before each test which allowed the participant to become familiar with the tests, and correct responses on 5 consecutive training trials were required before commencing with each test. The participant was not given performance feedback or knowledge of the results during data acquisition.

FIGURE 1. Images of the multisite vibrotactile stimulator. Stimulators are positioned by rotating each of the 4 independently positioned drums to maximize contact between fingers and the stimulator tips. During an experimental session, the patient was seated comfortably in a chair with the right arm resting on the arm rest attached to the head unit of the stimulator. Index and middle finger were positioned for D2 and D3 stimulation.

The sensory testing session was conducted by application of low frequency (25 Hz) vibration to right hand's index and middle finger(s). The protocols, from start to finish, lasted approximately 30 minutes and consisted of the following 5 modules: (1) static detection threshold; (2) dynamic detection threshold; (3) amplitude discrimination between 2 concurrent and stationary stimuli; (4) the impact of single-site adaptation on amplitude discrimination capacity; and (5) dynamic amplitude discrimination. Exemplary use, technical description, and neurobiologic basis of individual modules have been described in detail earlier.[5–10] An overview of the procedures and the earlier published normative findings is provided below.

Static Detection Threshold

Each participant's vibrotactile detection threshold was measured using a 20-trial 2 Alternative Forced Choice (2AFC) tracking protocol (for recent description with this experiment setup, see earlier studies[9–13]). The left panel of Figure 2A shows the schematic of the protocol. During each trial a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis to minimize participant's inattention and distraction. After each vibrotactile stimulus, the patient was prompted to select the skin site [index (D2) vs. middle (D3) finger] that was perceptually larger. After a 5-second delay, based on patient's response, the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the patient's response in the preceding trial. A 1-up/1-down algorithm was used for the purposes of amplitude modification in the first 10 trials. For example, the stimulus amplitude was decreased by 1 μm if the patient's response in the preceding trial was correct. However, it was increased by the same amount if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (2 correct/1 incorrect patient response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1-up/1-down algorithm in the first 10 trials was to expedite determination of patient's vibrotactile discriminative range without affecting the results, and this approach has been reported earlier.[6–10,14,15]

Dynamic Detection Threshold

At the beginning of each trial (as shown in Figure 2A, right panel), a delay period which includes no stimulation was applied. Four conditions of delay were used, in separate trials: 0, 1.5, 2, and 3 seconds. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The patient was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The patient's detection threshold was calculated as the average of the stimulus amplitude at the time of patient's response.

Amplitude Discrimination at Baseline

Each patient's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of earlier studies.[6–10,14,15] As shown in Figure 2B left panel, during

