TITLE

Questionnaire-based somatosensory profiling in breast cancer survivors: are we there yet? Associations between questionnaires and quantitative sensory testing.

RUNNING HEAD

Associations between questionnaires and QST

ARTICLE CATEGORY

Research paper

ABSTRACT

Purpose: Pain and sensory disturbances are common side effects of breast cancer treatment. Differential somatosensory functioning may reflect distinct pathophysiological backgrounds and therapeutic needs. Aim was to examine whether questionnaires evaluating signs and symptoms related to somatosensory functioning correlate sufficiently with quantitative sensory testing (QST) in breast cancer survivors to warrant consideration for somatosensory profiling in clinical practice.

Methods: One year after breast cancer surgery, 147 women underwent QST and completed following questionnaires: Douleur Neuropathique en 4 questions (DN4), Central Sensitization Inventory, Margolis Pain Diagram and Visual Analog Scales (VAS). Associations between the questionnaires and QST were evaluated using Spearman correlation coefficients (rs).

Results: Significant but weak (rs<0.30) correlations were found between total DN4 score and QST results at the inner upper arm for detection of sharp stimuli (rs=0.227), cold stimuli (rs=-0.186), and painful heat stimuli (rs=0.179), as well as between QST evaluating conditioned pain modulation and the Margolis Pain Diagram on one hand (rs=0.176) and minimum-maximum pain intensity differences (VAS) on the other (rs=-0.170).

Conclusion: Questionnaires evaluating signs and symptoms related to somatosensory functioning are insufficient for somatosensory profiling. Although somatosensory profiling may be valuable in a mechanism-based management, more research on the most appropriate clinical tools is needed.

Key words: breast cancer, quantitative sensory testing, sensory profiling, DN4, Central Sensitization Inventory, Margolis Pain Diagram, Visual Analog Scale

INTRODUCTION

Persistent pain and sensory disturbances are frequent side effects of treatment for breast cancer.[1, 2] One to two years after breast cancer surgery, approximately 31% of survivors report pain.[1] Given the importance of mechanism-based patient-centered care, clinicians should be able to recognize that some patients' pain or sensory experiences include a component of altered somatosensory processing as a significant contributor to their complaint. Recognizing altered somatosensory nervous system functioning is essential for understanding that person's unique presentation and appropriately addressing the patient's complaint.[3, 4]

The most commonly used method to quantify somatosensory functioning is quantitative sensory testing (QST).[5, 6] QST is an umbrella term for non-invasive assessment techniques evaluating the different qualities of the somatosensory nervous system by administering standardized objective stimuli and quantifying the self-reported sensory experience.[7] Through QST the function of small unmyelinated C fibers, myelinated A-alpha, A-beta and A-delta fibers, as well as corresponding central pathways can be evaluated for both loss and gain of function.[8] Grouping or stratifying patients according to loss or gain of their afferent function, so called somatosensory profiles, may offer indirect insights into underlying mechanisms of pathophysiology or mechanisms of pain generation and is consequently often used.[9, 10] In breast cancer survivors with persistent pain in the surgical area, somatosensory profiles including both loss and gain of function for mechanical and thermal stimuli were identified in the surgical area.[11] Other studies evaluating somatosensory functioning in the same population also report both local somatosensory loss as well as gain of function.[12-14] The breast as well as the intercostobrachial and intercostal nerve innervation areas are neuroanatomically susceptible regions for somatosensory disturbances following breast cancer surgery and adjuvant treatments.[15] Although somatosensory loss may be triggered by local disturbances in the functioning of afferent neurons, somatosensory gain can be caused by both local disturbances in peripheral afferent neurons (peripheral sensitization) as well as augmentation of responsiveness of central neurons to sensory input and impaired inhibition of nociception, a phenomenon called central sensitization.[16, 17]

Advanced QST protocols may provide insight into an individual's central somatosensory processing. First, conditioned pain modulation (CPM) explores the physiological phenomenon that noxious stimuli exert inhibitory effects over subsequent noxious stimuli (diffuse noxious inhibitory control) and is, as such, a way of evaluating the anti-nociceptive or inhibitory activity of the central nervous system.[18, 19] Second, temporal summation (TS) is related to "wind-up" of repeated nociceptive input to the central nervous system, in which the neuronal output increases with successive stimuli.[20] When somatosensory processing is altered, wind-up is

exaggerated in amplitude and duration.[21] Besides CPM and TS protocols, assessing pain thresholds at an area distant from the breast surgery may also provide more information on the extra segmental spreading of sensitization. In the case of altered central somatosensory processing, increased sensitivity often extends beyond the innervation area of a peripheral nerve.[20, 22] Altered central somatosensory processing has already been identified in breast cancer survivors with persistent pain.[13, 14, 23]

Even though QST may provide more information on the neuronal mechanisms underlying altered somatosensory functioning, it has its limitations for clinical practice in terms of costly equipment, time-consuming procedures and need for protocol-specific normative data to interpret and/or compare QST results.[7] To our knowledge, there are a number of questionnaires available that evaluate sensory signs and symptoms related to (altered) somatosensory functioning. First, the Douleur Neuropathique en 4 Questions (DN4), is a screening questionnaire that incorporates descriptors of sensory symptoms as well as an examination component to test for sensory loss and allodynia.[24] Originally the questionnaire was developed to evaluate whether pain is likely to be a consequence of a lesion or disease of the peripheral somatosensory nervous system, so called neuropathic pain.[25] Since this questionnaire captures different pain descriptors and qualities, it can also be used to characterize sensory disturbances more broadly.[26] However, the relationship between DN4 score and QST results has not yet been investigated.

Second, the Central Sensitization Inventory (CSI), is a self-reported questionnaire of health symptoms that may be related to altered central somatosensory processing.[27] The association between the CSI and QST methods to evaluate central somatosensory processing has only been explored in non-cancer populations. Studies expected a strong relationship between the CSI score and QST methods such as CPM, TS and pain thresholds at more remote sites. However, results varied from weak to moderate associations.[28-33]

Furthermore, a widespread or increased spatial distribution of symptoms as well as a disproportionate pattern of pain provocation are clinical features described as indicators of altered central somatosensory processing.[34] Spatial distribution of symptoms can be easily evaluated by the Margolis Pain Diagram by calculating the percentage pain surface area.[35] A Visual Analog Scale (VAS) may be used to evaluate the pattern of pain provocation. A disproportionate pain pattern is characterized by a higher mean pain intensity and a smaller variance between minimum and maximum pain intensity scores.[3] However, associations between these questionnaires and QST methods for evaluating central somatosensory processing have not yet been examined in women treated for breast cancer.

The aim of the current study was to examine whether questionnaires correlate sufficiently with QST to warrant consideration for use in somatosensory profiling in women treated for breast cancer. Exploring these associations is a preliminary step toward validating clinical tools for somatosensory profiling. If questionnaires show acceptable associations with QST, as standard for evaluating somatosensory functioning, they may help clinicians in identifying altered somatosensory processing in breast cancer survivors, potentially improving the management of persistent pain and sensory disturbances in this population.

METHODS

The study was reported following the COSMIN guidelines[36] and approved by the Ethical Committee of the University Hospitals Leuven (s60702). All participants gave written informed consent prior to their enrollment.

Study design

In this cross-sectional study, the results of QST (as proxy for evaluating somatosensory functioning) were compared with items from the following questionnaires: DN4, CSI, Margolis Pain Diagram and VAS. An overview of the questionnaires and the QST protocol is given in table 1 and table 2, respectively.

