Continuum of somatosensory profiles in breast cancer survivors with and without pain, compared to healthy controls and patients with fibromyalgia

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Running head: Somatosensory profiles in breast cancer survivors

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Abstract

Context:

The prevalence of persistent pain among breast cancer survivors (BCS) is high, and it is unclear what distinguishes those with persistent pain from those without. Research suggests that differences in somatosensory function evaluated by quantitative sensory testing (QST) may be responsible.

Objectives:

This study aimed to describe somatosensory profiles in terms of hyper- and hypoesthesia in BCS with and without persistent pain using reference data from healthy controls. Second, QST parameters of BCS with and without pain were compared with those of healthy controls (i.e., a negative control group) and patients with fibromyalgia (i.e., a positive control group).

Methods:

Participants (n=128) were divided into four equal groups: healthy controls, BCS with persistent pain, BCS without persistent pain, and patients with fibromyalgia. Nine QST parameters were evaluated at the trunk and at a remote location. Somatosensory profiles were determined by Z-score transformation of QST data using normative data from healthy controls.

Results:

At the trunk, compared to healthy controls, BCS with persistent pain exhibited sensory aberrations across five out of seven QST parameters: pressure pain threshold, mechanical detection and thermal thresholds. Pain-free BCS showed similar sensory aberrations across the four QST parameters compared to healthy controls: mechanical detection and thermal thresholds. Temporal summation and conditioned pain modulation were not significantly different between groups.

Conclusion:

BCS with persistent pain exert aberrations in peripheral processing of nociceptive signals, heightened facilitation of nociceptive signals and higher psychosocial burden when compared to pain-free BCS, healthy controls and patients with fibromyalgia.

Key words: Cancer-related pain, breast cancer, conditioned pain modulation, temporal summation

Significance

This study investigates the somatosensory function of breast cancer survivors with and without persistent pain using quantitative sensory testing and two control group (i.e., patients with fibromyalgia and healthy controls). Our results indicate somatosensory aberrations within the peripheral, but not central pathways in breast cancer survivors with persistent pain. Our findings contribute to a better understanding of the somatosensory mechanisms underlying persistent pain, which may inform future interventions to prevent the development of persistent pain, and improve treatment modalities.

Introduction

Approximately 30% of breast cancer survivors (BCS) experience persistent pain of mild to moderate intensity after finishing primary cancer treatments.(Belfer et al., 2013; Schreiber et al., 2014) Persistent pain is known to negatively impact emotional and physical functioning and quality of life in this population.(Gallaway et al., 2020)

It is still unclear why some BCS experience pain while others do not. It has been proposed that BCS with persistent pain exhibit impairments in nociceptive processing within the somatosensory nervous system.(Andersen et al., 2017; Edwards et al., 2013; Fernández-Lao et al., 2011; Gottrup et al., 2000; Mustonen et al., 2020; Schreiber et al., 2013; Vilholm et al., 2009)

Quantitative sensory testing (QST) can be used to evaluate the somatosensory function of the peripheral and central nervous system by assessing hyper- or hypoesthesia in response to standardized stimuli.(Mücke et al., 2021; Rolke et al., 2006) Hyperesthesia is defined as an increase in sensitivity to stimulation, whereas hypoesthesia is defined as a decrease in sensitivity to stimulation. So far, a number of studies have investigated somatosensory functioning in BCS with persistent pain after breast cancer surgery. In general, these studies showed the presence of hypoesthesia(Andersen et al., 2017; Gottrup et al., 2000; Mustonen et al., 2020), and hyperesthesia (hyperalgesia, allodynia) in the treated area and remote areas in comparison to pain-free BCS (Edwards et al., 2013; Gottrup et al., 2000; Schreiber et al., 2013; Vilholm et al., 2009) and healthy controls.(Fernández-Lao et al., 2011; Mustonen et al., 2020) Hypoesthesia was mainly present for the detection of thermal and mechanical stimuli locally, whereas hyperesthesia was found for pressure pain thresholds (PPTs) locally and remotely. In addition, aberrations in dynamic QST paradigms were found (e.g., decreased conditioned pain modulation (CPM) and exaggerated temporal summation of pain (TSP)).(Edwards et al., 2013; Gottrup et al., 2000; Schreiber et al., 2013; Vilholm et al., 2009) Unfortunately, studies either lacked a healthy control group (Edwards et al., 2013; Gottrup et al., 2000; Schreiber et al., 2013; Vilholm et al., 2009) or a control group consisting of pain-free BCS, limiting general conclusions.(Fernández-Lao et al., 2011; Mustonen et al., 2020) Furthermore, previous studies never used a control group with evidence of enhanced central processing of nociceptive signals.(O'Brien et al., 2018; Tampin et al., 2012) Patients with fibromyalgia are known to exhibit enhanced nociceptive sensitivity, as evidenced by impairments in the inhibitory descending pathways or heightened facilitation of endogenous nociceptive pathways.(O'Brien et al., 2018) Additionally, these patients demonstrate local hyperesthesia in PPTs, thermal and mechanical pain thresholds.(O'Brien et al., 2018; Staud et al., 2021; Tampin et al., 2012) Patients with fibromyalgia are considered a positive control group while healthy individuals are considered a negative control group.(Tampin et al., 2012)

The goal of this study is to compare QST data, describe the somatosensory profiles of BCS with and without persistent pain, and compare them with the somatosensory profiles of patients with fibromyalgia and healthy controls. We hypothesized that BCS with persistent pain will show hypoesthesia for the detection of thermal and mechanical stimuli in the area of breast cancer treatment, and hyperesthesia in PPT locally and remotely compared to healthy controls.