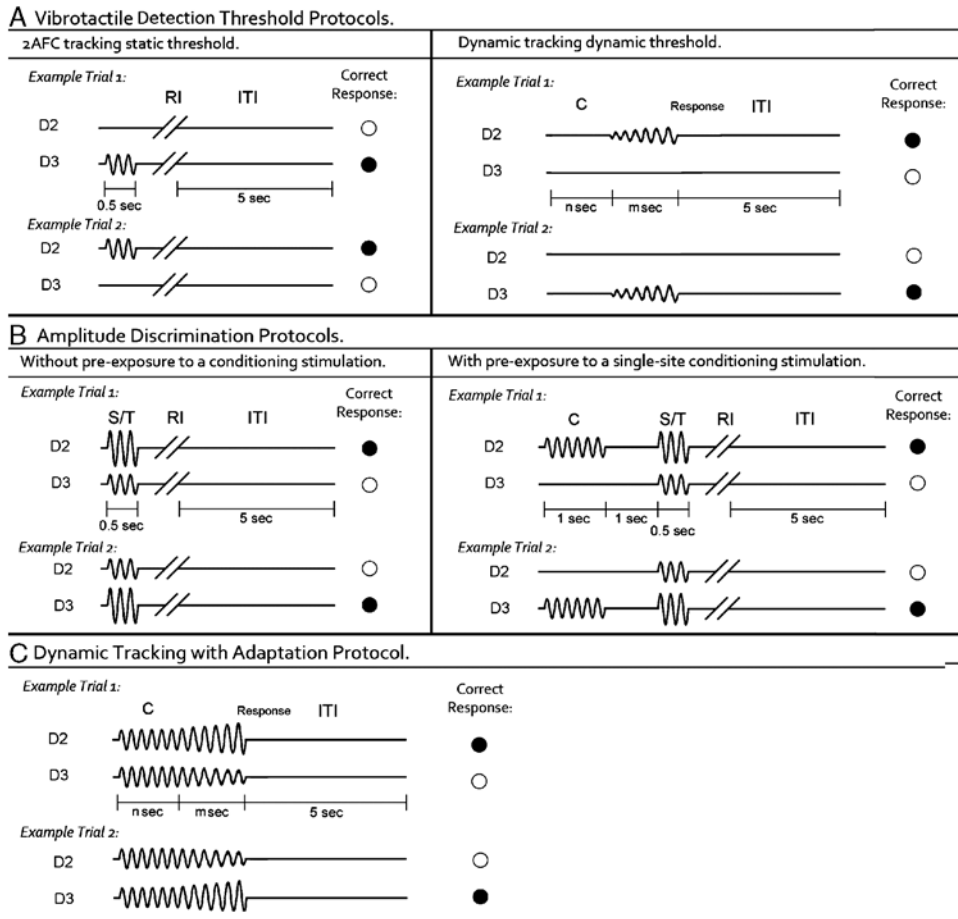

FIGURE 2. Schematics of the protocols used in this study. A, Vibrotactile detection threshold protocols. Left panel: 2 Alternative Forced Choice (2AFC) tracking protocol: In each trial, a 25 Hz vibrotactle test stimulus was delivered to either D2 or D3 for 0.5 second, followed by a patient response interval (RI). Participant was prompted to select the skin site that perceived the stimulus. A 5-second inter-trial interval (ITI) intervened between stimulus response and onset of the next trial. Right panel: Dynamic tracking protocol: A delay period (variable n = 0, 1.5, 2, or 3 s) without any stimulation was applied. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3. The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The stimulation was terminated with participant response to the perceived stimulus (variable m = subject response time). B, Amplitude discrimination protocols. Left panel: Amplitude discrimination at baseline: Two 25 Hz vibrotactile stimuli, the standard (S) and test (T), were delivered simultaneously for 0.5 seconds. Participant was asked to choose the stimulus that was perceptually larger. Right panel: Amplitude discrimination task with preexposure to conditioning stimulation. A 25 Hz conditioning stimulus (C) was delivered 1 second before the presentation of the test and standard stimuli. C, Dynamic tracking with adaptation protocol: Two identical 25 Hz vibrotactile stimuli (conditioning stimuli) were delivered simultaneously for a fixed interval (variable n = 0, 1.5, 2, or 3 s). After the initial constant stimulus period, the amplitude of the 2 stimuli were dynamically increased/decreased, in steps of 25 μm/s. Stimulation was terminated with patient response to the location at which the most intense stimulus was delivered (variable m = subject response time).

the 20-trial experimental run, a vibrotactile test stimulus (25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the participant's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The same tracking algorithm as that described for the tactile detection threshold protocol (2AFC tracking protocol) was used to track the participant's ability to determine the most intense stimulus between the test and standard stimuli [ie, the patient's difference limen (DL) was determined]. The step size was held constant at 10 μm throughout the experimental run.

Amplitude Discrimination With Single-site Adaptation

To measure the effects that conditioning stimuli have on subsequent test stimuli, the earlier described amplitude discrimination protocol was modified. As shown in Figure 2B right panel, a 25 Hz 200 μm conditioning stimulus was delivered 1 second before the presentation of the test and standard stimuli. When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation (reducing the perceived intensity) can be quantified by comparison of the amplitude discrimination DL obtained in the adapted versus nonadapted

conditions.[6–8,10] The amplitude discrimination tracking algorithm used in the earlier described protocol was used.

Dynamic Amplitude Discrimination

To further characterize the effects of adaptation on amplitude discrimination, a dynamic tracking protocol was implemented (for recent description with this experimental setup, see earlier study[10]). At the start of each run (shown in Figure 2C), 2 vibrotactile stimuli (25 Hz; initially identical in amplitude at 300 μm) were delivered simultaneously to D2 and D3. Four conditions of initial constant stimulus duration were used in separate experimental trials: 0, 1.5, 2, and 3 seconds. After the initial constant or stationary stimulus period, the amplitudes of both stimuli were dynamically altered such that the amplitude of 1 stimulus was increased and the amplitude of the other stimulus was decreased at the rate of 25 μm/s. The participant was instructed to indicate the location at which the most intense stimulus was delivered as soon as the 2 stimuli felt distinctly different in intensity. For each trial, the DL was recorded as the actual difference between the 2 test amplitudes at the time of participant's response. Averaged DLs were obtained for the 4 different durations of conditioning stimuli that preceded each trial.