Participants

All participants were consecutively recruited from a cohort of women participating in a larger randomized controlled trial examining the effectiveness of pain neuroscience education on pain, physical, emotional and work-related functioning after breast cancer surgery (named EduCan trial, NCT03351075)[37] at the Multidisciplinary Breast Center of the University Hospitals of Leuven between November 2018 and February 2021. To be eligible for inclusion, women aged 18 years or older had to have received surgery for unilateral breast cancer at least one year earlier. The surgical procedures included breast conserving surgery with axillary lymph node dissection or mastectomy (whether or not in combination with reconstructive surgery) with axillary lymph node dissection or sentinel node biopsy. Exclusion criteria are corresponding to those of the EduCan trial including metastatic disease, breast conserving surgery with sentinel lymph node biopsy or unable to speak and write Dutch.

Procedure

The DN4, Margolis Pain Diagram and VAS were administered by one of two researchers (LD or EVDG) during the same consultation that QST was performed. The CSI was completed by the participants themselves at home, either electronically via the digital patient record or paper

form, one week before or after QST. In the context of the EduCan trial, questionnaires (including the CSI) were completed by the participants outside the consultation in the hospital.

Suggestion to insert Table 1 and Figure 1 here.

Quantitative sensory testing

QST was performed by one of two researchers (LD or EVDG) in a quiet room with an approximate temperature between 21°C and 23°C. For each QST method, standardized test instructions were given prior to testing. Participants were placed in a sitting position, with the lower arms supported by a table.

Nine different QST methods were included in the QST protocol. In general, the protocol was applied according to the standardized QST protocol of the German Research Network on Neuropathic Pain (DFNS).[5] See table 2 for a comprehensive overview of all QST methods of the QST protocol. Absolute and relative inter- and intra-rater reliability of the applied protocol had been previously evaluated in a population of women at least six months after surgery for breast cancer.[46] The QST protocol was found to have a good ability to determine differences in somatosensory functioning (apart from measurement error) between women treated for breast cancer (relative reliability) and to be suitable for individual follow-up after breast cancer surgery (absolute reliability), except for the evaluation of CPM.[46]

Suggestion to insert Table 2 and Figure 2 here.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 27.0. Descriptive statistics for continuous values are presented as mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for not normally distributed data. Categorical variables are presented as frequency and proportion (%). If more than 20% of questionnaire items were not completed, data was considered as missing.

Correlations between the questionnaires on the one hand and somatosensory functioning evaluated with different QST methods on the other hand were tested using Spearman correlation coefficients (rs) for non-parametric variables (ordinal data). Tables 3 and 4 give a detailed overview of the hypotheses and their rationale. If available, the rationale was based on literature. The correlation coefficients were interpreted as follows: <0.3 weak, 0.3-0.5 moderate, 0.5-0.7 good and >0.7 very good.[50]

RESULTS

Participants

A total of 147 women treated for breast cancer with a mean (SD) age of 57 (11.3) were included in the present study. Two participants did not complete thermal testing at the affected trunk side because of fear of unpleasant tingling in the operative region previously experienced with QST. Data for the CSI were lacking for three participants because of the high number of incomplete items. Only the incomplete data, not the entire dataset, was omitted from the analysis for participants with incomplete data for thermal testing or CSI. Pain medication was used by 21% of participants (31/147) 24 hours before QST assessment, although this had no significant impact on the study's outcomes. Patient characteristics and details of scores on the different questionnaires and QST are summarized in table 5 and 6.

Associations between DN4 and QST evaluating local somatosensory functioning

Results of correlation analyses of the different items of the DN4 with QST in the innervation region of the intercostobrachial (ICB) nerve are presented in table 3. Three significant weak correlations were found between the total DN4 score and QST results at the inner upper arm for the detection of sharp stimuli (MDT rs = 0.227, $p<0.05$), for the detection of cold stimuli (CDT rs = -0.186, $p<0.05$) and for the detection of painful heat stimuli (HPT rs = 0.179, $p<0.05$). These results indicate that a higher DN4 score is associated with decreased sensitivity for sharp and cold stimuli as well as for painful heat stimulation in the innervation area of the ICB nerve.

Associations between CSI, Margolis Pain Diagram, VAS and QST evaluating central somatosensory functioning

Results of correlation analyses of the CSI, Margolis Pain Diagram (PPSA) and VAS (VAS mean or average pain intensity and VAS diff or difference between maximum and minimum pain intensity) with QST evaluating pain thresholds at a remote body region, CPM and TS are presented in table 4. Regarding CPM, significant but weak correlations were found between PPSA and VAS diff (PPSA – CPMmean rs = 0.176, $p<0.05$, VAS diff – CPM10s, rs = -0.170, $p<0.05$). These results suggest that increased spatial distribution of pain as well as a disproportionate nature of pain intensity are associated with altered central somatosensory processing.

DISCUSSION

The aim of the current study was to examine whether the self-reported questionnaires DN4, CSI, Margolis Pain Diagram and VAS correlate sufficiently with QST to warrant consideration for use in somatosensory profiling in women following surgery for breast cancer. Easily applicable clinical measurement tools could help stratifying breast cancer survivors based on somatosensory profile in daily clinical practice enhancing the mechanism-based, patient-centered management of pain and sensory disturbances after treatment for breast cancer. However, no clear associations between the questionnaires and QST could be identified in the present study.

Based on previous studies regarding somatosensory functioning in breast cancer survivors with persistent pain in the surgical area[11-14], it was hypothesized that scores on the DN4 would be associated with both sensory loss and gain in the surgical area. However, in the current study only weak significant associations with sensory loss were found. As part of a validity study of the Dutch version of the DN4 for detection of neuropathic pain in patients with chronic pain, Timmerman et al. (2017)[38] concluded that the patients' symptoms (DN4i) did not sufficiently correspond with clinical examination by a (pain) physician (including sensory testing of touch, pinprick, pressure, cold, heath and temporal summation) and therefore did not reliably reflect underlying pathophysiological mechanisms. These findings are in line with results of the current study.[38]

A first possible explanation of our findings may be that the use of patient-reported signs and symptoms to evaluate somatosensory functioning may have its limitations because sensory gain-loss can only be captured indirectly by asking the patients what they feel, which might lead to misinterpretation of the exact sensory event. In addition, these questions do not distinguish between deficits in mechanical or thermal sensations, limiting interpretation of results.[26] Consequently, information regarding sensory gain and sensory loss based on questionnaires may be less precise than with QST. In contrast to other questionnaires such as the PainDETECT[53, 54] and Neuropathic Pain Symptom Inventory (NPSI)[55] , the DN4 has not yet been used in studies to subgroup patients according to their pattern of sensory abnormalities. Associations between the PainDETECT, NPSI and QST results were previously investigated in populations with neuropathic pain.[55, 56] While Giertmühlen et al. (2018)[56] found weak to moderate associations between the PainDETECT and QST results, Attal et al. (2008)[55] reported moderate to high correlations between NPSI items and sensitivity for mechanical and thermal (cold) stimuli. Important to note here is that in the study of Attal et al. (2008)[55], mechanical and thermal sensitivity was not evaluated according to threshold detection (as

recommended in the standardized protocol of the DFNS) but by means of pain intensity ratings (score from 0 to 100 on a VAS).[55]

Despite the fact that the CSI is designed to evaluate symptoms that may be related to altered central somatosensory processing[27], CSI scores were not associated with results of QST protocols supposed to evaluate these processes. This finding is in line with previous studies in non-cancer populations. Weak and non-significant correlations between CSI and CPM were found in patients with chronic musculoskeletal pain.[28, 30-33] Further, CSI scores were also not found to be correlated with either pain thresholds at remote body regions or TS. One study in people with knee osteoarthritis identified significant moderate associations between CSI scores and PPT at a remote body region.[33] This result could not be confirmed in the present study or other studies in musculoskeletal populations.[29, 32]
Widespread pain as determined with the Margolis Pain Diagram and a disproportionate nature of pain intensity scores as evaluated with VAS, have been described as indicators of altered central somatosensory processing.[3, 27, 57] However, no strong associations could be found for these questionnaires in the present study. These findings may have been impacted by the low prevalence of widespread or disproportionate pain based on PPSA and VAS. Only 10% (15/146) of our sample had a PPSA above 20% and 32% (46/146) had a mean global pain intensity score of 30 or higher on a scale of 100. Further studies exploring associations on larger numbers of people with more widespread and disproportionate pain following breast cancer treatment are recommended.