Methods and materials

Participants were recruited between May 2020 and December 2022 as part of a larger cross-sectional study at the University of Leuven and University of Antwerp. This larger study investigated different pain mechanisms using different assessment methods in cancer survivors with pain (clinicaltrail.gov: NCT03981809) and received approval from the Ethical Committee of the University Hospitals Leuven (s62584) and the University Hospital of Antwerp (B322201940289). Participants were recruited consecutively from the larger study and provided written informed consent prior to enrollment. The study is reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.(von Elm et al., 2008)

Participants

First, a group of BCS with persistent pain was recruited with the following inclusion criteria: (1) ≥ 18 years, (2) completed primary treatment for primary breast cancer at least three months ago, and (3) complete remission. Ongoing hormonal treatment and targeted immunotherapy were permitted. BCS experiencing persistent pain needed to report mean pain intensity during activity ≥ 3/10 on the numeric rating scale (NRS) during the past week with 0 meaning no pain and 10 being the worst pain imaginable.(Belfer et al., 2013; Kaur et al., 2021) The NRS was conducted via telephone prior to inclusion. BCS experiencing persistent pain related to the treatment of breast cancer were recruited via the oncology department of the University Hospitals Leuven and University Hospital Antwerp (Belgium), as well as national and local cancer survivorship organizations. Persistent pain related to the treatment of breast cancer was defined based on its location and timing of onset. Pain in the area of breast or axillary surgery, area of radiation therapy, or the shoulder and upper limb was considered to be related to breast cancer treatment if it occurred concurrently or after its completion.

Second, a group of BCS without pain was recruited. The same inclusion criteria were used. In addition, they did not report a mean pain intensity during activity of ≥ 3/10 on the NRS during the past week. Pain-free BCS were recruited via national and local cancer survivorship organizations and via the research database of the Department of Rehabilitation Sciences of the KU Leuven, University of Leuven.

Third, patients with fibromyalgia were recruited. Patients with fibromyalgia were diagnosed by rheumatologists, rehabilitation physicians, or pain physicians and had painful symptoms for at least three months. Subsequently and prior to participating, patients with fibromyalgia were screened using the 2010 American College of Rheumatology (ACR) criteria.(Wolfe et al., 2010) Patients with

fibromyalgia were recruited via patient organizations, the Center for Algology and Pain Management of the University Hospitals Leuven, and the Pain Center of the University Hospital Antwerp.

Fourth, a reference group with healthy female controls was included if they did not have a history of cancer and no mean pain intensity during activity of ≥ 3/10 on the NRS during the past week. Healthy controls were recruited via local organizations and peers at the University Hospitals Leuven, KU Leuven, and University of Antwerp.

For all groups, participants were excluded if they had (1) any active metastasis, (2) a palliative status, (3) recurrence of cancer, (4) bilateral cancer, (5) pregnancy or breastfeeding, (6) inability to speak and read Dutch, and (7) physical and mental inability to complete the assessment.

Data collection

The following descriptive data for all participants were obtained via questionnaires: age, body mass index, hand dominance, and analgesic use. Data on breast cancer treatment were obtained via questionnaires and by consulting the electronic health records: type of breast surgery and axillary surgery, side of surgery, tumor size and lymph node stage, and type of (neo-)adjuvant treatment (radiotherapy, chemotherapy, and/or hormonal therapy). In addition, for each participant, three questionnaires assessing psychosocial factors were administered prior to the assessment. Participants accessed the questionnaires via REDcap, an online platform for electronic data capturing.(Harris et al., 2009) The following questionnaires were administered: 1) **Pain catastrophizing** was evaluated using the Pain Catastrophizing Scale (PCS). This self-report questionnaire consists of 13 questions evaluating thoughts and feelings of previous painful experiences on a scale from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 52 (with higher scores indicating a greater level of catastrophizing). In addition to the total sum of scores, three dimensions are present within the PCS: (1) rumination, defined as irrationals thoughts regarding pain (score range from 0 to 16); (2) magnification, defined as the increased threat value of pain (score range from 0 to 12); (3) helplessness, defined as the inability to handle perceptions of suffering (score range from 0 to 24).(Severeijns et al., 2004; Sullivan et al., 1995) 2) **Depression, anxiety, and stress** over the past week were evaluated using the Depression, Anxiety, and Stress Scale (DASS-21). The DASS-21 contains 21 questions (7 for each subscale: depression, anxiety, stress) with scores ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time).(de Beurs et al., 2001; Lovibond & Lovibond, 1995) 3) The Central Sensitization Inventory (CSI) is a self-report questionnaire that evaluates **health-related symptoms that may be related to the neurophysiological state, termed central sensitization**. The CSI contains 25 questions, each scaled from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 100, with a score of 40 or higher score indicating the suspected presence of central

