

Long-term alterations in somatosensory functioning in survivors of childhood cancer

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Abstract

Cancer and its treatment can have lasting consequences on somatosensation, including pain, which is often underrecognized and undertreated. Research characterizing the impact of cancer on pain and sensory processing in survivors of childhood cancer is scarce. This study aimed to quantify generalized differences in pain and sensory processing in survivors of childhood cancer compared with reference data using a standardized thermal and mechanical quantitative sensory testing (QST) protocol. The association between demographic, clinical (eg, leukemia vs other cancers and treatment exposures), and psychosocial (eg, anxiety and pain catastrophizing) variables and sensitivity to pain and sensory stimuli were also evaluated. Participants were 56 survivors of various types of childhood cancer (52% male, $M_{age} = 13.5$ years, $SD = 3.2$, range = 8-17 years). On average, children were 7 years ($SD = 4.1$, range = 1.2-16.5) post treatment. Almost all participants (86%) had at least 1 abnormal QST parameter compared with age- and sex-matched reference data; however, few participants self-reported the presence of sensory abnormalities. Generally, participants exhibited reduced sensitivity across the QST parameters examined ($P_s < 0.05$, $d_s = 0.40$ - 3.45). A significant minority (45%) also exhibited pain sensitization ($P < 0.001$, $d = 0.42$). Several risk factors for changes in sensory processing were identified, including current age, history of leukemia, certain treatment exposures (eg, vincristine cumulative dose, major surgery, and bone marrow or stem cell transplant), time off treatment, and higher anxiety and pain catastrophizing scores. Overall, this study demonstrated that somatosensory changes are prevalent in survivors of childhood cancer years after the completion of treatment. Future research is needed to understand long-term implications of altered somatosensation in this complex population.

Keywords: Pediatric oncology, Quantitative sensory testing, Cancer survivors, Cancer, Pain, Childhood cancer

1. Introduction

Therapeutic advancements have improved survival rates for children with cancer.⁶¹ However, cancer and its treatment place children at risk for long-term morbidity,⁵⁰ including pain,^{31,37} which is often underrecognized and undertreated.^{1,63}

The developing central nervous system (CNS) and peripheral nervous system (PNS) are vulnerable to the effects of cancer and its treatment. Childhood cancers may directly injure the CNS and PNS, and its treatment universally contributes to further tissue damage. Cancer treatments necessitate repeated punctate procedures, leading to local tissue damage and prolonged

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upregulation of nociceptive function.^{69,71} Chemotherapies exert toxic effects that can cause small- and large-fibre dysfunction, neuropathy, and other sequelae (eg, avascular necrosis) ultimately impacting nervous system functioning and pain.^{25,29,48,64} Radiotherapy³⁴ and major surgery^{12,58} are also associated with long-term nerve injury.

Cancer and its treatment can have lasting consequences on somatosensation. In adult survivors, altered pain and sensory processing, including changes in small- (A δ , C) and large-fibre (A β) function and pain sensitization, have been identified using quantitative sensory testing (QST).^{3,11,18,41} Research examining somatosensation in survivors of childhood cancer is scarce. Data specific to this population are needed given factors unique to the pediatric context. Insults to the nervous system in childhood—a time when developing neural circuits are especially vulnerable to experience^{2,5,70}—may result in sustained changes to the neurophysiology of sensory and pain perception. Quantitative sensory testing studies in healthy children have shown that sensitivity changes with age and by sex, with younger children and girls showing more sensitivity.⁹ The vulnerability of childhood is compounded by survivors' risk for anxiety⁶⁰ and catastrophic thinking about bodily symptoms.^{17,66} Conceptual models^{1,59} of pain after childhood cancer highlight the importance of these psychosocial factors, which modulate affective components of somatosensation.^{37,71}

Two QST studies have evaluated sensory processing after childhood cancer: one in survivors of acute lymphoblastic leukemia (ALL) treated with chemotherapy alone³⁶ and the other in survivors of ALL who received a stem-cell transplant (SCT).⁵⁶ In both studies, three quarters of participants exhibited signs of large-fibre dysfunction. A greater proportion of children who received a SCT showed signs of small-fibre dysfunction (88% vs 30%) and pain sensitization (50% vs 30%) compared with those treated with chemotherapy alone.^{36,56} Leukemia treatment protocols are notoriously neurotoxic given the type and amount of drugs required, the number of necessary invasive procedures, and the long duration of treatment.³⁸ Data on the somatosensory impacts of a broader range of childhood cancers are not available, and further information on risk factors for altered processing is needed.

The primary objective of this study was to quantify generalized differences in pain and sensory processing in survivors of childhood cancer compared with age- and sex-matched reference values using a standardized QST protocol. Survivors of childhood cancer were hypothesized to exhibit altered pain and sensory detection thresholds across the QST parameters. Secondary aims were to examine differences in sensitivity in children with a history of leukemia compared with children with a history of other cancers and to evaluate the association between demographic, treatment, and psychosocial variables and sensitivity to pain and sensory stimuli.