A third possible explanation of our findings may be that self-reported signs and symptoms evaluated by questionnaires are influenced by factors other than or in addition to factors related to somatosensory functioning. With regard to the CSI, strong associations have previously been found with various questionnaires focusing on psychosocial distress and different dimensions of psychopathology (anxiety, distress, depression, somatization) in different musculoskeletal pain populations.[29, 30, 32, 58, 59] The same significant associations with psychosocial stressor load and anxiety were found for the PPSA using a Margolis Pain Diagram by people with chronic non-cancer pain.[60] In addition, studies found that a widespread pain pattern was significantly associated with an increased use of pain management strategies.[60, 61] To the best of our knowledge, associations between psychosocial factors and CSI scores or PPSA have not yet been examined in women one year after surgery for breast cancer. However, positive associations between a disturbed psychosocial functioning and increased pain intensity have already been extensively described in breast cancer survivors.[62-64] As for central somatosensory processing, the measurement tools hypothesized to reflect local somatosensory functioning (DN4), may also be influenced by other mechanisms. For

example, Aho et al. (2020)[65] also found significant although weak correlations between the DN4i and psychological variables (anxiety rs = 0.179, depression rs = 0.245, pain catastrophizing rs = 0.213) in breast cancer survivors with post-surgical pain.

On the other hand, we should also address the limitations of QST in evaluating somatosensory functioning. The reaction of the participant to the applied stimuli (and thus the QST-result) may also be affected by psychosocial factors.[66] This makes QST a psychophysical evaluation method rather than a completely objective assessment of somatosensory functioning and it can at best be considered to evaluate one dimension of a pain experience. It is not the perfect test to evaluate somatosensory functioning but currently the best available test.[67, 68]
A further discrepancy that may have influenced our results relates to the timing of measurements. While the QST evaluation is a momentary snapshot of somatosensory functioning, the included questionnaires survey self-reported somatosensory signs and symptoms over the previous week. Over the period of a week, the impact of confounding factors may have been somewhat reduced in comparison to their potential influence at the time of the QST assessment (in particular psychosocial factors but also sleep, physical activity, caffeine intake).

Strengths of the present study are, first, the inclusion of 147 women treated for breast cancer. Sample sizes equal to or greater than 100 participants strengthen the level of evidence in measurement property studies.[36, 69] Second, stratification of participants on certain somatosensory outcomes (i.e. presence or absence of sensory loss or gain necessary for inclusion in the study) was not performed because this would possibly lead to a non-clinical situation in a population of breast cancer survivors with a mixed pattern of somatosensory disturbances[70], decreasing the validity and generalizability of the studied clinical instruments.[71, 72] As a result, the present study had a heterogeneous sample in which not all somatosensory assessments were disturbed. The higher the prevalence of somatosensory disturbances in the study sample, the higher the chance that a certain score on a clinical questionnaire indicates the presence of somatosensory disturbances.[73] Third, because use of analgesic medication might inhibit CPM response, we considered the use of pain medication 24 hours before QST assessment.[74] However, the results regarding the associations with CPM were the same when adjusting for the use of analgesics.

Limitations of the current study are, first, the evaluation of both CPM and TS at the affected side. Future research involving evaluation of sensory profiles could asses CPM and TS both at upper and lower limb to gain more confidence that pathophysiological mechanisms of altered somatosensory functioning are indeed central.[18] However, this remains challenging in a

population of breast cancer survivors treated with chemotherapy and/or hormonal therapy with possible somatosensory side effects in both upper and lower body. Second, as mentioned earlier the number of participants with widespread or disproportionate pain was rather limited, which makes our sample different to most typical chronic pain population on which hypotheses were based. Third, a neuropathic pain component (DN4 ≥4) was present in 48% (70/147) of participants. Hypotheses regarding local somatosensory functioning were based on the study of Mustonen et al. (2020)[11] where probable neuropathic pain (pain and at least one abnormal sensory finding at the site of pain) was required for inclusion.

Differences in somatosensory profiles may reflect distinct pathophysiological backgrounds with different responses to pharmacological as well as non-pharmacological treatments.[9, 10, 75] It is important that clinicians recognize that some peoples' experience of pain or sensory disturbances has a component of 'altered' somatosensory processing as a significant contributor to their presentation. Based on the findings of this study, no evidence-based recommendations can be made on the use of self-reported questionnaires to assess this somatosensory processing one year after breast cancer surgery. However, in attempt to optimize the evaluation and management of pain and sensory disturbances in this population, it is recommended to combine information on how individuals process and experience somatosensory stimulation (e.g. through the use of sensory testing) with information from the patient interview or questionnaires (e.g. breast cancer treatment, anxiety, maladaptive coping) to consider which biological, psychological and/or social factors drive or sustain these neurophysiological processes.[76] More research is needed on the best strategies for comprehensively evaluating (altered) somatosensory processing in a breast cancer population in clinical practice.

CONCLUSION

The current study could not establish clear associations between questionnaires assessing somatosensory signs and symptoms related to somatosensory functioning and QST in women one year after surgery for breast cancer. Although somatosensory profiling may be of significant value in a mechanism-based management of pain and sensory disturbances after treatment for breast cancer, more research is needed on the most appropriate tools for somatosensory profiling in clinical practice.

ACKNOWLEDGEMENT – DECLARATION OF INTEREST

The study is funded by Research Foundations – Flanders (FWO) (T005117N). Dr. Morlion reports personal fees from Pfizer, from Gruenenthal, from Kyowa-Kirin, from GSK, from Reckit and Benckiser, from Shionogi, outside the submitted work. The other authors have no conflicts of interest to declare.