sensitization.(Leysen et al., 2019; Neblett et al., 2013) In accordance with the 2010 ACR criteria for fibromyalgia, patients with fibromyalgia filled out the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS). Both questionnaires are a self-report measure for the **assessment of pain distribution** (WPI) and the **severity of symptoms** of fatigue, waking unrefreshed and cognitive symptoms (SSS).(Wolfe et al., 2010) The WPI assesses the presence of pain over the past week in 19 specific areas of the body, with each affected area presenting one point (0-19).(Wolfe et al., 2010) The SSS uses a scale from 0 (no problem) to 3 (severe) for each symptom category, with total scores ranging from 0 to 12.(Wolfe et al., 2010) Patients with fibromyalgia were eligible for inclusion when (1) pain was present for at least 3 months, (2) the patients did not have a disorder that could explain their pain symptoms, (3) the WPI score was greater or equal to 7 and SSS was greater or equal to 5, or WPI score was between 3 and 6 and SSS was greater or equal to 9.(Wolfe et al., 2010)

QST was performed in a quiet room at temperatures between 21°C and 23°C. Standardized test instructions were provided for each QST method before testing. Nine QST parameters were evaluated using five QST methods (Table 1). The examiner was not blinded during the comprehensive assessment. Participants were seated on a chair. The total duration of testing approximated 2 hours with an interval between each test varying between 2 and 3 minutes.

Static QST parameters were evaluated at the lateral trunk and the upper part of the opposite tibialis anterior muscle, four fingers below the tibial tuberosity. When chemotherapy-induced peripheral neuropathy or pain in the lower leg was reported, the location of symptoms were evaluated. When neuropathy or pain presented at the upper part of the tibialis anterior muscle, a non-painful location was chosen nearby or on the other leg. In the breast cancer population, the lateral trunk was assessed at the affected side. The lateral trunk was defined as the area innervated by the lateral intercostal nerve and marked by placing four fingers under the armpit fold at the lateral side of the trunk on the anterior axillary line.(Dams et al., 2021) The side of the lateral trunk in the fibromyalgia population and healthy controls was chosen using simple randomization (odd and even numbers). To facilitate reading of the paper, the chosen side in the fibromyalgia and healthy control groups is called the 'affected side' throughout the manuscript. CPM was evaluated at both forearms, and the TSP was evaluated only at the upper part of the opposite tibialis anterior.

The nine QST parameters were evaluated in the following order.

1. Pressure pain threshold (PPT)

A digital pressure algometer (Wagner FDX, Greenwich CT, USA) with a flat round rubber tip and a probe area of 1 cm^2 was used. The **PPT** was defined as the amount of pressure at which the sensation of pressure was first perceived as unpleasant and was determined by two series of ascending pressure

at a rate of approximately 0.1 kgf/s.(Rolke et al., 2006) The final threshold was the arithmetic mean of two trials (kgf/cm^2).(Edwards et al., 2013)

2. Mechanical thresholds

Mechanical detection and pain thresholds (MDT and MPT) were evaluated using a standardized set of 12 von Frey monofilaments (Optihair2, Marstock Nervtest, Germany) exerting forces between 0.25 and 512 mN. The monofilaments were applied at a rate of 2 seconds on and 2 seconds off, in an ascending and descending order respectively, starting with a 8 mN monofilament.(Mücke et al., 2021; Rolke et al., 2006)

For the assessment of **MDT** (e.g., the lowest mechanical force felt), the participants kept their eyes closed and verbally indicated when a force was detected. Similarly, for the assessment of **MPT** (e.g., the lowest mechanical force perceived as painful), the participants kept their eyes closed and verbally indicated when a force was experienced as unpleasant. To decrease guessing, two consecutive forces required detection (MDT) or needed to be perceived as painful (MPT) by the participant. The geometric mean of the ascending (first detected, or painful stimulus) and descending (last detected, or painful stimulus) sequence was calculated (mN).(Mücke et al., 2021; Rolke et al., 2006)

3. Thermal thresholds

Thermal thresholds were evaluated using a computer-controlled thermode system (Advanced Thermosensory Stimulator TSA-2, Medoc, Ramat Yishai, Israel) with a Peltier thermode (3 × 3 cm). The participant was instructed to push a computer-controlled button when he/she experienced a change from a thermo-neutral state to a distinct warm, or cold sensation (warmth and cold detection threshold respectively, **WDT**, **CDT**).(Mücke et al., 2021; Rolke et al., 2006) Thermal pain thresholds were evaluated by instructing the participant to push the computer-controlled button when the sensation of warmth (heat pain threshold, **HPT**) or cold (cold pain threshold, **CPT**) was experienced as unpleasant.(Mücke et al., 2021; Rolke et al., 2006) The baseline temperature was 32°C and the temperature was decreased or increased at a rate of 1°C/s. The temperature was limited to 50°C for heat and 0°C for cold. The final thermal detection and pain thresholds were defined as the arithmetic mean of three consecutive measurements.(Mücke et al., 2021; Rolke et al., 2006)

