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Vibrotactile perception in Dupuytren disease

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ABSTRACT

Purpose: Dupuytren disease (DD) has been associated with enlarged Pacinian corpuscles (PCs) and with PCs having a greater number of lamellae. Based on these associations, we hypothesized that subjects with DD would have altered sensitivity to high-frequency vibrations and that the changes would be more prominent at 250 Hz, where healthy subjects demonstrate the highest sensitivity.

Methods: A novel device was created to deliver vibrations of specific frequencies and amplitudes to the fingers and palm. Using a Psi-marginal adaptive algorithm, vibrotactile perception thresholds (VPTs) were determined in 36 subjects with DD and 74 subjects without DD. Experiments were performed at 250 Hz and 500 Hz at the fingertip and palm. The VPTs were statistically analyzed with respect to disease status, age, gender, location tested, and frequency tested.

Results: We found that VPT increases with age, which agrees with findings by others. Women showed greater sensitivity (i.e. lower VPT) than men. Men exhibited lower sensitivity in DD versus healthy subjects, but the results were not statistically significant. In subjects with DD presenting unilaterally, the unaffected hand was more sensitive than the affected hand, in particular for a 250 Hz stimulus applied to the finger.

Conclusions: The data on vibration sensitivity obtained from a large group of subjects with and without DD present interesting trends that may serve as a useful reference to future DD researchers. Understanding additional symptoms of DD may facilitate development of novel diagnostic or prognostic protocols.

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1. Introduction

Dupuytren disease (DD) is a progressive fibroproliferative disorder of the palmar fascia with characteristic nodules and cords. Its incidence has been estimated at approximately 3 cases per 10,000 adults [1], with higher prevalence in individuals of Scandinavian descent [2]. Fibroblasts proliferate and differentiate into myofibroblasts, which produce collagen and exhibit higher contractility, leading to progressive shortening and contraction of the cords [3]. The disease usually presents clinically after age 50, and the ring finger is most commonly affected [2]. Progression of DD is divided into three grades: Grade 1 has a thickened nodule and/or band in the palmar aponeurosis but no discernable contracture; Grade 2 presents as permanent contracture with flexion angle less than 60°; and Grade 3 has flexion greater than 60° [4]. The progression is highly variable and unpredictable [5]. The etiology is unknown, and, although there is a strong genetic component, there is currently no genetic test for DD [3]. Available treatments include fasciectomy [6], needle aponeurotomy [7], collagenase injections [8], and radiation [9].

Patients with DD have been found to exhibit structural changes in the Pacinian corpuscles (PCs) of the affected tissue [10–14]. As cutaneous mechanoreceptors in the deep dermis and subcutaneous tissue, PCs are sensitive to pressure changes and vibration in the frequency range of 20–1000 Hz [15]. Structurally, PCs consist of concentric lamellae surrounding an RA II nerve ending [16]; this structure acts as a high-pass filter and enables high sensitivity to vibrational stimuli via interconnected collagen fibers [15,16]. Ehremantant et al. reported that PCs from subjects with

DD exhibited larger size and more numerous lamellae. The mean area of PCs from non-DD subjects was $1.0 \pm 0.5 \text{ mm}^2$, whereas the mean area of the PCs from subjects with DD was $2.6 \pm 0.4 \text{ mm}^2$ ($p \leq 0.001$); the number of layers increased from 40 ± 9 in subjects without DD to 64 ± 14 ($p \leq 0.01$) [12]. Given the PC's role in vibrotactile sensing, one may ask whether the structural changes associate with perception changes.

To estimate the effect of the more lamellated and larger PCs, the frequency of peak sensitivity was calculated based on our previous theoretical analysis [17]. Using a lamellar modulus of 1 kPa [18,19], interlamellar fluid viscosity of 1.4 mPa·s [18,20], lamellar thickness of 0.35 μm , outer radii of 0.56 mm and 0.91 mm [12], and number of lamellae of 40 and 64 for healthy PCs and DD-associated PCs, respectively [12], we calculated a peak frequency of 264 Hz for healthy PCs and of 833 Hz for those with DD. In the same model, increasing the number of lamellae causes a decrease in overall threshold amplitude [17]. Based on those estimates, we hypothesized that subjects with DD would have reduced sensitivity, or higher VPT, at the affected fingers/palms compared to healthy controls and that the reduced vibrosensitivity in the subjects with DD to be more prominent at 250 Hz, where the healthy subjects are the most sensitive. Vibrotactile perception thresholds (VPT) have been studied in the healthy population [21,22] and have been used to evaluate clinical neurology [23–25], but the vibrotactile sensitivity of people with DD has not yet been investigated. Therefore, we conducted a study comparing VPT in healthy subjects versus DD patients under different stimulus frequencies and locations.