REFERENCES

1. Wang L, Cohen JC, Devasenapathy N et al. Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: a systematic review and meta-analysis of observational studies. Br J Anaesth. 2020;125(3):346-57.
2. Flowers KM, Beck M, Colebaugh C, Haroutounian S, Edwards RR, Schreiber KL. Pain, numbness, or both? Distinguishing the longitudinal course and predictors of positive, painful neuropathic features vs numbness after breast cancer surgery. Pain Rep. 2021;6(4):e976.
3. Beales D, Mitchell T, Moloney N, Rabey M, Ng W, Rebbeck T. Masterclass: A pragmatic approach to pain sensitivity in people with musculoskeletal disorders and implications for clinical management for musculoskeletal clinicians. Musculoskelet Sci Pract. 2020:102221.
4. Edwards RR, Dworkin RH, Turk DC et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. Pain. 2016;157(9):1851-71.
5. Rolke R, Magerl W, Campbell KA et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77-88.
6. Mucke M, Cuhls H, Radbruch L et al. Quantitative sensory testing (QST). English version. Schmerz. 2016.
7. Hall T BK, Schafer A, Tampin B, Moloney N. Quantitative Sensory Testing: Implications for clinical practice. In: Jull G, Moore A, Falla D, Lewis, J, McCarthy C, Sterling M, editors. Grieve's Modern Musculoskeletal Physiotherapy. 4th edition. UK: Elsevier Health Sciences; 2015. p. 194-201. 2015.
8. Maier C, Baron R, Tolle TR et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010;150(3):439-50.
9. Baron R, Maier C, Attal N et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. Pain. 2017;158(2):261-72.
10. Vollert J, Magerl W, Baron R et al. Pathophysiological mechanisms of neuropathic pain: comparison of sensory phenotypes in patients and human surrogate pain models. Pain. 2018;159(6):1090-102.
11. Mustonen L, Vollert J, Rice ASC, Kalso E, Harno H. Sensory profiles in women with neuropathic pain after breast cancer surgery. Breast Cancer Res Treat. 2020;182(2):305-15.
12. Andersen KG, Duriaud H, Kehlet H, Aasvang EK. The Relationship Between Sensory Loss and Persistent Pain 1 Year After Breast Cancer Surgery. J Pain. 2017;18(9):1129-38.
13. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. Sensory function and pain in a population of patients treated for breast cancer. Acta Anaesthesiol Scand. 2009;53(6):800-6.
14. Caro-Moran E, Fernandez-Lao C, Diaz-Rodriguez L et al. Pressure Pain Sensitivity Maps of the Neck-Shoulder Region in Breast Cancer Survivors. Pain Med. 2016;17(10):1942-52.
15. Andersen KG, Aasvang E, Kroman N, Kehlet H. Intercostobrachial nerve handling and pain after axillary lymph node dissection for breast cancer. Acta Anaesthesiol Scand. 2014;58(10):1240-8.
16. Leone C, Biasiotta A, Cesa SL, Stefano GD, Cruccu G, Truini A. Pathophysiological mechanisms of neuropathic pain. Future Neurology. 2011;6(4):497-509.
17. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-s15.
18. Yarnitsky D, Bouhassira D, Drewes AM et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain. 2015;19(6):805-6.

19. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain. 2009;144(1-2):16-9.
20. Arendt-Nielsen L, Morlion B, Perrot S et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain. 2018;22(2):216-41.
21. Starkweather AR, Heineman A, Storey S et al. Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. Appl Nurs Res. 2016;29:237-41.
22. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol. 2010;6(10):599-606.
23. Rasmussen GHF, Madeleine P, Arroyo-Morales M, Voigt M, Kristiansen M. Pain sensitivity and shoulder function among breast cancer survivors compared to matched controls: a case-control study. J Cancer Surviv. 2021.
24. Bouhassira D, Attal N, Alchaar H et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.
25. Treede RD, Jensen TS, Campbell JN et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630-5.
26. Baron R, Förster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. Lancet Neurol. 2012;11(11):999-1005.
27. Mayer TG, Neblett R, Cohen H et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12(4):276-85.
28. Bezerra MC, Bittencourt JV, Reis FJJ, de Almeida RS, Meziat-Filho NAM, Nogueira LAC. Central Sensitization Inventory is a useless instrument for detection of the impairment of the conditioned pain modulation in patients with chronic musculoskeletal pain. Joint Bone Spine. 2020:105127.
29. Coronado RA, George SZ. The Central Sensitization Inventory and Pain Sensitivity Questionnaire: An exploration of construct validity and associations with widespread pain sensitivity among individuals with shoulder pain. Musculoskelet Sci Pract. 2018;36:61-7.
30. Gervais-Hupé J, Pollice J, Sadi J, Carlesso LC. Validity of the central sensitization inventory with measures of sensitization in people with knee osteoarthritis. Clin Rheumatol. 2018;37(11):3125-32.
31. Caumo W, Antunes LC, Elkfury JL et al. The Central Sensitization Inventory validated and adapted for a Brazilian population: psychometric properties and its relationship with brain-derived neurotrophic factor. J Pain Res. 2017;10:2109-22.
32. Kregel J, Schumacher C, Dolphens M et al. Convergent Validity of the Dutch Central Sensitization Inventory: Associations with Psychophysical Pain Measures, Quality of Life, Disability, and Pain Cognitions in Patients with Chronic Spinal Pain. Pain Pract. 2018;18(6):777-87.
33. Moore RL, Clifford AM, Moloney N, Doody C, Smart KM, O'Leary H. The Relationship Between Clinical and Quantitative Measures of Pain Sensitization in Knee Osteoarthritis. Clin J Pain. 2020;36(5):336-43.
34. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (± leg) pain. Man Ther. 2012;17(4):336-44.
35. Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain. 1986;24(1):57-65.
36. Mokkink LB, Terwee CB, Knol DL et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol. 2010;10:22.
37. De Groef A, Devoogdt N, Van der Gucht E et al. EduCan trial: study protocol for a randomised controlled trial on the effectiveness of pain neuroscience education after breast cancer surgery on pain, physical, emotional and work-related functioning. BMJ Open. 2019;9(1):e025742.
38. Timmerman H, Steegers MAH, Huygen F et al. Investigating the validity of the DN4 in a consecutive population of patients with chronic pain. PLoS One. 2017;12(11):e0187961.

39. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory. Pain Pract. 2017;17(2):166-75.
40. Neblett R, Hartzell MM, Cohen H et al. Ability of the central sensitization inventory to identify central sensitivity syndromes in an outpatient chronic pain sample. Clin J Pain. 2015;31(4):323-32.
41. Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement Properties of the Central Sensitization Inventory: A Systematic Review. Pain Pract. 2018;18(4):544-54.
42. Kregel J, Vuijk PJ, Descheemaeker F et al. The Dutch Central Sensitization Inventory (CSI): Factor Analysis, Discriminative Power, and Test-Retest Reliability. Clin J Pain. 2016;32(7):624-30.
43. Trahan LH, Cox-Martin E, Johnson CE et al. Psychometric Study of the Pain Drawing. J Appl Biobehav Res. 2017;22(4).
44. Kjeldsen HB, Klausen TW, Rosenberg J. Preferred Presentation of the Visual Analog Scale for Measurement of Postoperative Pain. Pain Pract. 2016;16(8):980-4.
45. Harrington S, Gilchrist L, Sander A. Breast Cancer EDGE Task Force Outcomes: Clinical Measures of Pain. Rehabil Oncol. 2014;32(1):13-21.
46. Dams L, Haenen V, Van der Gucht E, Devoogdt N, Smeets A, Bernar K, et al. Absolute and relative reliability of a comprehensive quantitative sensory testing protocol in women treated for breast cancer. Pain Med. 2021 Dec 15;pnab343.
47. Edwards RR, Mensing G, Cahalan C et al. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. J Pain Symptom Manage. 2013;46(1):30-42.
48. Cathcart S, Winefiels AH, Rolan P, Lushington K. Reliability of temporal summation and diffuse noxious inhibitory control. Pain Res Manag. 2009;14(6):433-8.
49. Granovsky Y, Miller-Barmak A, Goldstein O, Sprecher E, Yarnitsky D. CPM Test-Retest Reliability: "Standard" vs "Single Test-Stimulus" Protocols. Pain Med. 2016;17(3):521-9.
50. Portney LG. Foundations of Clinical Research: Applications to Evidence-Based Practice. In: WM. PL, editor. Philadelphia: F.A. Davis Company; 2020.
51. Gerhardt A, Eich W, Janke S, Leisner S, Treede RD, Tesarz J. Chronic Widespread Back Pain is Distinct From Chronic Local Back Pain: Evidence From Quantitative Sensory Testing, Pain Drawings, and Psychometrics. Clin J Pain. 2016;32(7):568-79.
52. Hübscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. Pain. 2013;154(9):1497-504.
53. Baron R, Tölle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: Differences in demographic data and sensory symptoms. Pain. 2009;146(1-2):34-40.
54. Mahn F, Hüllemann P, Gockel U et al. Sensory symptom profiles and co-morbidities in painful radiculopathy. PLoS One. 2011;6(5):e18018.
55. Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? Pain. 2008;138(2):343-53.
56. Gierthmühlen J, Binder A, Förster M, Baron R. Do We Measure What Patients Feel?: An Analysis of Correspondence Between Somatosensory Modalities Upon Quantitative Sensory Testing and Self-reported Pain Experience. Clin J Pain. 2018;34(7):610-7.
57. Lluch E, Nijs J, Courtney CA et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. Disabil Rehabil. 2018;40(23):2836-45.
58. Hendriks E, Voogt L, Lenoir D, Coppieters I, Ickmans K. Convergent Validity of the Central Sensitization Inventory in Chronic Whiplash-Associated Disorders; Associations with Quantitative Sensory Testing, Pain Intensity, Fatigue, and Psychosocial Factors. Pain Med. 2020.
59. van Wilgen CP, Vuijk PJ, Kregel J et al. Psychological Distress and Widespread Pain Contribute to the Variance of the Central Sensitization Inventory: A Cross-Sectional Study in Patients with Chronic Pain. Pain Pract. 2018;18(2):239-46.
60. Visser EJ, Ramachenderan J, Davies SJ, Parsons R. Chronic Widespread Pain Drawn on a Body Diagram is a Screening Tool for Increased Pain Sensitization, Psycho-Social Load, and Utilization of Pain Management Strategies. Pain Pract. 2016;16(1):31-7.