Analysis

Repeated-measures analysis of variance was used to evaluate the difference of the participant's performance under different conditions. Data are presented as means and standard errors. A probability of less than 0.05 was considered statistically significant.

RESULTS

This study compared women with vulvodynia and matched healthy controls in a series of sensory perceptual measures that assessed: (1) vibrotactile detection threshold on the fingertip; (2) amplitude discrimination capacity; and (3) the impact of conditioning stimuli on amplitude discrimination capacity. The results show that patients with vulvodynia deviated very little from that of healthy controls in most of the sensory measures obtained in the absence of conditioning stimuli – such as threshold detection and amplitude discriminative capacity, although the patients with vulvodynia demonstrated a tendency to have lower tactile thresholds on the fingertips than controls. Most importantly, the measures of the effects of conditioning stimuli on amplitude discrimination revealed that the patients' data clustered into 2 distinct subgroups (which will be referred to as group A and group B). Group B data was very similar to that obtained from healthy controls, and group A demonstrated a significantly reduced impact of adaptation on the sensory percept. Although the average ages and demographics of the 2 subgroups were not significantly different, there was a significant difference in the duration that the 2 subgroups of patients had pain: group A (n = 7) patients had suffered from vulvodynia for a long duration (average duration: 9.3 ± 1.4 y; average age: 35.7 ± 3.2 y); and group B (n = 5) patients with vulvodynia for a relatively shorter duration (average duration: 3.4 ± 1.3 y; average age: 34.6 ± 4.3 y).

Patients With Vulvodynia Exhibit Slightly Lower Tactile Detection Thresholds

Figure 3 summarizes the group-averaged detection thresholds. As shown in the left panel of Figure 3, the group-averaged static thresholds observed were 12.37 ± 1.34 μm for controls, 9.77 ± 2.23 μm for patients in group A, and 10.32 ± 1.85 μm for patients in group B. The data suggest an elevated sensitivity for patients with vulvodynia compared with controls, although this difference was not statistically significant (group A vs. controls: $P = 0.35$; group B vs. controls: $P = 0.51$). This finding is consistent with data reported by Pukall et al[16] that showed that women with vulvodynia had a lower tactile threshold than controls at sites distant to the genitalia area.

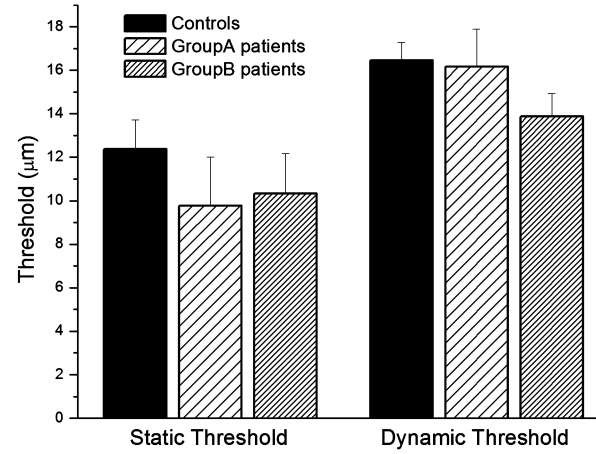

FIGURE 3. Summary of group-averaged vibrotactile detection thresholds obtained with 2 different methods on 2 subgroups of patients with vulvodynia and controls. Static threshold: No significant differences were observed on the static thresholds between any patients group and controls (group A vs. controls: $P = 0.35$; and group B vs. controls: $P = 0.51$). Dynamic threshold: The group-averaged dynamic thresholds of patients with vulvodynia did not significantly differ from that of controls, whereas data from patients in group B show a trend for lower dynamic threshold than controls.

As several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile thresholds,[17,18] in this study, the participant's vibrotactile threshold was also measured by a dynamic tracking protocol. The group-averaged dynamic thresholds are shown in the right panel of Figure 3. There was no significant difference between the controls and 2 vulvodynia patients groups, although data from patients in group B showed a lower (although not statistically significant) dynamic threshold than controls.