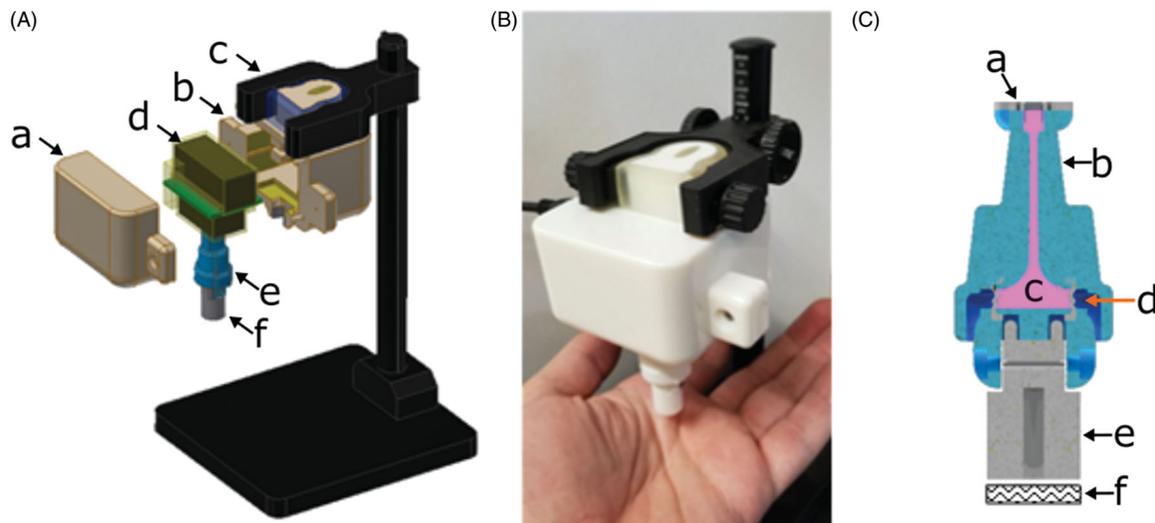


Figure 1. The probe used to measure vibrosensitivity. (A) Schematic design of the pneumatic force sensor: a the front cover, b the back cover, c the adjustable boom, d electronics, e pneumatic force sensor, f piezo holder. (B) Testing the fabricated device on a palm. (C) The force sensor's structure: a the location of the barometer, b the solid body, c compressed air in empty chamber, d the deformable area, e the piezo holder, f the piezo.

2. Materials and method

2.1. Patient selection

All the patients gave informed consent before the experiment and gave consent to publish the data. Vibration sensitivity was measured in 74 healthy volunteers and 36 subjects diagnosed with DD. Most of the healthy subjects were tested at the Driven to Discover Research Facility at the 2018 Minnesota State Fair. With assistance from the Fairview Research Administration, the majority of the subjects with DD were identified as recent patients (seen within 3 years) of the University of Minnesota or Fairview Clinics, aged between 60 and 70 years old and having a diagnosis of DD at any stage. Subjects with Raynaud's disease, peripheral neuropathy, or diabetic neuropathy were eliminated because they were expected to have non-Dupuytren-related lack of sensitivity. Although subjects were asked to record their use of vibrating power tools, there was confusion (e.g. some subjects considered an electric toothbrush a power tool whereas others only considered large machinery like jackhammers); therefore, data concerning exposure to vibration were included in neither eligibility criteria nor analysis. Most subjects (80%) reported never or rarely (once per month or less) using vibrating power tools. Subjects were recruited via letters and tested at the University of Minnesota in a private conference room. The experiments were IRB-approved (IDs: 1605M87741 and STUDY00002660) and were performed under IRB guidelines by a CITI-trained investigator.

2.2. Experimental device

The oscillating force probe used to measure palm/finger sensitivity at various frequencies is shown in Figure 1. Vibrotactile stimuli were delivered with an 8.9 mm diameter piezoelectric disk bender (American Piezo 20-1330, American Piezo Ceramics Inc., Mackeyville, PA) wired to a digital-to-analog signal generator (Syscomp WGM-201 or CGR-201, Syscomp Electronic Design Ltd, Ontario, Canada) and amplification system (Gemini XGA-3000, Nevada, NJ). The piezo probe did not have a surround. The piezos were characterized under no load with a vibrometer controller and fiber interferometer (Polytec, OFV-2500/OFV-352, Irvine, CA) and produced distortion-free sinusoids of the input frequency. The noise from the nearby fan of the amplifier overwhelmed the

sound from the piezo probe such that frequencies under 600 Hz could not be heard from more than 10 cm away. In addition, the environmental noise, especially at the fairground, was much greater than that of the piezo. For these reasons, hearing protection was not worn by subjects in this study. The normal force applied to the palm/finger needed to be standardized for all subjects because the sensitivity depends not only on the oscillation frequency and amplitude but also on the static normal force used during the application, and internal comparison of VPTs could be more accurate with the variable of force removed. The normal force was, therefore, measured and displayed during the device operation so that it could be maintained at a desired value by the experimenter manually adjusting the stand. The normal force was measured via the pressure inside a chamber whose volume changes with applied force. As seen in Figure 1(C), the deformable portion of the device compresses the deformable area, resulting in a change in the pressure in the chamber. The pressure inside the chamber was measured in real-time using the barometer chip LPS25HB. The barometer chip had a sensitivity of 0.01 mbar, leading to the overall device having a sensitivity of 0.0154 (N/mbar) and a high resolution of 1.5×10^{-4} N in terms of force measurement. The pressure sensor and the vibrating piezo were both controlled via an in-house code. The device was designed in Autodesk Inventor and fabricated using the Stratasys J750 PolyJet 3D printer (14 μ m layer accuracy). The flexible part of the probe that deformed to compress the entrapped air inside was made of Agilius Clear (Shore 60A), and the hard body of the probe was made of Vero White.