61. Grande-Alonso M, Muñoz-García D, Cuenca-Martínez F et al. Relationship between healthcare seeking and pain expansion in patients with nonspecific chronic low back pain. PeerJ. 2020;8:e8756.
62. Schreiber KL, Kehlet H, Belfer I, Edwards RR. Predicting, preventing and managing persistent pain after breast cancer surgery: the importance of psychosocial factors. Pain Manag. 2014;4(6):445-59.
63. Bovbjerg DH, Keefe FJ, Soo MS, Manculich J et al. Persistent breast pain in post-surgery breast cancer survivors and women with no history of breast surgery or cancer: associations with pain catastrophizing, perceived breast cancer risk, breast cancer worry, and emotional distress. Acta Oncol. 2019;58(5):763-8.
64. Kelly DL, Yang GS, Starkweather AR, Siangphoe U, Alexander-Delpech P, Lyon DE. Relationships Among Fatigue, Anxiety, Depression, and Pain and Health-Promoting Lifestyle Behaviors in Women With Early-Stage Breast Cancer. Cancer Nurs. 2020;43(2):134-46.
65. Aho T, Mustonen L, Kalso E, Harno H. Douleur Neuropathique 4 (DN4) stratifies possible and definite neuropathic pain after surgical peripheral nerve lesion. Eur J Pain. 2020;24(2):413-22.
66. Backonja MM, Attal N, Baron R et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. Pain. 2013;154(9):1807-19.
67. Versi E. "Gold standard" is an appropriate term. Bmj. 1992;305(6846):187.
68. Versi E. Discriminant analysis of urethral pressure profilometry data for the diagnosis of genuine stress incontinence. Br J Obstet Gynaecol. 1990;97(3):251-9.
69. Bittencourt JV, de Melo Magalhães Amaral AC, Rodrigues PV, Corrêa LA, Silva BM, Reis FJJ, et al. Diagnostic accuracy of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain. Arch Physiother. 2021;11(1):2.
70. Leysen L, Adriaenssens N, Nijs J et al. Chronic Pain in Breast Cancer Survivors: Nociceptive, Neuropathic, or Central Sensitization Pain? Pain Pract. 2019;19(2):183-95.
71. Mathieson S, Maher CG, Terwee CB, Folly de Campos T, Lin CW. Neuropathic pain screening questionnaires have limited measurement properties. A systematic review. J Clin Epidemiol. 2015;68(8):957-66.
72. Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. Bmj. 2001;323(7305):157-62.
73. Altman DG, Bland JM. Diagnostic tests 2: Predictive values. Bmj. 1994;309(6947):102.
74. Goubert D, Danneels L, Cagnie B et al. Effect of Pain Induction or Pain Reduction on Conditioned Pain Modulation in Adults: A Systematic Review. Pain Pract. 2015;15(8):765-77.
75. Vollert J, Maier C, Attal N et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: algorithm and sample size recommendations. Pain. 2017;158(8):1446-55.
76. Schreiber KL, Zinboonyahgoon N, Xu X et al. Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes After Breast Surgery. J Pain. 2019;20(5):540-56.

FIGURE CAPTIONS

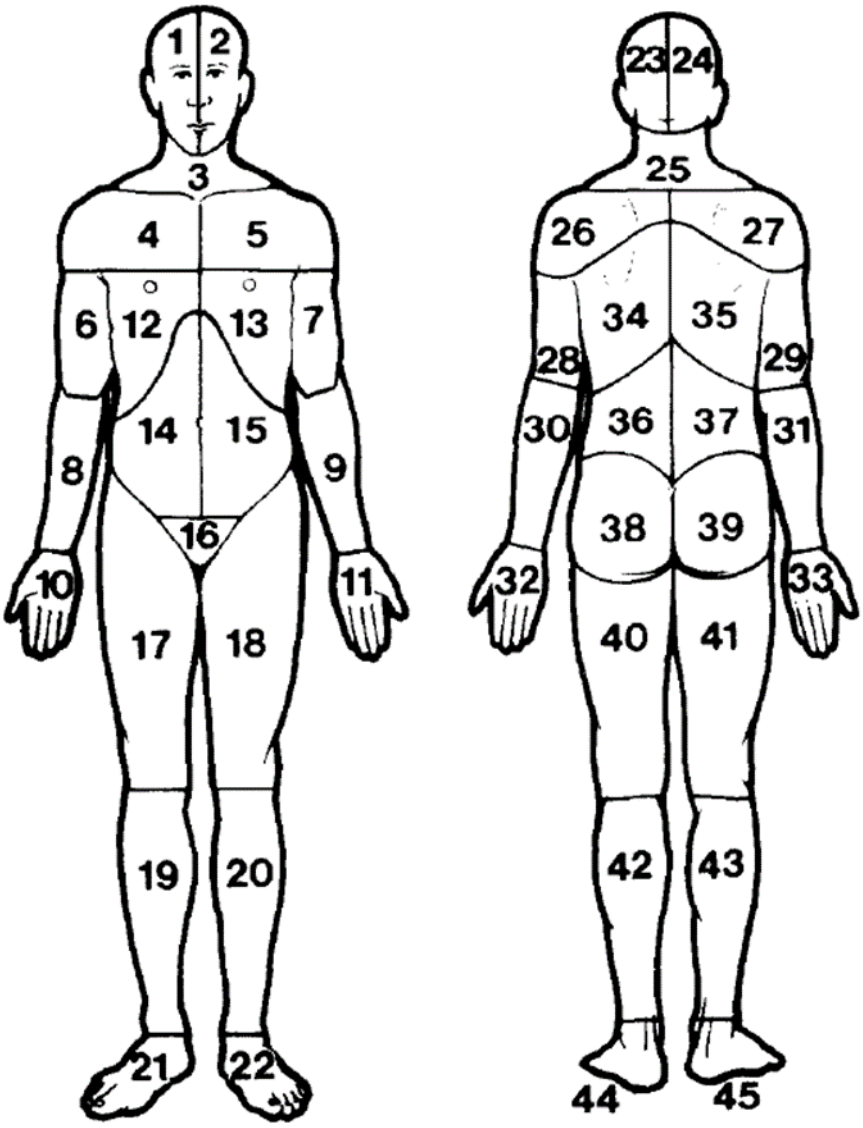
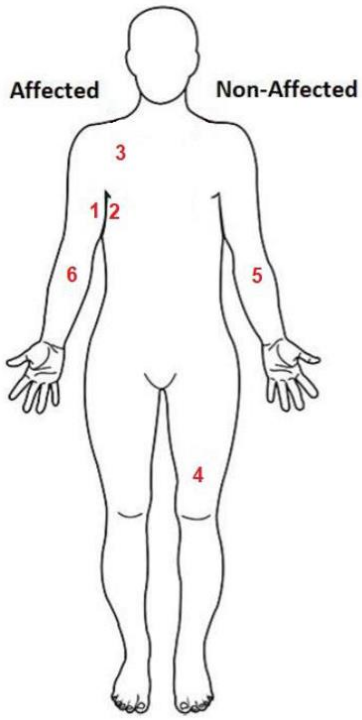