Although Amplitude Discrimination Capacity Was Not Significantly Different Between the Controls and Patients With Vulvodynia, the Impact of Conditioning Stimuli on Performance During This Task Revealed That the Vulvodynia Patients Were Clustered Into 2 Distinct Subgroups

Figure 4 summarizes the group-averaged performance during amplitude discrimination tests for the controls and 2 subgroups of patients with vulvodynia. Weber's fractions (WF) were determined by normalizing each participant's DL to the amplitude of standard stimulus (100 μm). As shown in the left panel of Figure 4, during which amplitude discrimination was measured in the absence of conditioning stimulus, there was no significant difference in performance between the controls and groups of vulvodynia patients.

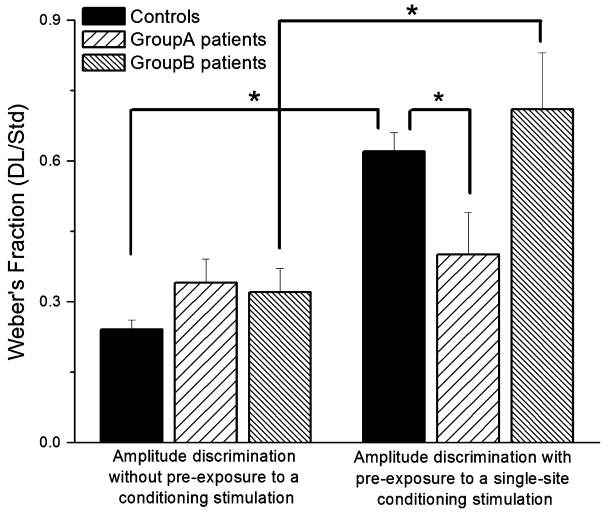

FIGURE 4. Comparison of Weber's fraction obtained with amplitude discrimination protocols (without/with preexposure to a single-site conditioning stimulus). In the absence of conditioning stimulus, no significant difference was observed between the performance of controls and subgroups of vulvodynia patients. Preexposure to a single-site conditioning stimulation (1 s in duration) caused a significant degradation of performance in the controls ($P<0.01$) and the patients in group B ($P=0.017$). In contrast to controls and group B, patients in group A performed equally well under both adapted and unadapted conditions. Under the condition with adaptation, the group-averaged performance is significantly different between controls and group A ($P=0.036$). DL indicates difference limen; Std, standard. * indicates $P< 0.05$.

Specifically, control participants were able to discriminate the difference between the test and standard stimuli that is 24.4% of the standard amplitude (WF = 0.244), and the patients in groups A and B were able to discriminate, respectively, 33.5% (WF = 0.335) and 31.6% (WF = 0.316) of the standard amplitude. However, preexposure to a single-site conditioning stimulus dramatically changed the participants' performance (shown in Figure 4, right panel). Although the WF of controls and patients in group B is significantly elevated in the adapted condition compared with the unadapted condition, patients in group A performed equally well under both adapted and unadapted conditions. Earlier reports have shown that single-site adaptation impairs control participant's amplitude discrimination capacity.[6–8,10] One interpretation of the impairment observed in this study is that a 1-second conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a test stimulus with amplitude of approximately 162% (controls)/ 171% (group B) of the standard amplitude was perceived nearly the same in intensity as the standard stimulus. Comparing with the significant degradation of performance of the controls ($P < 0.01$) and the patients in group B ($P = 0.017$) because of adaptation, no change was observed in the patients in group A ($P = 0.52$). Moreover, under the adapted condition the group-averaged performance is significantly different between controls and patients in group A ($P = 0.036$). Therefore, conditioning stimulation significantly impaired the performance of the controls and the patients in group B, but has no effects on the patients in group A.

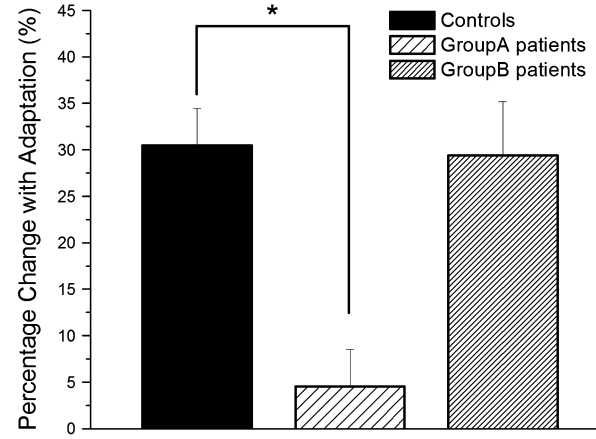

FIGURE 5. Weber's fraction obtained under the condition with adaptation was normalized on a patient-by-patient basis to the unadapted condition. The 1-second conditioning stimulus significantly impaired the participants' amplitude discrimination capacity by nearly 30% for both the controls and the patients in group B, whereas there were much lesser effects (3%) of adaptation observed in the patients in group A. * indicates $P< 0.05$.