4. Temporal summation of pain (TSP)

Temporal summation of pain (TSP) was measured only at the upper part of tibialis anterior muscle, opposide to the side of the assessed trunk, by applying a train of pinprick stimuli using a von Frey monofilament with a stimulation force of 256mN (Optihair2-Set, Marstock Nervtest, Germany). After the first stimulus, a train of stimuli was delivered during 30 seconds at a rate of 1 stimulation/s. Participants were asked to score the pain after the first stimulus on a 0-10 NRS and immediately after

the series of stimuli.(Cathcart et al., 2009; Staud, 2013) The difference between the NRS after the last stimulus and the NRS after the first stimulus was used.(Dams et al., 2021; Edwards et al., 2013)

5. Conditioned pain modulation (CPM)

The **CPM** protocol was performed using the same computer-controlled thermode system (Advanced Thermosensory Stimulator TSA-2; Medoc, Ramat Yishai, Israel). First, the intensity of the stimulus was individualized for each subject, that is, the Pain4 Temperature. A Peltier thermode (3x3 cm) was applied first on the volar side of the forearm of the non-affected side.(Dams et al., 2021; Granovsky et al., 2016) The temperature required to evoke a painful sensation with a rating of 4 on a 0-10 NRS (Pain4) was determined by administering a series of heat stimuli to the unaffected forearm. The baseline temperature was 32°C, which increased at a rate of 2°C/s and decreased at a rate of 1°C/s. During the first stimulation, temperature rose to 43°C. If a score above or below 4/10 on the NRS was given, the temperature of the next stimulation was decreased or increased by 1°C respectively. A maximum of five stimulations was administered to search for the Pain4 temperature. The minimum and maximum temperatures of the test stimulus were 39 and 46°C, respectively. After determining the Pain4 test stimulus, a parallel CPM paradigm was introduced. The Pain4 test stimulus was administered to the volar side of the affected forearm for 45 seconds (Phase A, Figure 1). Participants were asked to verbally rate the intensity of the test stimulus at 10, 20, 30, and 40 seconds using a 0-10 NRS. A 120 second break followed, after which the conditioning stimulus was administered to the volar side of the unaffected forearm for 65 seconds (Phase B, Figure 1). The conditioning stimulus was set 0.5 °C warmer than the Pain4 test stimulus. Twenty seconds after the initiation of the conditioning stimulus, the Pain4 test stimulus was applied parallel to the volar side of the affected forearm. Verbal ratings of pain intensity for the affected forearm were obtained at 10, 20, 30, and 40 seconds of stimulation (0-10 NRS). The arithmetic means of the four NRS scores during phases A and B were calculated. The mean NRS score of Phase B was subtracted by the mean NRS score of Phase A. A negative score indicated the presence of efficient CPM.(Granovsky et al., 2016) CPM results were presented together with QST data measured at the opposite tibialis anterior muscle.

The QST protocol was found to be reliable in breast cancer survivors with pain, with the exception of CPM. Intra and inter rater reliability (absolute and relative) ranged from moderate to excellent for most paradigms. Intra and inter rater reliability of CPM ranged from weak to moderate.(Dams et al., 2021)

Figure 1: A schematic overview of the CPM protocol sequence.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Macintosh, Version 28.0.(IBM Corp, 2021) All graphs were made using GraphPad Prism for Macintosh, Version 9.4.1.(GraphPad Software, n.d.)

Descriptive statistics for non-normally distributed and continuous variables were presented as median and interquartile range (IQR), and normally distributed variables were presented as mean and standard deviation (SD). Categorical variables were presented as frequencies and proportions (%).

All QST data with the exception of HPT, CPT, TSP and CPM were transformed into decadic logarithms to achieve normal distributions.(Magerl et al., 2010; Rolke et al., 2006) HPT and CPT were not transformed as this was not recommended by Rolke et al., whereas TSP and CPM contained negative scores which did not allow for logarithmic transformation.(Magerl et al., 2010; Rolke et al., 2006) For comparison of QST data between groups, we used log-transformed and raw QST data. The Kruskal-Wallis test was used for continuous, non-normally distributed variables, and analysis of variance (ANOVA) was used for continuous, normally distributed variables. Dunn's post hoc multiple comparison tests with Bonferroni multiple-comparison correction were performed to evaluate differences between the different groups. The χ^2 test with Bonferroni multiple comparison correction was used for categorical variables. Sensitivity analyses were performed to assess the impact of covariates such as age and psychosocial factors on QST outcomes (Appendix S1). Statistical significance was defined as $p < 0.05$.

Furthermore, the QST data were z-transformed using the mean and standard deviation of the healthy control data as follows: *Z-score = (mean single participant – mean controls) / SD*. To ensure clear data presentation, the algebraic sign of the Z-score was adjusted to align with the participants' sensitivity to the parameters being tested. A positive Z-score represented hyperesthesia, whereas a negative Z-score represented hypoesthesia. A Z-score of zero was defined as the mean of healthy controls. Z-scores outside the 95% confidence interval (CI) of the healthy controls data were considered as somatosensory aberrations.(Moloney et al., 2015; Mustonen et al., 2020)

Results

Participants

The participant characteristics and breast cancer treatment-related factors are summarized in Table 2. The participants had a similar BMI ($p = 0.133$) but differed significantly in age ($p < 0.001$); BCS with persistent pain were significantly older than healthy controls ($p = 0.008$) and patients with

fibromyalgia ($p < 0.001$). In addition, the pain-free BCS group was significantly older than the fibromyalgia group ($p < 0.001$).