Figure 1. Scoring template for the Margolis Pain Diagram



Reference points

- Inner upper arm **1**
  = four fingers under the armpit fold at the height of the upper arm
  (n. intercostobrachialis)
- Lateral trunk **2**
  = four fingers under the armpit fold at the lateral trunk
  (n. intercostalis lateralis)
- Pectoral region **3**
  = index finger of the ipsilateral hand of the examiner at the height of the ipsilateral coracoid process of the patient, reference point under the ring finger at the m. Pectoralis Major
  (n. intercostalis medialis)
- Quadriceps **4**
  = wrist at the patellar base, reference point under the middle finger at the m. Quadriceps (n. femoralis)
- Lower arm **5-6**
  = middle volar side lower arm (n. cutaneus antebrachii medialis)

Figure 2. Test locations QST protocol

TABLES

Table 1. *Overview of questionnaires*

Description-scoring	Study procedure	Psychometric properties
Douleur Neuropathique en 4 Questions (DN4)		
Items 10 7 items about pain descriptors (DN4i) 3 items related to physical examination **Scale** Dichotomous yes (1) - no (0) scale **Score range** DN4i 0-7, total DN4 0-10 **Interpretation** DN4i scores ≥3 and total DN4 scores ≥4 suggest a neuropathic pain component[24]	• Evaluated for intercostobrachial + intercostal nerve innervation area • DN4i assessed over the past week • Executed during QST assessment	Excellent test-retest reliability Dutch version of DN4 in chronic pain population[38]
Central Sensitization Inventory (CSI)		
Items 25 (part A) **Scale** Five-point Likert scale from 0 (never) to 4 (always) **Score range** 0-40 **Interpretation** Higher score represents greater symptomatology associated with altered central somatosensory functioning[27]	• Not evaluated under supervision • Part B not considered for analysis	Excellent test-retest reliability and internal consistency English[27, 39-41] and Dutch version[42] of CSI in population with chronic musculoskeletal pain and in healthy controls[42]
Margolis Pain Diagram		
Items Dorsal and ventral drawing of the body **Scale** Presence-absence of pain is checked on the drawing for 45 predefined areas. Weights are assigned to the different body areas equal to the covering body surface percentage. **Score range** 0-100 **Interpretation** Weighted score representing total percentage pain surface area (PPSA)[35, 43]	• Assessed over the past week • Evaluated during QST assessment • Pain drawings scored by using transparent plastic templates containing the 45 different areas as defined by Margolis et al. (1986)[35] (see figure 1)	Excellent inter-rater reliability in population with cancer treatment-induced neuropathic pain[43]
Visual Analog Scale (VAS)		
Scale Horizontal 100-mm line with two endpoints representing “no pain” and “worst pain possible” **Score range** 0-100 **Interpretation** Higher score represents higher pain intensity[44]	• 3 VAS scales were completed: 1.VASmean: global average pain intensity over the past week 2.VASmax: pain intensity at its maximum over the past week 3.VASmin: pain intensity at its minimum over the past week • VASdiff = VASmax - VASmin	Good psychometric properties to evaluate pain in women diagnosed with breast cancer[45]

diff = difference, max = maximum, min = minimum, QST = quantitative sensory testing.

Table 2. *Overview of QST protocol*

Study procedure	Device	Outcome	Test location (see figure 2)
Mechanical detection (MDT) - pain (MPT) threshold			
Algorithm Method of limits[5, 6] Detection: series of ascending and descending stimulus intensities are given and the stimulus intensity that is first/last identified is recorded Pain: series of ascending and descending stimulus intensities are given and the stimulus intensity that is first/last identified as painful (not unbearable) is recorded 2 consecutive stimuli to rule out coincidence **Response** Verbal by saying 'yes' **Rate** Skin contact of 2s on-2s off **Min-Max** 8mN-512mN	Von Frey monofilaments (Optihair2-Set, Marstock, Germany,0.25-512 mN)	Geometric mean of ascending and descending stimulation (i.d. the first and last detected stimulus) (mN)[5, 6]	Local Inner upper arm Remote Quadriceps (only MPT)
Pressure pain threshold (PPT)			
Algorithm Method of limits: amount of pressure by which the perception of pressure turns for the first time into a painful (not unbearable) sensation[5, 6] **Response** Verbal by saying 'stop' **Rate** 0.1 kgf/s **Min-Max** 0 kgf/s-12kgf/s	Digital algometer (Wagner FDX, Greenwich CT, USA) rubber tip 1 cm²	Arithmetic mean 2 trials (kgf)[47]	Local Trunk Remote Quadriceps
Thermal detection - pain threshold			
Algorithm Method of limits[5, 6] Detection: temperature when a change from a thermoneutral state to a distinct warm (WDT) or cold (CDT) sensation is experienced Pain: temperature when a change from a thermoneutral state to a painful (not unbearable) warm (HPT) or cold (CPT) sensation is experienced Sequence: 1.WDT, 2.CDT, 3.HPT, 4.CPT **Response** Pushing computer-controlled button **Rate** 1°C/s **Min-Max** 0°C-50°C	Thermode system (TSA II Medoc, Israel) with a 3 × 3 cm Peltier thermode	Arithmetic mean 3 trials for each thermal threshold (WDT, CDT, HPT, CPT) (°C)[5, 6]	Local Inner upper arm Remote Quadriceps (only HPT and CPT)
Temporal summation (TS)			
Algorithm Pain rating after single stimulation, after 30s of stimulation and 15s after final stimulation[48] **Response** Verbal **Rate** 1/s **Min-Max** 0-10	Von Frey monofilament (Optihair2-Set, Marstock, Germany,256 mN)	Wind-up = pain rating after 30s stimulation - pain rating single stimulation (NRS 0-10) Aftersensations = pain rating 15s after final stimulation (NRS 0-10)	Local Pectoral region
Conditioned pain modulation (CPM)			
Algorithm: Parallel heat design[49] * 1. Test stimulus (45s): Individually determined test stimulus (temperature Pain4) applied alone. Pain rating (NRS 0-10) at 10s, 20s, 30s and 40s of stimulation. 2. Break (120s) 3. Conditioning stimulus (temperature Pain4 + 0.5°C) (65s) + test stimulus in parallel (45s). Pain rating (NRS 0-10) at 10s, 20s, 30s and 40s of stimulation. **Response** Verbal **Rate** 1°C/s **Min-Max** 39°C-46,5°C	Thermode system (Q-sense Medoc, Israel) with two 3 × 3 cm Peltier thermodes	CPM diff = difference in NRS (0-10) conditioning + test and NRS test stimulus without conditioning for each 10s-long epoch. (0 or - values = normal CPM, + values = abnormal CPM) CPM mean = mean differences in NRS conditioning + test stimulus and NRS test stimulus without conditioning for 4 10s-long epochs	Remote Lower arm

CDT = cold detection threshold, CPT = cold pain threshold, HPT = heat pain threshold, kgf = kilogram-force, mN = millinewton, NRS = numerical rating scale, s = seconds, WDT = warmth detection threshold. * See Appendix I for a detailed description of the complete CPM protocol.