2. Methods

2.1. Participants

Participants were survivors of childhood cancer (defined as having completed cancer-related treatment) identified from the IWK Health Centre's pediatric hematology or oncology database and an accompanying parent. The IWK Health Centre is the tertiary care referral center for Maritime Canada representing 3 provinces and a population base of 1.8 million. Children were eligible to participate if they (1) were between the ages of 8 and 17 years, (2) were previously diagnosed with any type of cancer, (3) had completed cancer-related treatment and had not

experienced a recurrence or secondary cancer, and (4) were able to speak and understand English. Exclusion criteria were (1) the presence of a medical condition with an associated pain manifestation unrelated to cancer and its effects (eg, juvenile idiopathic arthritis), (2) parent-reported cognitive difficulties that would impact the child's ability to participate in the study tasks, and (3) hearing or vision impairments not corrected with glasses or hearing aids. Participants and their parents or guardians were initially contacted through a letter by a member of the clinical team to introduce the study. Study staff then followed up by telephone to further explain the study and confirm eligibility.

2.2. Procedure

Ethical approval was obtained from the IWK Research Ethics Board (#1023720). Informed written parental consent was obtained for all participants before participation. Youth between the ages of 13 and 17 years who were deemed to have the capacity to consent according to the procedure published by Nadin et al.⁴⁵ were asked to provide their consent to participate, whereas those aged 8 to 12 years provided assent. The study conformed to the standards set by the Declaration of Helsinki. The study employed best practices in patient-oriented research, including engagement of patient partners throughout all steps of the research process.⁴⁹

Participants were recruited between April 2019 and March 2020. Children completed self-report measures (described below) to assess psychosocial functioning, and parents completed a demographic questionnaire. Children completed their questionnaires separately from their parents in a testing room with a research assistant. Children then took part in the QST tasks to assess sensory function while parents waited in the research centre lobby. At the end of the study visit, children and parents were debriefed and were each given a \$20 gift card as an honorarium. Parents received an additional \$15 or \$30 gift card based on the distance travelled, to assist with travel costs.

2.3. Measures

2.3.1. Demographic and medical data

Parents reported on their child's age, sex, and race and completed a medication record detailing their child's current medications and timing of last dose taken. Clinical information including primary diagnosis, age at diagnosis, chemotherapy, radiation, major surgery, bone marrow or stem cell transplant, and date of final treatment were abstracted from medical records. The Intensity of Treatment Rating Scale 3.0 (ITR-3) was used to classify the overall intensity of treatment received. The ITR-3 is a validated oncology-specific measure that classifies the level of treatment intensity received from 1 (minimally intensive) to 4 (most intensive) based on diagnosis, disease stage, and treatments.³² Ratings were completed by 2 trained independent raters based on information from participants' medical records, with input from a pediatric oncologist, as needed. No rating discrepancies in ITR-3 ratings occurred.

2.3.2. Pain catastrophizing

Children reported on their tendency to engage in catastrophic thinking when they are in pain using the Pain Catastrophizing Scale for Children (PCS-C).¹⁶ The Pain Catastrophizing Scale for Children contains 13 items across 3 subscales, the tendency to (1) magnify the threat value, (2) ruminate about, and (3) feel helpless in the face of pain. Each item is rated on a 5-point Likert

scale ranging from 0 (not at all) to 4 (extremely). Total scores range from 0 to 52 with higher scores indicating greater tendency to catastrophize; clinical reference points are low (0-14), moderate (15-25), and high (≥ 26) catastrophizing.⁵¹ Internal consistency in this sample was excellent ($\alpha = 0.92$).

2.3.3. Anxiety

Children reported on their anxiety symptoms using the 15-item Total Anxiety subscale of the Revised Children's Anxiety and Depression Scale short version (RCADS-25).¹⁹ Children indicated how often each item applies to them on a 4-point Likert scale ranging from 0 (never) to 3 (always). Total scores range from 0 to 45, with higher scores indicating more frequent anxiety symptoms. An established cutoff score of ≥ 12 was used to identify participants with clinical symptoms of anxiety.³³ Internal consistency in this sample was good ($\alpha = 0.86$).