Patients with fibromyalgia reported a mean of 12.6 ± 3.0 on the WPI, and a mean of 10.1 ± 1.6 on the SSS (Table 2). Participants with persistent pain (BCS with pain and fibromyalgia) reported a mean VAS score of over 50/100 for pain during the past seven days. In addition, psychosocial factors differed significantly between the groups ($p < 0.001$). Post hoc comparison revealed that participants with persistent pain (BCS and fibromyalgia) reported significantly higher scores regarding psychosocial factors (i.e., worse psychosocial functioning) than pain-free BCS and healthy controls: DASS-21, $p < 0.001$; PCS, $p < 0.001$; CSI, $p < 0.01$. Furthermore, the BCS with persistent pain group exhibited significantly lower CSI scores than the fibromyalgia group ($p < 0.01$).

Table 2. Participant demographics. Values are reported as mean ± standard deviation and median (Interquartile Range), unless mentioned otherwise.

Quantitative sensory testing (Table 3, 4, S1 and Figure 2, 3, S1, S2)

Comparison of QST results

The QST results are presented in supplementary Table S1. In Table 3, the overall p-value for the comparison of QST parameters between groups (Kruskal-Wallis) is given together with the results of the post hoc analyses of the parameters that were found to be significant.

1. Pressure pain threshold (PPT)

The **PPTs** at the *opposite tibialis anterior muscle* and *trunk* differed significantly between the groups ($p < 0.001$).

Post hoc tests revealed that patients with fibromyalgia had significantly lower PPTs at the *opposite tibialis anterior* than healthy controls ($p = 0.01$), pain-free BCS ($p < 0.001$), and BCS with pain ($p = 0.003$). There were no significant differences between the healthy controls and the BCS (with or without pain) in PPTs at the *opposite tibialis anterior*.

At the *trunk*, pain-free BCS showed significantly higher **PPTs** than BCS with pain ($p < 0.001$) and patients with fibromyalgia ($p = 0.003$) in post hoc analysis. In addition, PPTs of BCS with pain were significantly lower than the **PPTs** of healthy controls ($p = 0.005$), in contrast to the PPTs of pain-free BCS, which did not show a significant difference compared to healthy controls ($p = 0.072$).

2. Mechanical thresholds

Overall, a significant difference was found between the groups concerning **MDT** at the *opposite tibialis anterior* ($p < 0.001$) and **MDT** at the *trunk* ($p < 0.001$).

Post hoc analyses revealed that BCS with and without persistent pain had significantly higher **MDTs** in comparison to healthy controls (respectively, $p < 0.001$ and $p = 0.004$) at the *opposite tibialis anterior*. In addition, BCS with pain also had a significantly higher **MDTs** than patients with fibromyalgia ($p = 0.012$). Concerning **MDT** measured at the *trunk*, all four groups differed significantly from each other, except for the comparison between the two BCS groups. All patient groups had significantly higher **MDT** scores than healthy controls: pain-free BCS ($p < 0.001$), BCS with pain ($p < 0.001$), and fibromyalgia ($p = 0.022$). Both BCS groups showed significantly higher **MDTs** than the fibromyalgia group: pain-free BCS ($p < 0.001$) and BCS with pain ($p = 0.003$).

The **MPT** was significantly different between the groups at the *opposite tibialis anterior* ($p = 0.010$) and *trunk* ($p < 0.001$). Post hoc analyses revealed that the fibromyalgia group had significantly lower **MPTs** than healthy controls ($p = 0.007$) and pain-free BCS ($p = 0.026$) groups at the *opposite tibialis anterior*. At the *trunk*, fibromyalgia participants showed significantly lower **MPTs** than healthy controls ($p < 0.001$) and pain-free BCS ($p = 0.001$).

3. Thermal thresholds

Regarding the thermal thresholds measured at the *opposite tibialis anterior*, only **CPT** differed significantly between the groups ($p = 0.002$). Post hoc testing revealed that the **CPT** of pain-free BCS differed significantly ($p < 0.001$) in patients with fibromyalgia.

Thermal thresholds (**WDT, CDT, HPT, CPT**) measured at the *trunk* differed significantly between the groups ($p < 0.001$ (WDT), $p < 0.001$ (CDT), $p < 0.001$ (HPT), and $p = 0.002$ (CPT)). Both BCS groups differed significantly from the healthy controls and fibromyalgia group in terms of WDT, CDT, and HPT, with $p < 0.001$ for each thermal threshold. BCS without pain generally showed lower CDT/CPT and higher WDT/HPTs. Pain-free BCS also exerted lower CDTs and higher WDTs; however, pain-free BCS exerted higher CPT and lower HPT. Regarding CPT, only the pain-free BCS group had significantly higher thresholds than the fibromyalgia group ($p < 0.001$).

4. Temporal summation of pain

TSP was measured only at the *opposite tibialis anterior* and differed significantly between groups ($p < 0.001$). Post hoc tests revealed significantly higher scores for patients with fibromyalgia than for healthy controls ($p = 0.007$) and pain-free BCS ($p = 0.001$). In addition, BCS with pain exerted higher TSP than pain-free BCS ($p = 0.021$).