2.3. Experimental study design

The building at the Minnesota State Fair was open-air and did not have air-conditioning, so the temperature varied. The subject was seated and placed his or her hand/finger in the device under the vibrating probe with his or her arm comfortably supported. The hand was tested at the center volar pulp (fingertip) and the distal palmar flexion crease (palm) (Figure 2). The testing locations were selected because changes in the PC associated with DD were found around the nodules and cords and because VPT measurements are commonly conducted in fingertips. The vibrating probe was lowered on the adjustable boom until the force sensor

reached 0.5 N. After the device was in place, the subject received instructions through a graphical user interface (GUI) on a tablet computer and gave all responses via the computer's touchscreen; the examiner remained present to adjust the sensor as needed and to aid in transitioning between the locations tested. There were two locations tested – fingertip and palm – and two frequencies tested – 250 Hz and 500 Hz. Based on the differences in peak frequencies discussed earlier, we selected to test at 250 Hz, where healthy subjects were expected to be most sensitive, and at 500 Hz, which was high enough for an effect without causing the piezo to produce audible sounds. The order of locations was the subject's choice, and the order of the frequencies was selected randomly. At each frequency, the subject was presented with a continuous stimulus and asked whether s/he felt the vibration. Amplitudes were adjusted according to a psi-marginal adaptive algorithm [26,27] in which the amplitude of each stimulus was increased or decreased based on the responses already received to produce a rapid estimate of the VPT. Each frequency was tested with 30 individual trials (Figure 3), and the time between trials was

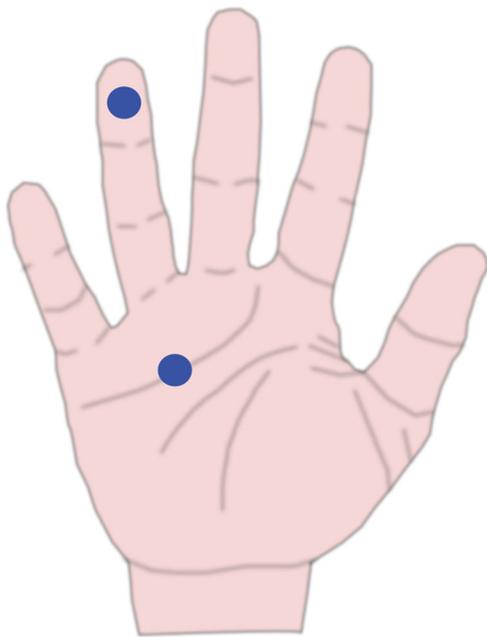


Figure 2. Hands were tested at the distal palmar flexion crease and the center volar pulp.

randomly distributed between 0.5 and 2 s. Before recording the responses, there were four practice trials where the stimulus was either at the maximum vibration amplitude ($10\ \mu\text{m}$) or not vibrating; during this practice phase, the subject was told of the stimuli on the GUI and, in most cases, verbally by the examiner to confirm that the subject understood the experiment. The subject could redo the four practice trials if desired.

Subjects were seated for approximately 3 min while completing the pre-experiment survey, then their hand/finger was in the device for about a minute for the practice trials. Upon changing to another location of the palm/fingertip, the recorded data started immediately or after a pause to rest; the practice trials were not repeated unless the subject selected to do so. Including completing the consent form and a brief explanation of their results by the examiner, the entire procedure took 15 min for healthy subjects, who were only tested on their dominant hand. Subjects with DD who came to the University of Minnesota were tested on both hands and, in many cases, multiple fingers; the experiment took an average of one hour with several breaks to rest and to discuss their medical history with respect to DD. Preliminary studies indicated that continuous measurements for longer than 20 min may affect the thresholds, so there were mandatory breaks every 10 or 15 min for the subjects who were tested on multiple hands or fingers. Although testing additional frequencies or locations would provide useful and novel data, the study was limited so as to prevent subject fatigue.

The amplitudes and responses for each trial were recorded, and the psi-marginal adaptive algorithm calculated a final threshold and standard error value. The majority of the data gave a clear threshold value as in Figure 3(A) and were used for analysis without adjustment; there were, however, three scenarios that were deemed failures and eliminated or required additional analysis. The first failure case occurred when the subject selected that they could feel the vibration for two or more trials when the amplitude was zero, i.e. no vibration was present (Figure 4(A)); this was likely due to the subject misunderstanding the experimental question or due to the subject misreading the response buttons. This case occurred in 5.3% (27/508) of the measurements, and this occurrence drastically decreased when the experimenter verbally provided instructions for the initial practice trials. The second failure case occurred when the final standard error of the threshold was greater than $4\ \mu\text{m}$ (Figure 4(B)); this happened in 3.7% (21/508) of the measurements and was likely due to the subject moving during the experiment and re-positioning the probe at a different location, due to the subject becoming distracted during the course of the experiment, or due to the subject