Table 3. *Hypotheses and results of associations between DN4 and QST evaluating local somatosensory functioning*

Association	Hypothesis	Rationale	Spearman correlation
DN4i – Interview part			
DN4i and MDT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between DN4i score and detection of sharp stimuli at the affected inner upper arm	Local decreased sensitivity mechanical detection (sensory loss) BCS with neuropathic pain.[11]	0.131
DN4i and MPT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between DN4i score and pain sensitivity for sharp stimuli at the affected inner upper arm	Local decreased sensitivity mechanical pain (sensory loss) BCS with neuropathic pain.[11]	-0.168*
DN4i and PPT trunk	A **moderate negative correlation** (between -0.3 and -0.5) is expected between DN4i score and pain sensitivity for sharp stimuli at the affected trunk	Local increased sensitivity pressure pain (sensory gain) BCS with neuropathic pain.[11]	-0.137
DN4i and WDT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between DN4i score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity warmth detection (sensory loss) BCS with neuropathic pain.[11]	0.037
DN4i and CDT arm	A **moderate negative correlation** (between -0.3 and -0.5) is expected between DN4i score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity cold detection (sensory loss) BCS with neuropathic pain.[11]	-0.109
DN4i and HPT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between DN4i score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity heat pain (sensory loss) BCS with neuropathic pain.[11]	0.104
DN4i and CPT arm	A **moderate negative correlation** (between -0.3 and -0.5) is expected between DN4i score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity cold pain (sensory loss) BCS with neuropathic pain.[11]	0.014
DN4 – Interview + examination part			
DN4 and MDT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between total DN4 score and detection of sharp stimuli at the affected inner upper arm	Local decreased sensitivity mechanical detection (sensory loss) BCS with neuropathic pain.[11]	0.227*
DN4 and MPT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between total DN4 score and pain sensitivity for sharp stimuli at the affected inner upper arm	Local decreased sensitivity mechanical pain (sensory loss) BCS with neuropathic pain.[11]	-0.151
DN4 and PPT trunk	A **moderate negative correlation** (between -0.3 and -0.5) is expected between total DN4 score and pain sensitivity for sharp stimuli at the affected trunk	Local increased sensitivity pressure pain (sensory gain) BCS with neuropathic pain.[11]	-0.068
DN4 and WDT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between total DN4 score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity warmth detection (sensory loss) BCS with neuropathic pain.[11]	0.098
DN4 and CDT arm	A **moderate negative correlation** (between -0.3 and -0.5) is expected between total DN4 score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity cold detection (sensory loss) BCS with neuropathic pain.[11]	-0.186*
DN4 and HPT arm	A **moderate positive correlation** (between 0.3 and 0.5) is expected between total DN4 score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity heat pain (sensory loss) BCS with neuropathic pain.[11]	0.179*
DN4 and CPT arm	A **moderate negative correlation** (between -0.3 and -0.5) is expected between total DN4 score and detection of thermal stimuli at the affected inner upper arm	Local decreased sensitivity cold pain (sensory loss) BCS with neuropathic pain.[11]	-0.074

BCS = breast cancer survivors, CDT = cold detection threshold, CPT = cold pain threshold, DN4 = Douleur Neuropathique en 4 Questions questionnaire, DN4i = DN4 interview part, HPT = heat pain threshold, MDT = mechanical detection threshold, MPT = mechanical pain threshold, PPT = pressure pain threshold, WDT = warmth detection threshold.
*Correlation significant at 0.05 level (2-tailed)

Table 4. *Hypotheses and results of associations between CSI, Margolis Pain Diagram, VAS and QST evaluating central somatosensory functioning*

Association	Hypothesis	Rationale	Spearman correlation
CSI			
CSI and MPT Qceps	A **moderate negative correlation** (between -0.3 and -0.5) is expected between total CSI score and pain sensitivity for sharp stimuli at a remote body region	Moderate negative correlation CSI & PPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[32, 33]	0.005
CSI and PPT Qceps	A **moderate negative correlation (**between -0.3 and -0.5) is expected between total CSI score and pain sensitivity for dull stimuli at a remote body region	Moderate negative correlation CSI & PPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[32, 33]	0.074
CSI and HPT Qceps	A **weak negative correlation** (between 0 and -0.3) is expected between total CSI score and pain sensitivity for warm stimuli at a remote body region	Weak negative correlation CSI & HPT at a remote body region (sensory gain) in a non-cancer population with shoulder pain.[29]	**-0.052**
CSI and CPT Qceps	A **weak positive correlation** (between 0 and 0.3) is expected between total CSI score and pain sensitivity for cold stimuli at a remote body region	Weak negative correlation CSI & HPT at a remote body region (sensory gain) in a non-cancer population with shoulder pain.[29]	0.007
CSI and TS	A **weak positive correlation** (between 0 and 0.3) is expected between total CSI score and temporal summation at the pectoral region	Weak positive correlation CSI & TS in non-cancer populations with chronic pain.[30]	Wind-up: **0.150** Aftersensations: **0.160**
CSI and CPM	A **weak positive correlation** (between 0 and 0.3) is expected between total CSI score and conditioned pain modulation	Weak positive correlation CSI & CPM in non-cancer populations with chronic pain.[28, 30, 33]	CPM10s: -0.105 CPMmean: **0.008**
Margolis Pain Diagram			
PPSA and MPT Qceps	A **moderate negative correlation** (between -0.3 and -0.5) is expected between PPSA and pain sensitivity for sharp stimuli at a remote body region	Moderate negative correlation number painful areas & PPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[33]	0.066
PPSA and PPT Qceps	A **moderate negative correlation** (between -0.3 and -0.5) is expected between PPSA and pain sensitivity for dull stimuli at a remote body region	Moderate negative correlation number painful areas & PPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[33, 51]	0.047
PPSA and HPT Qceps	A **moderate negative correlation (**between -0.3 and -0.5) is expected between PPSA and pain sensitivity for warm stimuli at a remote body region	Moderate negative correlation number painful areas & HPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[51]	0.038
PPSA and CPT Qceps	A **weak positive correlation** (between 0 and 0.3) is expected between PPSA and pain sensitivity for cold stimuli at a remote body region	Weak positive correlation number painful areas & CPT at a remote body region (sensory gain) in non-cancer populations with chronic pain.[51]	**0.001**
PPSA and TS	A **moderate positive correlation** (between 0.3 and 0.5) is expected between PPSA and temporal summation at the pectoral region	Moderate positive correlation number painful areas & TS at local region (sensory gain) in non-cancer populations with chronic pain.[51]	Wind-up: -0.001 Aftersensations: 0.064
PPSA and CPM	A **moderate positive correlation** (between 0.3 and 0.5) is expected between PPSA and conditioned pain modulation	Weak positive correlation number painful areas & CPM in non-cancer populations with chronic pain.[33]	CPM10s: -0.004 CPMmean: 0.176*