5. Conditioned pain modulation (CPM)

No significant differences were found in **CPM** between the groups; however, a trend was observed (p = 0.051). Post hoc tests revealed a significant difference between healthy controls and patients with fibromyalgia. Missing data was present in the following groups: pain-free BCS (n=5), BCS with pain (n=3), and fibromyalgia (n=7). For the majority of BCS with missing CPM data, determination of the Pain4 temperature was not possible because the heat stimulus was not perceived as unpleasant (VAS 4/10). For the patients with fibromyalgia (n=7), data is missing as the baseline heat of 43˚C caused excessive pain.

Table 3. Comparison of QST results between healthy controls, breast cancer survivors with and without persistent pain, and patients with fibromyalgia, using a Kruskal-Wallis test and Dunn's post hoc multiple comparisons test.

Comparison of somatosensory profiles

Somatosensory profiles using the Z-scores for both BCS groups and patients with fibromyalgia are presented in Figure 2 and 3 for the *opposite tibialis anterior* and *trunk*, respectively.

At the *opposite tibialis anterior*, no somatosensory aberrations exceeding the 95% CI were observed, except for BCS with persistent pain, showing hypoesthesia in **MDT** (Figure 2).

Group comparison using the proportion of somatosensory aberrations revealed a significant difference between the groups for **PPT** (p = 0.018) (Figure S1, Table 4). Post hoc tests revealed a significant difference in the amount of patients with FM showcasing hyperesthesia in **PPT** in comparison to the pain-free BCS group (Table 4). No other significant differences between groups were found. (Figure S1, Table 4).

Figure 2. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data were measured at the *opposite tibialis anterior* muscle.

At the *trunk*, the somatosensory profiles of both BCS groups were similar for most QST parameters, overall presenting hypoesthesia in these parameters (Figure 3). Nevertheless, both groups differed in **PPT**, with the pain-free BCS showing a limited decrease in pressure sensitivity and the BCS with persistent pain in contrast, showing an increase in pressure sensitivity (Figure 3).

Comparing the proportions of somatosensory aberrations, a significant difference was found between the groups for all QST parameters, with the exception of **CPT** (Figure S2, Table 4). BCS with pain showed a significantly higher frequency of hyperesthesia in **PPT** than the pain-free BCS and fibromyalgia group (p < 0.001). Both BCS groups showed a similar frequency of hypoesthesia in **MDT**

and were significantly different from the fibromyalgia group ($p < 0.001$). In contrast, the fibromyalgia group showed a significantly higher frequency of hyperesthesia in **MPT** compared to both BCS groups, which had similar frequencies of hypoesthesia (Table 4). Regarding the thermal thresholds (**WDT, CDT, HPT** – not **CPT**), both BCS groups showed similar frequencies of hypoesthesia, and both were significantly different from the fibromyalgia group ($p < 0.001$) (Table 4).

Figure 3. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data measured at the *trunk*.

Table 4. Summary of QST aberrations (e.g., hyperesthesia or hypoesthesia) across all groups and locations.

Discussion

This study aimed to compare QST data and describe somatosensory profiles between BCS with and without persistent pain by comparing them to each other and to reference data from healthy controls (i.e., negative control group) and patients with fibromyalgia (i.e., positive control group).

Looking at the comparison of QST parameters, our study found that BCS with persistent pain had significantly lower PPTs (hyperesthesia) at the *trunk* compared to healthy controls and pain-free BCS. BCS with and without persistent pain had significantly higher MDTs (hypoesthesia) at both the *opposite tibialis anterior* muscle and *trunk* compared to healthy controls and at the *trunk* compared to the fibromyalgia group. Regarding MPT, patients with FM showed significantly higher thresholds than healthy controls and pain-free BCS. Thermal thresholds (WDT, CDT, and HPT) measured at the *trunk* were significantly different in BCS with and without persistent pain compared to healthy controls and patients with fibromyalgia, indicating hypoesthesia for thermal stimulation. Regarding CPT, only the pain-free BCS and patients with fibromyalgia differed significantly from each other at both locations, with the pain-free BCS showing lower CPTs. Comparing QST parameters, we did not find any significant differences in CPM across the four groups, however, BCS with persistent pain showed a significantly higher score for TSP than pain-free BCS. However, when comparing somatosensory profiles and the proportion of somatosensory aberrations exceeding the 95% CI at the *opposite tibialis anterior*, no significant differences were found between both BCS groups.

At the *trunk*, BCS with and without persistent pain in general showed similar hypoesthesia for most QST parameters, apart from PPT showing an decrease in threshold (hyperesthesia). When comparing

both BCS groups based on their somatosensory profiles and the proportion of somatosensory aberrations exceeding the 95% CI at the *trunk*, no significant differences were found, except for BCS with persistent pain exhibiting a higher frequency of hyperesthesia in PPT than pain-free BCS.
Age and psychosocial burden was significantly different between groups. Sensitivity analyses however did not find a significant influence of age or psychosocial burden on QST outcomes. Differences in QST outcomes between groups are unlikely to be attributed to variations in age or psychosocial burden.