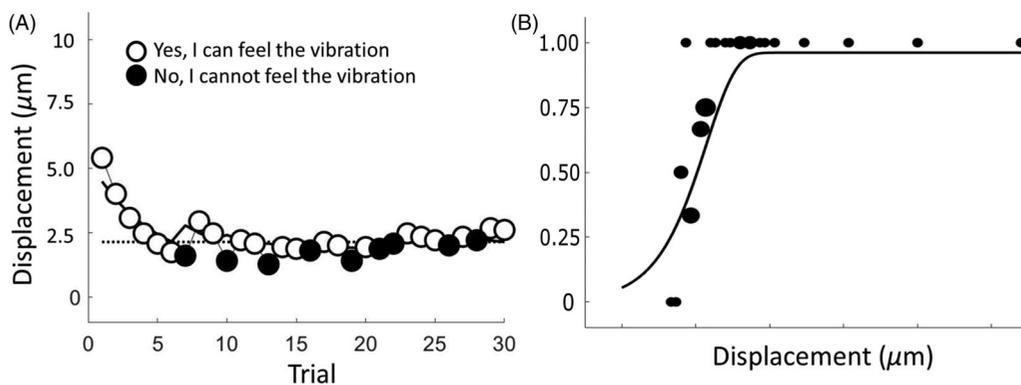


Figure 3. Examples of responses with the Psi-marginal adaptive method. (A) Example stimulus and responses. The open circles show where the subject selected that he or she could feel the vibration for each of the 30 trials. The filled circles indicate where the subject selected that they could not feel the vibration. The dotted line is the final threshold value calculated with the psi-marginal adaptive method. (B) The dots indicate the likelihood of the same subject's response. A value of 1 corresponds to "Yes, I can feel the vibration" whereas 0 corresponds to "No." The size of the dot correlates to the number of individual trials at that amplitude. The line is the best-fitting Weibull probability function.

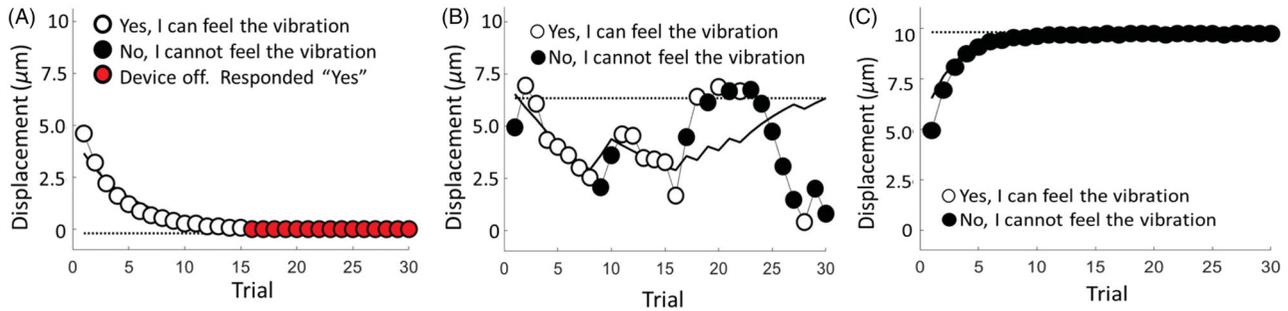


Figure 4. Examples of failed and censored experiments. (A) The subject selected that he or she could feel the vibration when the device was off and not vibrating. (B) The calculated error in the threshold was greater than 4 µm. (C) The subject could not feel the vibration.

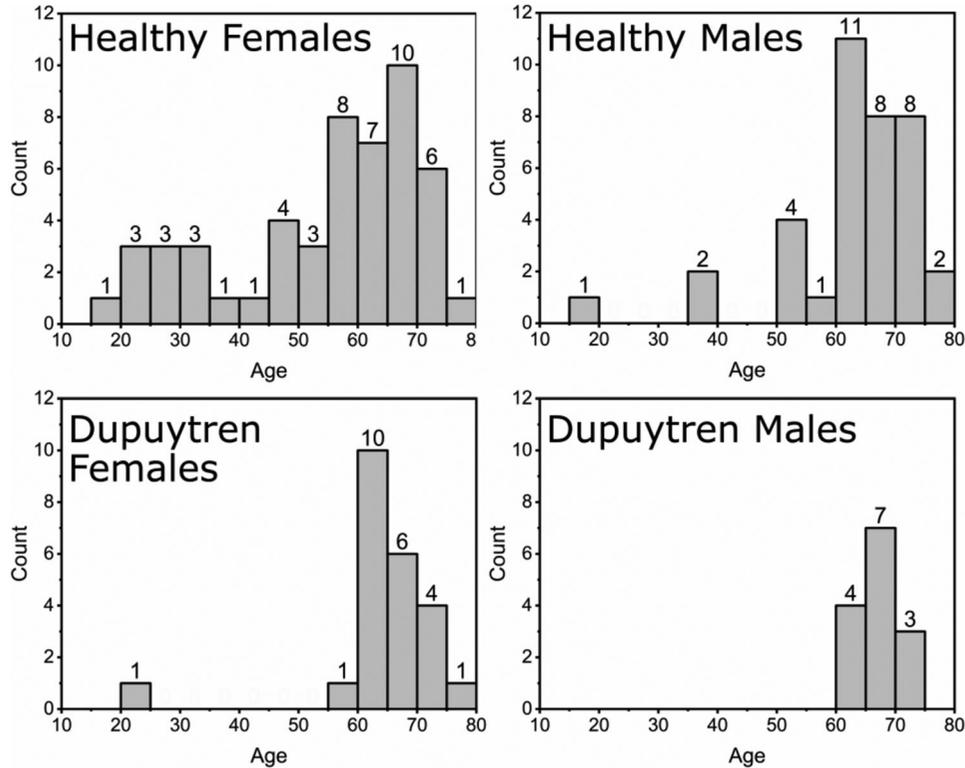


Figure 5. Histograms of the age distribution of all subjects.

not selecting the true response. The third failure was the inability to sense the vibrations at the maximum amplitude (Figure 4(c)). Data associated with the first and second cases of failure were eliminated from further analysis; data associated with the subject’s inability to sense the vibration at maximum amplitude were treated as right-censored data and recorded as an amplitude of 10 µm.