VAS difference maximum-minimum pain intensity			
VASdiff and MPT Qceps	A **moderate positive correlation** (between 0.3 and 0.5) is expected between VAS maximum-minimum and pain sensitivity for sharp stimuli at a remote body region	Sensory profiling in neuropathic pain: mechanical sensory gain mostly central sensitization.[9]	-0.022
VASdiff and PPT Qceps	A **moderate positive correlation** (between 0.3 and 0.5) is expected between VAS maximum-minimum and pain sensitivity for dull stimuli at a remote body region	Sensory profiling in neuropathic pain: mechanical sensory gain mostly central sensitization.[9]	0.055
VASdiff and HPT Qceps	A **weak positive correlation** (between 0 and 0.3) is expected between VAS maximum-minimum and pain sensitivity for warm stimuli at a remote body region	Sensory profiling in neuropathic pain: thermal sensory gain mostly peripheral sensitization.[9]	**0.082**
VASdiff and CPT Qceps	A **weak negative correlation (**between 0 and -0.3) is expected between VAS maximum-minimum and pain sensitivity for cold stimuli at a remote body region	Sensory profiling in neuropathic pain: thermal sensory gain mostly peripheral sensitization.[9]	**-0.031**
VASdiff and TS	A **moderate negative correlation** (between -0.3 and -0.5) is expected between VAS maximum-minimum and temporal summation at the pectoral region	Moderate positive correlation pain intensity & TS at local region (sensory gain) in non-cancer populations with chronic pain.[52]	Wind-up: -0.019 Aftersensations: 0.060
VASdiff and CPM	A **moderate negative correlation** (between -0.3 and -0.5) is expected between VAS maximum-minimum and conditioned pain modulation	Increased pain rating indication of presence altered pain inhibition-facilitation.[21]	CPM10s: -0.170* CPMmean: 0.038
VAS mean pain intensity			
VASmean and MPT Qceps	A **moderate negative correlation** (between -0.3 and -0.5) is expected between VAS maximum-minimum and pain sensitivity for sharp stimuli at a remote body region	Sensory profiling in neuropathic pain: mechanical sensory gain mostly central sensitization.[9]	0.058
VASmean and PPT Qceps	A **moderate negative correlation** (between -0.3 and -0.5) is expected between VAS maximum-minimum and pain sensitivity for dull stimuli at a remote body region	Sensory profiling in neuropathic pain: mechanical sensory gain mostly central sensitization.[9]	-0.009
VASmean and HPT Qceps	A **weak negative correlation** (between 0 and -0.3) is expected between VAS maximum-minimum and pain sensitivity for warm stimuli at a remote body region	Sensory profiling in neuropathic pain: thermal sensory gain mostly peripheral sensitization.[9]	**-0.040**
VASmean and CPT Qceps	A **weak positive correlation** (between 0 and 0.3) is expected between VAS maximum-minimum and pain sensitivity for cold stimuli at a remote body region	Sensory profiling in neuropathic pain: thermal sensory gain mostly peripheral sensitization.[9]	-0.004
VASmean and TS	A **moderate positive correlation** (between 0.3 and 0.5) is expected between VAS maximum-minimum and temporal summation at the pectoral region	Moderate positive correlation pain intensity & TS at local region (sensory gain) in non-cancer populations with chronic pain.[52]	Wind-up: 0.048 Aftersensations: 0.136
VASmean and CPM	A **moderate positive correlation** (between 0.3 and 0.5) is expected between VAS maximum-minimum and conditioned pain modulation	Increased pain rating indication of presence altered pain inhibition-facilitation.[21]	CPM10s: -0.104 CPMmean: 0.098

CPM = conditioned pain modulation, CPM10s: CPM effect after 10s of stimulation, CPMmean: mean of CPM effect after 10,20,30 and 40s of stimulation, CPT = cold pain threshold, CSI = Central Sensitization Inventory, HPT = heat pain threshold; MPT = mechanical pain threshold, PPSA = percentage pain surface area, PPT = pressure pain threshold, Qceps = quadriceps muscle, TS = temporal summation, VAS = Visual Analog Scale.

*Correlation significant at 0.05 level.

Spearman correlation coefficients of the hypotheses that were accepted are indicated in bold

Table 5. *Demographic characteristics and clinical outcomes for participants (frequency (%) unless specified otherwise) (n = 147)*

Age (years), Mean (SD, range)	57.0 (11.3)
BMI (kg/m²), Median (SD)	24.7 (6.7)
Time since surgery (months), Median (IQR)	12.0 (0.4)
Type of breast surgery	
Breast conserving surgery + axillary lymph node dissection	12 (8%)
Mastectomy + sentinel lymph node biopsy	64 (44%)
Mastectomy + axillary lymph node dissection	71 (48%)
Surgery at dominant side	74 (50%)
Radiotherapy	117 (80%)
Breast	14 (10%)
Thorax (n = 145)	97 (66%)
Median subclavian and parasternal nodes (n = 145)	105 (72%)
Axilla region (n = 145)	11 (8%)
Hormonal Therapy (ongoing)	114 (78%)
Tamoxifen	19 (13%)
Aromatase inhibitors	96 (65%)
Chemotherapy	95 (65%)
Epirubicin Cyclophosphamide (EC)	56 (38%)
Fluorouracil Epirubicin Cyclophosphamide (FEC)	1 (1%)
Paclitaxel (Taxol)	64 (43.5%)
Docetaxel (Taxotere)	35 (24%)
Doxurubicine	2 (1%)
Xeloda	6 (4%)
Target therapy (ongoing)	36 (24.5%)
Herceptin	35 (24%)
Perjeta	21 (14%)
DN4	
DN4i <3	110 (75%)
DN4i ≥3	37 (25%)
DN4 <4	77 (52%)
DN4 ≥4	70 (48%)
CSI (n = 144)	
Total CSI score - part A, Mean (SD)	32.9 (14.2)
Percentage pain surface area (Margolis Pain Diagram), Median (IQR), min-max	5.5 (10.7), 0-71
Pain intensity (VAS) (n = 146)	
Average global pain intensity past week, Median (IQR), min-max	19 (34), 0-84
Difference max-min global pain intensity, Median (IQR), min-max	27.5 (53), -1-96
No pain (VAS = 0)	35 (24%)
Global pain past week VAS <30	100 (68%)
Global pain past week VAS ≥30	47 (32%)

DN4 = Douleur neuropathique en 4 questions questionnaire, DN4i = DN4 interview part, CSI = Central Sensitization Inventory, IQR = interquartile range, max = maximum, min = minimum, SD = standard deviation, VAS = Visual Analog Scale

Table 6. *QST results for participants – Unless specified otherwise, Median (IQR) are given for mechanical and thermal thresholds, frequency (%) for temporal summation and conditioned pain modulation (n = 147)*

Mechanical thresholds (mN)	
MDT Local	5.7 (21.2)
MPT Local	362.0 (331.0)
Remote	512.0 (150.0)
Pressure pain thresholds (kgf)	
PPT Local	1.1 (1)
Remote	2.6 (2.5)
Thermal thresholds (°C)	
WDT Local (n = 146)	36.6 (6.5)
CDT Local (n = 146)	28.7 (4.4)
HPT Local (n = 145)	45.6 (6.0)
Remote	44.6 (5.3)
CPT Local (n = 146)	18.3 (24.0)
Remote	23.6 (21.1)
Temporal summation	
No wind-up	19 (13%)
Wind-up 1-2 NRS	63 (43%)
Wind-up ≥3NRS	65 (44%)
No aftersensations	95 (65%)
Aftersensations 1-2 NRS	31 (21%)
Aftersensations ≥3NRS	21 (14%)
Conditioned pain modulation (n = 146)	
CPM10s (NRS), Mean (SD)	-0.9 (1.6)
CPMmean (NRS), Mean (SD)	-0.3 (1.1)
CPM10s disturbed (NRS ≥0)	62 (42%)
CPMmean disturbed (NRS ≥0)	59 (40%)

CPM = NRS score when test stimulus is applied without conditioning stimulus minus NRS score when test stimulus is applied together with conditioning stimulus (negative values indicate efficient conditioned pain modulation). CPM10s: CPM effect after 10s of stimulation, CPMmean: mean of CPM effect after 10,20,30 and 40s of stimulation, CDT = cold detection threshold, CPT = cold pain threshold, HPT = heat pain threshold, MDT = mechanical detection threshold, mN = millinewton, MPT = mechanical pain threshold, NRS = numerical rating scale, PPT = pressure pain threshold, WDT = warmth detection threshold