Our findings are in line with previous research and suggest the presence of aberrant nociceptive processing at the *trunk* (e.g., hypo- and hyperesthesia).(Andersen et al., 2017; Gottrup et al., 2000; Mustonen et al., 2020) The underlying cause of hypoesthesia in the trunk remains unclear, with previous research failing to ascribe the handling of the intercostobrachial nerve during axillary lymph node dissection as potential a contributor.(Mustonen et al., 2020) In the trunk, nerves such as the long thoracic nerve, the lateral cutaneous branches of the intercostal nerves and the thoracodorsal nerve are also susceptible to peri- and postoperative injury.(Jung et al., 2003) In our study, BCS with persistent pain exhibited a higher frequency of individuals with aberrant hyperesthesia in PPT (i.e., lowered PPT) at the treated area in comparison to all other groups. These findings are in line with previous studies and suggest the presence of hyperalgesia or allodynia at the treated area of the breast.(Gottrup et al., 2000; Mustonen et al., 2020) Both BCS groups had an equal amount of ALND, whereas a lower percentage of BCS with persistent pain received breast conserving surgery (15.6%) in comparison to the pain-free group (37.5%). Previous studies have demonstrated that BCS who received breast conserving surgery presented with lower PPT, and more frequently demonstrated persistent pain in the area of the breast.(Andersen et al., 2017; Tasmuth et al., 1995) In contrast to other studies, PPT at the opposite tibialis anterior did not significantly differ from the other groups, suggesting absence of widespread mechanical hyperalgesia.(Fernández-Lao et al., 2010; Mustonen et al., 2020) Further prospective studies using QST are needed to understand the causal factors of these sensory changes and pain in BCS.

Besides aberrations in the peripheral processing of nociceptive signals, we explored whether BCS also exert impairments in the inhibitory descending pathways or exert heightened facilitation of ascending nociceptive pathways. Previous research indicates that impairments in the central processing of nociceptive signals are present in BCS.(Edwards et al., 2013; Gottrup et al., 2000; Vilholm et al., 2009) These studies have solely compared BCS with pain to pain-free BCS, without including healthy controls for comparison.(Edwards et al., 2013; Gottrup et al., 2000; Vilholm et al., 2009) First, we did not find any significant differences in CPM across the four groups. Edwards et al., who performed a CPM

paradigm using a cold pressor test in BCS with and without persistent pain found decrements in CPM in BCS that developed pain after cancer treatment, decreased inhibition of nociceptive signals by descending pathways.(Edwards et al., 2013) The fact that we did not find any changes in CPM in the current study could be due to limitations in our CPM methodology (i.e., modality of conditioning stimulus, lack of spatial summation, a two-thermodes protocol instead of a single stimulus protocol(Granovsky et al., 2016)), simplified responder analysis based on Z-scoring instead of the methodology suggested by Kennedy et al. (Kennedy et al., 2020), and the amount of missing data due to pain or the absence of unpleasantness during testing. These limitations might be debatable, as we found a significant difference between the healthy control group and the fibromyalgia group, suggesting that our CPM methodology is able to detect decreased inhibition of nociceptive signals. Second, regarding TSP measured at the opposite tibialis anterior muscle and using raw QST data, BCS with persistent pain showed a significantly higher score for TSP than pain-free BCS. However, when comparing the proportion of somatosensory aberrations using Z-scores which exceed the 95% CI, we found no significant differences between BCS groups. This divergence in findings aligns with previous research on TSP measured at remote locations, which has yielded inconsistent results. Edwards et al. found significant differences between BCS with and without pain, whereas Schreiber et al. found no differences.(Edwards et al., 2013; Schreiber et al., 2013) By using the opposite tibialis anterior muscle as a remote test location for TSP, we aimed to provide evidence of widespread increased responsiveness of nociceptive neurons.(Merskey & Bogduk, 1994) Despite the inconclusive findings in the comparison of proportions, the significant difference observed in raw QST data provides modest evidence for the presence of widespread increased responsiveness of nociceptive neurons in BCS with persistent pain.

In regards to the psychosocial burden, BCS with persistent pain exhibited significantly higher PCS scores, higher DASS-21 scores, and higher CSI scores than healthy controls and pain-free BCS. BCS with persistent pain had similar scores to those of patients with fibromyalgia, with the exception that patients with fibromyalgia showed even worse CSI scores. These psychosocial factors are associated with changes in the central somatosensory nervous system and persistent pain following breast cancer surgery.(Leysen et al., 2019; Manfuku et al., 2019; Schreiber et al., 2013) The results of our study acknowledge earlier research in BCS with and without pain and also indicates that further research into the assessment of central somatosensory processing of nociceptive signals in BCS remains needed.(Andersen et al., 2017; Edwards et al., 2013; Fernández-Lao et al., 2011; Gottrup et al., 2000; Mustonen et al., 2020; Schreiber et al., 2013; Vilholm et al., 2009)