2.4. Statistical analysis

The data were manually sorted to eliminate the tests that were deemed failures. There were some data from subjects with DD on their non-clinically presenting hands (e.g. they had a cord on their right ring finger but their left hand appeared unaffected by DD); these data were temporarily removed from the larger analysis and analyzed separately. The remaining data were grouped by gender and DD status (data provided in the repository). The mean VPT was calculated on a log-normal scale with an in-house code applying a tobit model that accounted for the censored thresholds. The model calculated a linear regression of the log of the

VPT with respect to age for the healthy subjects. Additionally, the mean VPT from subjects over 50 years old was calculated for data from subjects with and without DD. A multivariate ANOVA was performed to determine the effects of the four groups: location (fingertip versus palm), frequency (250 Hz versus 500 Hz), gender (male versus female), and DD status (non-DD versus clinically presenting DD). Ad hoc T-tests with Bonferroni correction were performed for each comparison with an in-house code. For the subjects who had DD and were additionally tested on their non-clinically presenting hands, a one-way repeated measures ANOVA was calculated [28] and the difference in VPT was determined with paired T-tests using the standard deviation from the psi-marginal algorithm. All statistical comparisons were made with two-tailed tests.

3. Results

The dataset included 36 cases (14 male and 22 female) of DD and 74 cases (31 male and 43 female) of controls. The age distribution for the different groups is provided in Figure 5. The thresholds

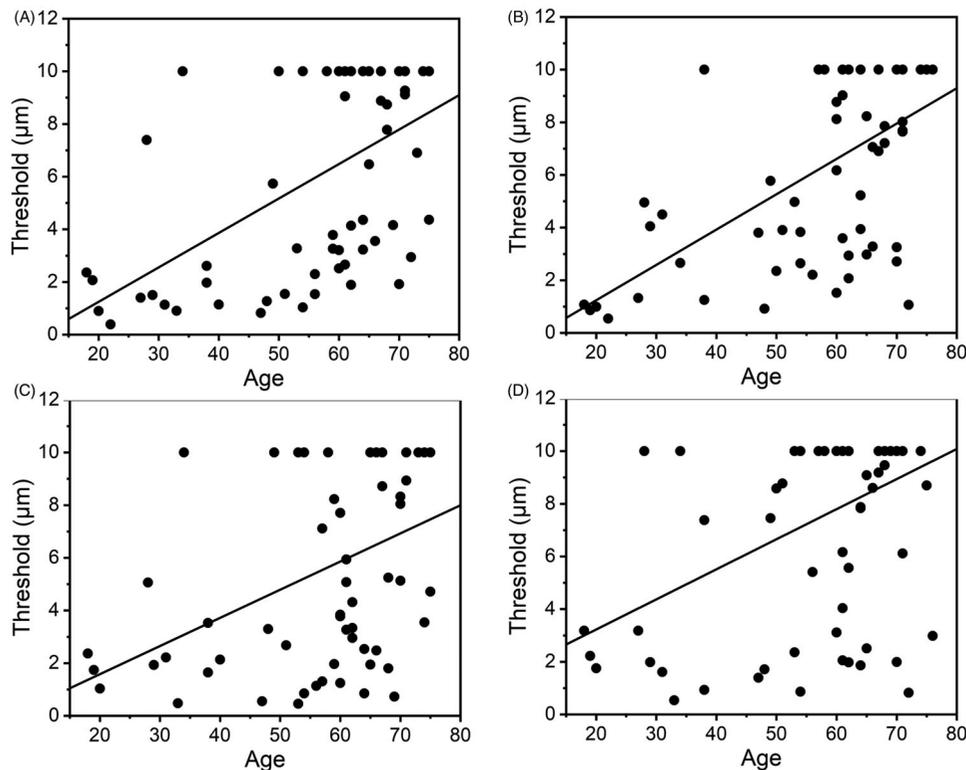


Figure 6. Threshold data for healthy subjects at (A) all ages at 250 Hz at the fingertip, (B) 250 Hz at the palm, (C) 500 Hz at the fingertip, and (D) 500 Hz at the palm. The lines were calculated by tobit analysis.

fits for the data from healthy subjects are shown in Figure 6. The slope of the tobit fits for healthy subjects are similar for both frequencies and both locations, and the VPT increases with age.

The individual VPTs and fits are provided in Figure 7. The mean and standard error of the data for subjects above age 50 separated by gender and DD status are shown in Figure 8. When the data were analyzed by ANOVA, no effect (disease status, frequency, locations, or gender) had a significant influence on VPT for either the ring finger only ($F(15,247) = 0.81, p = 0.67$) or for all the fingers combined ($F(15,344) = 1.09, p = 0.36$). When each effect was investigated separately in T-tests, gender affected the VPT ($p_{\text{gender, ring}} = 0.08, p_{\text{gender, all}} = 0.04$), but no other group had a significant effect (all other $p > 0.1$). The differences in gender are visible in Figure 8 and appear to be exaggerated in the DD subjects.