2.3.4. Self-report symptoms of peripheral neuropathy

Children reported on symptoms of peripheral neuropathy using the interview items from the pediatric-modified Total Neuropathy Score (ped-mTNS).²⁴ The questions assess the presence or absence of children's sensory symptoms ("Do you have any parts of your body that are tingly, numb (can hardly feel) or hurt?"), functional symptoms ("Do you have trouble buttoning shirts or zipping zippers?", "Do you have trouble walking such as tripping frequently?" and "Do you have trouble going up or down stairs?"), and autonomic symptoms ("Do you feel dizzy or light-headed when you get up out of bed?" and "Do your hands or feet feel hotter or colder than normal?"). If children answer yes to any of the questions, the severity is rated on a 5-point Likert scale ranging from 0 (none) to 4 (symptoms extend above knee or elbow) for sensory function questions, 0 (not difficult) to 4 (I can't do that at all) for functional symptoms questions, and 0 (never) to 4 (almost always) for autonomic symptom questions. The highest severity score in each symptom category is recorded as the overall score for Sensory Symptoms, Functional Symptoms, and Autonomic Symptoms. Deficits are defined as overall symptom scores >0 .

2.4. Quantitative sensory testing

The QST protocol was an abbreviated version of the German Research Network on Neuropathic Pain (DFNS) standardized protocol⁵⁵ for children and adolescents.⁸ Quantitative sensory testing was performed in the same quiet room for all participants. The mean room temperature was 22.7°C (SD = 0.92). The QST tests were performed on the thenar eminence of the right hand by a trained female research assistant. The thermal thresholds were established using the method of limits, where the thermal stimulus is gradually increased until the participant reports detection of the sensation (thermal detection thresholds) or the experience of pain (thermal pain thresholds). The mechanical detection threshold (MDT) and mechanical pain threshold (MPT) were determined using a modified method of constant stimuli. In this procedure, mechanical stimuli of ascending intensity are applied, and after each stimulus, participants report whether the stimulus was detected or painful. The threshold is determined when 2/3 applications are detected (MDT) or painful (MPT).²⁸ Skin surface temperature was measured at the test site immediately before beginning the QST protocol using an infrared thermometer (Easy@Home JXB-178, China), the mean of which was 36.2°C (SD = 0.52). All participants were familiarised with the equipment and instructions before the test. Test trials were conducted on

areas not tested during the QST session to introduce participants to the procedures. Comprehension of the test instructions was confirmed by having participants repeat the instructions back in their own words. See supplementary materials for a copy of the QST script (available at <http://links.lww.com/PAIN/B496>). All participants wore a blindfold during testing. Concentration was maintained throughout the protocol, and breaks were provided as needed. Overall, the QST protocol took 24.07 minutes (SD = 3.43) to complete.

2.4.1. Mechanical detection threshold

Mechanical detection thresholds (MDTs) were determined using a set of standardized von Frey hairs (North Coast Medical) that exert fixed forces between 0.008 g and 300 g upon bending. The hairs were applied perpendicularly to the skin, bending for 1 second on a contact area of 0.5 mm in diameter. Participants were asked to report whether they felt the sensation of the hair. If the participant answered no, either the same hair or the next heaviest hair was randomly chosen to be applied to keep the participant blinded to the algorithm. The hairs were applied in an ascending order until participants responded that they felt the hair. When the participant first reported a sensation, the same filament was applied an additional 2 times. The threshold was identified when the participant reported feeling the sensation at least 2 of 3 times. The final threshold was the geometric mean of 3 threshold measures.

2.4.2. Mechanical pain threshold

A set of 7 weighted pinprick stimulators (MRC Innovative Treatment Solutions) with standardized intensity forces (8, 16, 32, 64, 128, 256, and 512 mN) were used to assess MPT. Starting with the lowest intensity, pinpricks were applied perpendicularly to the skin at the centre of the thenar eminence. Participants were asked to reply sharp if the stimulus was perceived as sharp, pricking, or stinging. The stimulus was applied an additional 2 times. The threshold was identified when the participant-reported responses were sharp at least 2 of 3 times. The final threshold was the geometric mean of the 3 threshold measures.

2.4.3. Mechanical pain sensitivity and dynamic mechanical allodynia

Mechanical pain sensitivity (MPS) was determined using the set of 7 weighted pinprick stimulators. Dynamic mechanical allodynia (ie, DMA; pain to light touch) was determined using a set of 3 light tactile stimulators: a cotton wisp, a Q-tip fixed to an elastic strip, and a standardized soft brush (Somedic, Sweden). The 7 pinpricks and 3 light tactile stimulators were each applied 5 times in a pseudorandomized order for a total of 50 stimuli (35 pinprick and 15 tactile). Stimuli were applied with a 10-second interstimulus interval. Participants were asked to give a pain rating using a numerical rating scale ranging from 0 (no pain) to 10 (the worst pain you could imagine). The final MPS was the geometric mean of the 35 pinprick pain ratings. The final DMA was the geometric mean of the 15 pain ratings across the 3 types of light stimuli.