Strengths and limitations

This study offers several strengths, including the presence of healthy controls acting as a negative control group and patients with fibromyalgia acting as a positive control group. This is the first study of its kind to incorporate both a negative and positive control group. Furthermore, the use of two measurements locations, made it possible to infer both peripheral and central processing of nociceptive signals within somatosensory nervous system, thus creating a comprehensive sensory profile. The limitations of this study include a lack of control over pain medication use. Participants with pain self-reported the use of pain medication but were not asked to stop their medication prior to testing. Tricyclic antidepressants, gabapentinoids or SNRIs may influence QST outcomes. Second, due to limited access and time constraints, we deviated from the German Research Network on Neuropathic Pain (DFNS) QST protocol regarding the MPT and TSP.(Rolke et al., 2006) Instead of the recommended pinprick stimulation, we used von Frey monofilaments to assess MPT. This deviation in MPT methodology makes it difficult to compare the results with those of other studies. Additionally, only one train of TSP was performed using the spherical end of a 256 mN von Frey monofilament rather than pinprick stimulation, which created a floor effect as stimulation was below the level of nociceptive stimulation in several participants (e.g., NRS 0/10). Moreover, the study did not assess other QST parameters, such as mechanical pain sensitivity and thermal sensory limen, owing to limited access to material and time.(Rolke et al., 2006) Third, the overall small sample size and relative youth of the healthy controls and patients with fibromyalgia compared with the BCS cohorts is a limitation of this study. As healthy controls tend to exert a high variability in QST a bigger sample size would increase reliability.(Rolke et al., 2006) Finally, we did not perform an a priori sample size calculation.

Conclusion

Our study found differences and similarities in the somatosensory profiles of BCS with and without persistent pain compared to a healthy control group and patients with fibromyalgia. These findings further confirm that BCS with pain exert impairments in peripheral nociceptive processing. These disruptions manifest as hypoesthesia for thermal and mechanical stimuli and hyperesthesia to pressure. BCS with pain also showed high psychosocial burden and heightened facilitation of nociceptive signals, similar to patients with FM. Even though our findings are in line with those of previous research, further longitudinal research is needed to improve our understanding of somatosensory functioning in relation to pain in BCS. Improved understanding of this relationship can contribute to the improvement of pain management strategies for BCS dealing with persistent pain.

Author Contributions

- V.H. designed the study and developed the research questions.
- V.H. conducted the data collection and analysis with input from A.D.G., M.M., N.D., and B.M..
- V.H. wrote the first draft of the manuscript.
- M.M., N.D., B.M., L.D., A.D.G., and A.D.G. contributed to the writing and revision of the manuscript.
- All authors critically reviewed and discussed the results.
- All authors approved the final version of the manuscript.

Figure legends

Figure 1: A schematic overview of the CPM protocol sequence.

Phase A: application of Pain4 heat on the affected forearm, Phase B: application of Pain4 + 0.5˚C heat (conditioning stimulus) on the non-affected forearm for 65 seconds and concurrently the application of Pain4 heat (test stimulus) on the affected forearm for 45 seconds. NRS= Numeric rating scale.

Figure 2. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data were measured at the *opposite tibialis anterior* muscle.

Presented mean Z-scores ± 95% confidence interval. Z-scores outside the 95% confidence interval of healthy control data (dotted line) were considered aberrant.
PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, TSP= Temporal summation of pain, CPM= Conditioned pain modulation.

Figure 3. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data measured at the *trunk*.

Presented mean Z-scores ± 95% confidence interval. Z-scores outside the 95% confidence interval of healthy control data (dotted line) were considered aberrant.
PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold.

Tables legends

Table 1. Overview of the nine QST parameters.
MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, NRS= Numeric rating scale, TSA-2= Advanced Thermosensory Stimulator.

Table 2. Participant demographics. Values are reported as mean ± standard deviation and median (Interquartile Range), unless mentioned otherwise.
Post hoc tests: a, b, c: same letters marking the values of categories within a given row denote mutually statistically different groups. Significant p-values ($p < 0.05$) are indicated in bold.
VAS= Visual Analogue Scale, SNRI= Serotonin and norepinephrine reuptake inhibitors, NSAID= Non-steroidal anti-inflammatory drugs, LE= Lumpectomy, ME= Mastectomy, SLND= Sentinel lymph node biopsy, ALND= Axillary lymph node dissection, DASS-21= Depression, anxiety, stress scale.

Table 3. Comparison of QST results between healthy controls, breast cancer survivors with and without persistent pain, and patients with fibromyalgia, using a Kruskal-Wallis test and Dunn's post hoc multiple comparisons test.
The mean original data ± SD are shown for CPT, HPT, TS, and CPM. All other QST parameters were log transformed.
P_{KW} = Kruskal-Wallis p-value, $Z_{Dunn's}$= Dunn's post hoc test z-statistic, P_{Bonf}= Bonferroni p-value. Significant p-values ($p < 0.05$) are indicated in bold.
HC= Healthy controls, $BCS_{pain\text{-}free}$= Breast cancer survivors without persistent pain, BCS_{pain}= Breast cancer survivors with persistent pain, FM= patients with fibromyalgia, BCS= Breast cancer survivor, PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warm detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, TSP= Temporal summation of pain, CPM= Conditioned pain modulation.

Table 4. Summary of QST *aberrations* (e.g., hyperesthesia or hypoesthesia) across all groups and locations. *P-values represent comparisons between the three groups using the $\chi 2$ test. Post hoc tests: a, b, c: same letters marking the values of categories within a given row denote mutually statistically different groups. Significant p-values ($p < 0.05$) are indicated in bold.*
PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, TS= Temporal summation of pain, CPM= Conditioned pain modulation.

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