The paired VPT of subjects with unilaterally clinically-presenting DD are shown in Figure 9. The hand with DD is less sensitive than the unaffected hand for 250 Hz on the fingertip ($F(1,16) = 6.29, p_{250 \text{ Hz, fingertip}} = 0.037$), but the trend is less consistent for the other frequencies and locations ($H(1,16) = 0.35, p_{250 \text{ Hz, palm}} = 0.35, F(1,14) = 0.56, p_{500 \text{ Hz, fingertip}} = 0.48, F(1,16) = 0.028, p_{500 \text{ Hz, palm}} = 0.87$).

4. Discussion

In this study, we tested whether subjects with DD have reduced and/or shifted vibrosensitivity at the location of the affected fingers and palms compared to healthy controls. We also investigated the effects of age and gender. Our key findings are as follows:

- As found previously by others [22,25,29,30], VPT increased with age.
- Women showed greater sensitivity (i.e. lower VPT) than men ($p_{\text{gender, ring}} = 0.08, p_{\text{gender, all}} = 0.04$).

- Men exhibited lower sensitivity (i.e. higher VPT) in DD versus healthy subjects, but the results were not statistically significant ($p_{\text{male, ring}} > 0.4, p_{\text{male, all}} > 0.15$).
- In subjects with DD presenting unilaterally, the unaffected hand was more sensitive than the affected hand, in particular for a 250 Hz stimulus applied to the fingertip ($p_{250 \text{ Hz, fingertip}} = 0.037$).

These results are discussed in further detail below.

The VPT of healthy subjects decreased with age at all frequencies and locations tested (Figure 6). This result is consistent with previous studies [22,25,29,30]. The reduced sensitivity is believed to be caused by degenerative changes in PCs (e.g. demyelination) as well as changes in the central nervous system with age.

The measured VPTs were different between men and women with women in the same age range showing greater sensitivity to vibration (Figures 7 and 8). A sensitivity difference with gender was reported by Peters et al. [31] and explained by women having smaller fingers and, therefore, a higher density of a related mechanoreceptor, the Meissner corpuscle, although Peters et al. tested passive spatial tactile acuity and not vibration sensing. As shown in Figures 7 and 8, the male subjects with DD exhibited slightly lower vibrosensitivity than the healthy controls under all conditions except 500 Hz at the palm, yet this effect fell within acceptable error.

The study focused on the typical range of the PC because its structure is known to be affected by DD [10–14], and we expected a shift in the sensitivity due to the structural changes, but additional changes within the sensory neuron may also occur, which may affect perception. There were no significant changes between subjects with and without DD, although men with DD had slightly lower sensitivity than men without DD. Our failure to observe significant changes with respect to DD may be due to a combination of the limited number of individual subjects and the