To determine whether the differential effects of adaptation observed between groups were consistent within patients, each patient's WF obtained under the adapted condition was normalized to the unadapted condition. As shown in Figure 5, The 1-second conditioning stimulus significantly impaired amplitude discrimination capacity by nearly 30% for both the controls and the patients in group B, whereas there was much less of an effect (3%) of adaptation observed in the patients in group A ($P < 0.01$).

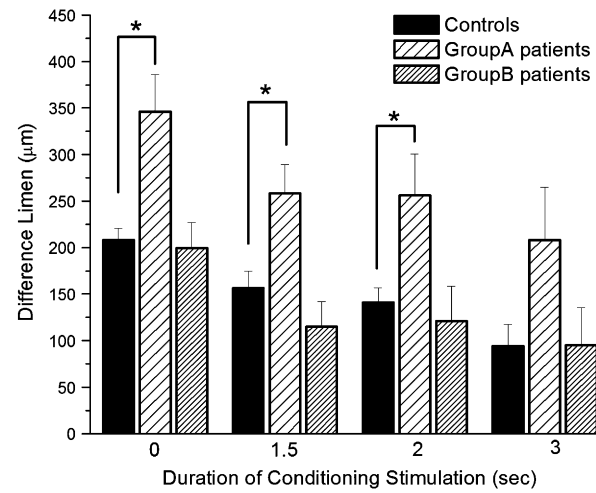

FIGURE 6. Comparison of the group-averaged performance with dual-site adaptation at the 4 different durations of dual-site conditioning stimulation (0, 1.5, 2, and 3 s) for the controls and 2 subgroups of patients with vulvodynia. Increasing the duration of the conditioning stimuli led to an improvement of performance (ie, reduced DL). As the data obtained from patients in group B deviated very little from that of controls, DLs obtained from patients in group A were significantly higher compared with controls and showed only little effect with adaptation. DL indicates difference limen. * indicates $P< 0.05$.

Dynamic Amplitude Discrimination

A dynamic amplitude discrimination protocol was used which is able to effectively compare the degree to which a patient adapts to simultaneously delivered dual-site vibrotactile stimuli at different durations of conditioning stimulation. Figure 6 summarizes the group-averaged performance with dual-site adaptation at the 4 different durations of conditioning stimulation (0, 1.5, 2, and 3 s) for the controls and 2 subgroups of patients with vulvodynia. The results show that increasing the duration of the conditioning stimuli delivered to both sites of skin led to an improvement of a patient's capacity to detect the difference in amplitude between the 2 stimuli. For example, after preexposure to 1.5, 2, or 3 second conditioning stimulus, control participants were, on average, able to attain a DL (156, 141, and 94 μm) that was approximately 73%, 66%, or 42% of the DL (208 μm) obtained without adaptation, respectively. Compared with controls, 2 subgroups of patients with vulvodynia have distinct performance differences. Specifically, the DLs were significantly higher in patients of group A compared with controls (0 s adaptation: $P < 0.01$; 1.5 s adaptation: $P = 0.01$; 2 s adaptation: $P < 0.01$; and 3 s adaptation: $P = 0.06$), but there was no significant difference between patients of group B and controls in the DLs obtained under all the conditions. In summary, data obtained from patients in group A showed little effect with conditioning stimulation whereas the data obtained from patients in group B deviated very little from that of controls.