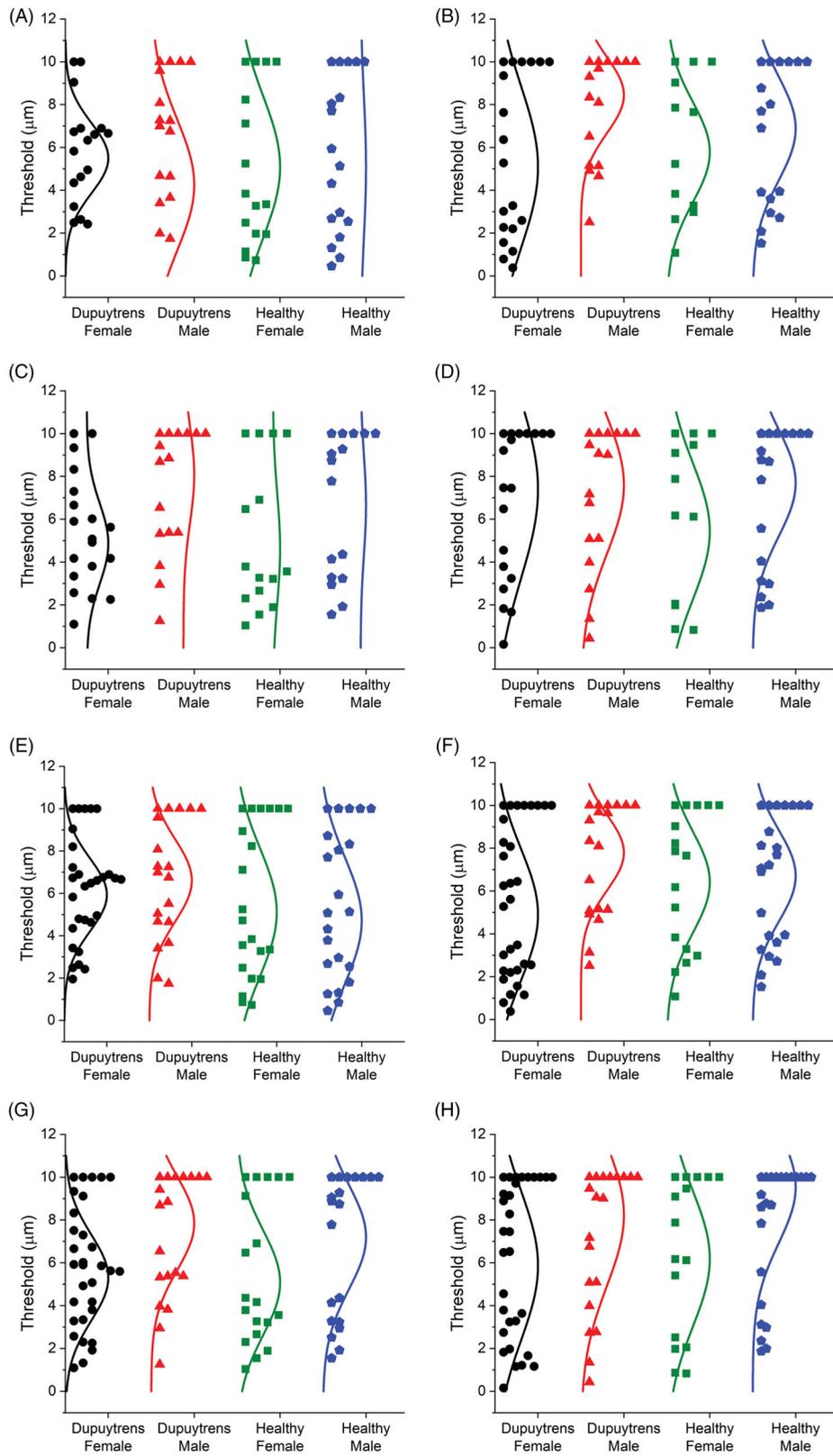


Figure 7. Thresholds of subjects over 50years old for the ring finger only at 250 Hz at the fingertip, (B) 250 Hz at the palm, (C) 500 Hz at the fingertip, (D) 500 Hz at the palm, and (E) for all the fingers combined at 250 Hz at the fingertip, (F) 250 Hz at the palm, (G) 500 Hz at the fingertip, and (H) 500 Hz at the palm.

presence of four independent variables (comparing the effects of gender, frequency, location, and DD status). Tests on additional frequencies, including stimuli that target other mechanoreceptors, could be informative, but the scope of this study was limited to minimize subject fatigue.

The maximum vibration of the system, 10 μm , was the same for both 250 Hz and 500 Hz; the input voltage was directly proportional to the piezo displacement. Therefore, we selected to use displacement as the VPT measurement. The maximum values of the device were 148 dB and 160 dB for 250 Hz and 500 Hz,

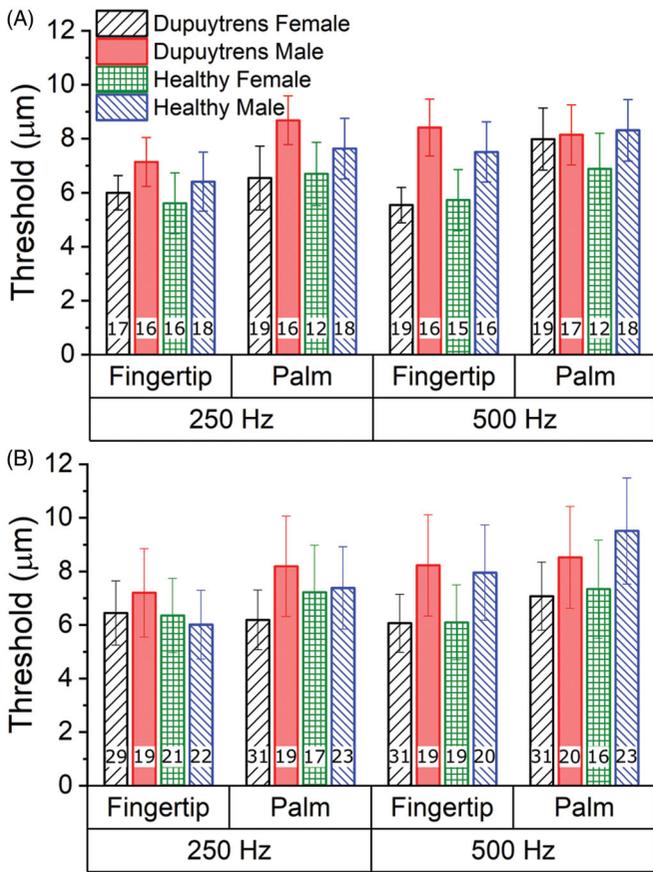


Figure 8. Threshold and standard error values (A) for the ring finger and (B) for any finger.

respectively. The mean VPTs for both subjects with and without DD were higher than those of the same frequencies previously reported, which were between 0.1 µm and 1 µm for subjects with a mean age between 30 and 40 years old [21,24]. Despite higher amplitudes than those commonly tested, approximately 20% of the subjects could not feel the vibration at the maximum value. These higher-than-expected VPTs may be due to the larger diameter of the device, lack of surround of the probe, lower force of the probe, use of a disc bender as the stimulation source, or older mean subject age. Given the differences in devices and methods from standards and previously published results, this study was intended for internal comparisons.

A notable feature of all our experiments was the very wide scatter of the data. Individual experiments were reproducible and gave small error estimates, but the population showed considerable variability. This variation is not surprising given the many factors that could confound the experiment, discussed in the following paragraph, but it presents a considerable challenge. The observable trend in the paired study versus the cross-sectional study emphasizes the importance of individual variability and suggests that a longitudinal study could be more informative.

First, we consider variability arising from our testing system. The force applied to the finger/hand by the probe was maintained at 0.5 N, but variations in individual finger dimensions, fat versus muscle content, and tissue stiffness could all affect that force and vibration sensing differently, leading to variation in the measured result. The piezo probes providing the stimulus had nodes such that the displacement was not necessarily distributed evenly across the entire probe. Also, although our probe was fairly large (8.9 mm diameter) and, thus, was expected to fall within the receptive fields of many PCs [32], the vibrational signal attenuates through the skin [33,34], so the exact location of the

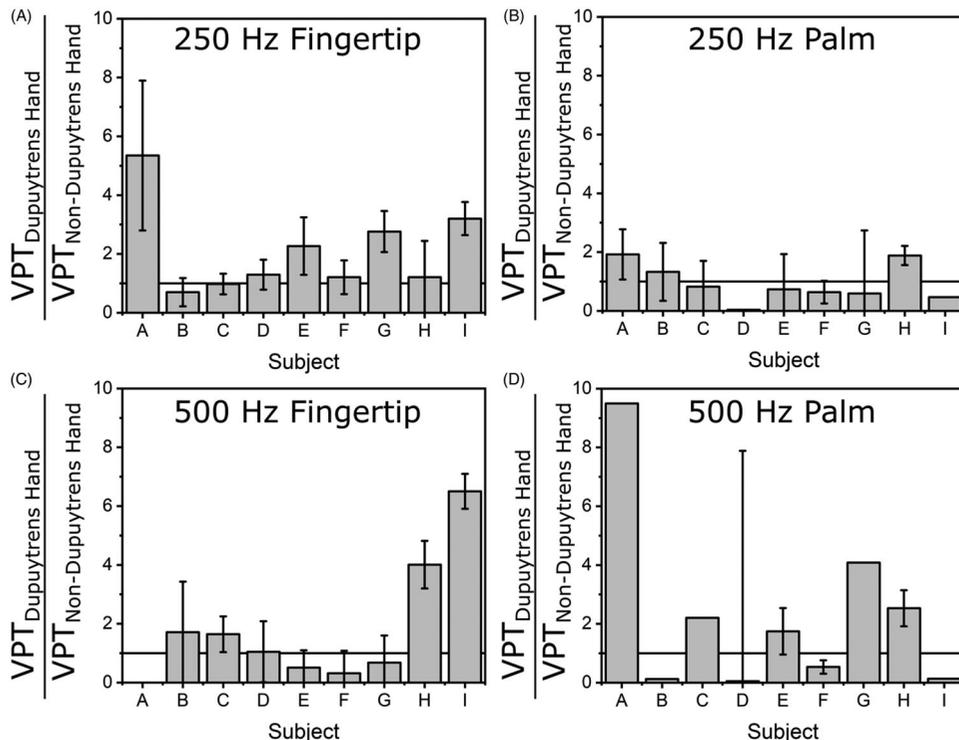


Figure 9. Paired data for each subject with the ratio of the VPT of the Dupuytren hand against the hand that does not have clinically-presenting DD. The threshold and relative standard deviations for separate subjects A-I are shown for (A) 250 Hz fingertip, (B) 250 Hz palm, (C) 500 Hz fingertip, and (D) 500 Hz palm. A value greater than 1 indicates a relative lack of sensitivity in the affected hand.

PCs within the finger or hand being tested – which is obviously unknowable – would affect the measured sensitivity. Finally, it is noted that within an individual, there is wide variation in PC properties [35], which would also lead to more variability in our measurements.

The individual subjects who had clinically presenting unilaterally DD exhibited higher VPTs at 250 Hz on the fingertip. However, the trend did not continue at the other frequencies and locations (Figure 9); a few subjects showed VPT trends opposite from what was expected (e.g. 3 of the 9 had lower VPTs in their DD hand at 250 Hz on the palm), and there were some large discrepancies (e.g. several of the subjects could not feel the 500 Hz vibration on their palm with either hand). It is possible that the PCs on the subjects' affected hand are not different from the other hand, or, conversely, it is possible that the subjects have enlarged PCs on both hands but have not yet developed nodules or cords on their non-clinically presenting hand. A longitudinal study is needed for more definite conclusions.

There are several factors for which this study does not account but which may affect the vibrosensitivity. First, the subjects had different stages of DD; some subjects had minor nodules on a single finger (stage I) whereas others had contracture greater than 90° on several fingers (grade III). Second, the subjects had different treatments; some subjects had surgery or collagenase injections to one or multiple fingers. Third, some subjects had particularly aggressive forms of DD; there is currently no measurement of aggressiveness in DD, yet some subjects claimed that they had surgery and the cords and contracture returned within months whereas other subjects stated they have not noticed a change since diagnosis. Finally, although any volunteers who stated that they have peripheral nerve disorders were eliminated from the study, it is possible that there were subjects with undiagnosed neuropathy. It is possible that the PC growth, and, therefore, subsequent changes in vibrosensitivity, may be related to the stage, treatment, or aggressiveness of DD. For subjects without DD, the VPTs can be affected by the subject's health and habits (e.g. smoking or alcohol use), ethnicity, and profession. A longitudinal study would be required to investigate these effects.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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