DISCUSSION

In this study, sensory perceptual measures were obtained in 12 patients diagnosed with vulvodynia and 20 healthy controls. Five tests were performed to assess: (1) detection threshold on the fingertips; (2) amplitude discrimination capacity; and (3) the effects of adaptation on tactile discrimination capacity. The results suggest that women with vulvodynia have—although not statistically significantly—lower tactile thresholds on the fingertips than do control participants. Furthermore, as amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, the impact of single-site conditioning (or adaptation) on performance of the dual-site task showed a remarkable difference. Specifically, the observations of the conditioned sensory measures revealed that the patients with vulvodynia were clustered into 2 distinct subgroups. Group B had data that was very similar to that obtained from healthy controls, whereas group A demonstrated a significantly reduced impact of adaptation on the sensory percept. The primary difference between the compositions of the 2 subgroups is the duration or longevity of pain of the patients in each subgroup. Group B was composed of patients who reported pain for an average of 3.4 ± 1.3 years, whereas group A was composed of patients who reported pain for an average duration of 9.3 ± 1.4 years.

The reduction of the adaptation metric in patients with vulvodynia studied in this study has not been reported earlier. There have been few studies to date that have assessed the changes in perception that normally result from repetitive vibrotactile stimulation on the population of chronic pain patients, although Hollins and colleagues[19] did report decreased effects of adaptation in patients with temporomandibular disorders. Neurophysiologic studies have shown that repetitive stimulation results in temporal changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single-cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons[20–30]; alternatively, for review of short-term cortical neuron dynamics in visual cortex[31]; and for review of short-term primary somatosensory cortical neuron dynamics[32–36]). Optical imaging studies have also characterized the short-term dynamics of the population-level response of squirrel monkey contralateral primary somatosensory cortex using different amplitudes and durations of vibrotactile stimulation.[37–39]

Guided by the scientific work mentioned above, our research group has designed a series of tactile sensory diagnostics which effectively assess the impact that adaptation has on perception.[5,7–10,15] For example, the protocols used in this study directly measure the change in amplitude discrimination capacity that occurs with prior conditioning stimuli. Earlier studies using this measure showed that a patient's ability to discriminate between 2 simultaneously delivered vibrotactile stimuli—differing only in amplitude and location—was very robust and repeatable across a large number of healthy controls, but it was also very sensitive to varying conditions of conditioning stimuli. For instance, changing the duration of the conditioning stimulus delivered to 1 of the 2 sites before the amplitude discrimination task significantly altered a patient's ability to determine the actual difference between the 2 stimuli in a predictive and quantifiable manner. As a result, these methods could be viewed as a reliable indicator of the influence of adapting stimuli on central nervous system (CNS) response, as changes in the peripheral response are not significantly changed at these short stimulus durations (for discussion, see Refs. 5, 8, 9, 40, 41).

Centrally mediated adaptation is dependent on several factors [eg, γ-aminobutyric acid (GABA)ergic and *N*-methyl-D-aspartate receptor-mediated neurotransmission, neuron-glial interactions) which play significant roles in the way in which cortical information processing capacities of a number of clinically identified patient populations are impacted by their respective disorder. For example, conditioning stimuli do not have as pronounced impact on the amplitude discriminative capacity of patients with autism as it does with typically developing patients (for discussion of GABA-deficiencies in autism, see Refs.5,6,41). In addition, patients administered with a relatively small dose of an *N*-methyl-D-aspartate receptor antagonist (60 mg of dextromethorphan) also demonstrated a degraded adaptation metric.[7]

Two aspects of the adaptation process were measured in this study. The first, the gain effects of adaptation, was derived from the amplitude discrimination task in which a conditioning stimulus was delivered on 1 of the 2 test sites. The effect of that conditioning stimulus was on the gain of the conditioned site—that site was now perceived to be much smaller and thus, a reduction in gain was manifested, and subsequently, patients (normally) become worse at the task. The second facet of adaptation that was measured was a contrast effect, in which contrast between 2 stimuli

improve after conditioning stimuli have been delivered to both of the test sites, and the patients (normally) perform better after conditioning than they do without. In this study, the data obtained from the patients with vulvodynia are clustered into 2 distinct subgroups consistently with both of these aspects of adaptation. The patients in group B performed very similar as healthy controls did, and the performance of the patients in group A showed a significantly reduced impact of conditioning stimulation on the sensory percept. However, other sensory measures obtained in the absence of conditioning stimuli—such as threshold detection and amplitude discriminative capacity—showed no statistically significant difference between the 2 subgroups. The primary difference between the compositions of the 2 subgroups of note is the duration that patients of the subgroups have had pain, whereas average age of the 2 subgroups was not significantly different. Considering the metrics of adaptation (measuring the effects of conditioning stimulation on sensory perception) could be a reliable indicator of systemic alterations on central nervous function, it is speculated that the performance difference between the 2 subgroups of patients with vulvodynia observed in this study might reflect the level of dysregulation of their CNS due to chronic vulvar pain.

The involvement of both peripheral and central mechanisms in the development and maintenance of vulvodynia has been supported by a series of studies.[3,16,42–47] For example, it has been found that patients with vulvodynia have increased sensitivity to sensory stimulation at both genital regions and sites distant to it.[3,16,44] This suggests that not only peripheral sensitization but also a generalized central abnormality is involved in vulvodynia and could be similar to that observed in patients with other pain syndromes, implying a widespread disturbance in the CNS.[45] The observation of increased tactile sensitivity of the skin area distant to the vulvar region—including the static thresholds of all patients with vulvodynia in this report—is consistent with altered central sensitization that develops with chronic pain.

All participants, including controls, demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the 2 tasks is consistent with earlier reports.[10,18] Although this could possibly be explained by the influence that psychophysical measurement methods have on tactile detection,[17,18] we believe an alternate explanation is much more plausible. Mechanistically, this phenomenon could be the result of feed-forward inhibition that is generated by the initial subthreshold stimulus that occurs when the threshold test is ramped from zero to the detectable level.[48] The significance of this is that this type of feed-forward inhibition takes place in somatosensory cortical input layer 4,[49] in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their receptive field properties.[50–55] These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells, and thus, subthreshold or weak stimulus inputs will have the effect of raising the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. Thus, although not statistically significant, the observation of the difference between the groups A and B patients in their dynamic thresholds is that the difference between the ratio of the respective dynamic and static thresholds are clearly evident, and suggestive of below normal feed-forward inhibition. If this alteration is, as we believe, sensitive to the time dependency of the GABAb receptor, then the measure itself might be an indicator that GABAb efficiency has been compromised in some individuals.

Our data on patients with vulvodynia is consistent with existing constructs in the pain literature and supports the notion that the relative contribution of peripheral and central factors differ in subgroups of women with vulvodynia, and that clinical signs and symptoms alone are insufficient in identifying the underlying mechanism of pain as peripheral, central, or a combination of both. A wide range of therapies for vulvodynia have been proposed that include topical therapies, pharmacologic regimens, physical therapy, surgery, and cognitive-behavioral therapy.[56] However, outcomes with these therapies vary widely. For example, as a commonly reported therapy for localized vestibular dysesthesia, vestibulectomy is most effective for a specific subset of patients, specifically for women below 30 years of age who have localized vulvar pain and provoked pain.[57,58] These findings suggest that it is possible that this type of pain represents a localized nociceptor mechanism, whereas unprovoked and generalized pain could have a different mechanism. Our data suggest that women with vulvar pain for long duration or with unprovoked pain have more CNS involvement or dysregulation. The CNS involvement occur de novo (eg, genetic polymorphism) or secondary to an intractable pain state; the latter is the likely mechanism by which women with provoked vulvodynia transition into unprovoked or chronic pain state. It is well documented that an intractable peripheral process can lead to neuroplastic changes (through central sensitization) at all levels of the CNS and "generalization of pain."[59]

The findings in this study are consistent with the idea that chronic pain, caused by vulvodynia, alters central sensitization that leads to changes in sensory information processing. These changes are manifested in lower sensory thresholds (or higher sensitivity) in sites without provoked pain—because of a change in the balance between excitation and inhibition (or glutamatergic and gabaergic neurotransmission). Lower thresholds are consistent with this imbalance; decreasing inhibition will result in less suppression of cortical activity. In other words, a simple stimulus on the skin will generate more cortical activity if altered central sensitization has resulted in decreased inhibition or increased excitation. However, threshold testing has not been considered as an efficient method in measuring altered central sensitization because of large inter-individual variability. And to show these small differences, group differences of repeated measurements are normally necessary. Alternatively, using a measure—such as an adaptation metric—in which the patient provides their own individual baseline (ie, the adaptation metric is derived on how amplitude discriminative capacity is impacted by conditioning)—could prove to be a more effective indicator of altered central sensitization that can be obtained reliably and efficiently (protocols used in this study can be obtained within 2 to 3 min). Sensory-based measures of altered central sensitization seem to differentiate chronicity within subgroups of vulvodynia, and future studies will continue to investigate the changes in sensitization that seem to occur with the time course of the history of vulvodynia.

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