2.4.4. Wind-up ratio

The wind-up ratio (WUR) was determined by comparing the perceived intensity of a single pinprick (256 mN) applied to a 1-cm

area on the thenar eminence to the perceived intensity of a series of 10 repetitive stimuli (at a frequency of 1/second) of the same force. Participants were asked to give a pain rating from 0 (no pain) to 10 (the worst pain you could imagine) immediately after the first stimulus and again after the series of 10 stimuli. This was done in 5 repetitions. The WUR was calculated as the ratio between the rating for the single stimulus and the series of stimuli (the mean rating of the 5 series divided by the mean rating of the 5 single stimuli). The WUR measures the temporal summation of pain.⁵⁵

2.4.5. Cool and warm detection and cold and heat pain thresholds

Thermal thresholds were determined using a computer-operated thermal sensory testing device (Neurosensory Analyzer TSA-II, Medoc Inc, Ramat Yishai, Israel). A 30 × 30 mm thermode was attached to the child's thenar eminence using a Velcro strap. The baseline temperature was 32°C, and the upper and lower cutoff limits were 0 and 50°C. Thresholds were determined using ramped stimuli at a rate of 1.5°C/second for cool detection (CDT) and warm detection (WDT) and 1.0°C/second for cold pain (CPT) and heat pain (HPT). Participants were asked to identify when they first felt a change in temperature for CDT and WDT and when the sensations first became painful for CPT and HPT by pressing a button. The temperature was automatically recorded once the button was pressed, and the thermode temperature returned to baseline at a rate of 1°C/second for the detection thresholds and 10°C/second for the pain thresholds. CDT and WDT were repeated 4 times, and CPT and HPT were repeated 3 times. The final thresholds were calculated as the arithmetic means of the consecutive trials and expressed as change in degrees from the baseline temperature.

2.5. Statistical analysis

Analyses were performed using SPSS version 26 (SPSS Inc, Chicago, IL) and GraphPad Prism 9 (GraphPad Software, Inc) according to standard DFNS procedures for children.⁸

2.5.1. Data processing

Absolute QST data are presented as mean ± SD. Quantitative sensory testing parameters (except CPT and HPT) were logarithmically transformed before analysis to achieve a normal distribution. CDT values were multiplied by -1 to allow for log transformation. A negligible constant (+0.1) was added to MPS and DMA pain ratings to avoid loss of zero-rating values. When log transformations were performed, the log-scores were used for the calculation of z-scores, *t*-tests, and correlations. For clarity, absolute values representing the original units of each test are reported in tables and used in figures, unless otherwise indicated. *P* < 0.05 was considered statistically significant for all tests.

In line with similar QST studies,^{21,26} no adjustments were made for multiple comparisons. Past research suggests that such corrections are considered to be overly conservative in cases in which outcome variables are correlated,⁵³ as is the case among QST parameters.⁶ Thus, corrections were not made in the current study.

2.5.2. Calculation of Z-scores

Log-transformed QST data were standardized using a z-transformation based on published age, sex, and site-specific

reference values.⁸ The z-transformation was calculated using the following formula: $z\text{-score} = (\text{mean}_{\text{participant}} - \text{mean}_{\text{refvalues}}) / \text{SD}_{\text{refvalues}}$.

For ease of interpretation of gain and loss of sensitivity and in line with the DFNS protocol,⁴⁰ the sign of the z-score was reversed such that scores >0 reflect gain in sensitivity (eg, lower intensity stimuli required for detection or pain) and scores <0 reflect loss of sensitivity (eg, higher intensity stimuli required for detection or pain). As such, the z-scores for CDT, WDT, HPT, MDT, and MPT were reversed. Z-scores outside the 95% confidence interval of the reference values were considered abnormal, with scores >1.96 indicating gain of somatosensory sensitivity and scores <-1.96 indicating loss of somatosensory sensitivity. Raw data for DMA are presented, and mean values > 0 were considered abnormal.⁸

2.5.3. Missing data

For 6 participants, the WUR could not be calculated because the single pinprick stimulus (the denominator) was rated as 0 across all trials.⁵⁵ In 6 additional cases, participants rated the single pinprick stimulus as 0 for only one of the 5 trials. Here, this value was replaced with the mean value of the other 4 single pinprick scores, and a WUR was calculated.⁵⁴ Five participants had incomplete WUR data (3 participants completed 3/5 trials, and 2 participants completed 2/5 trials). These participants were retained in the analysis using a last observation carried forward approach for the incomplete trials per published recommendations.^{23,68} Missing questionnaire data were minimal (<1%). For questionnaires where at least 80% of items were complete, the individual's mean score was used as a replacement for missing items.

2.5.4. Comparison with reference values

Participants' mean (SD) z-transformed QST data were compared with published age- and sex-matched reference values⁸ at a mean of 0 and SD of 1 with an equal number of cases per parameter using 2-sided independent samples *t*-tests according to Magerl and colleagues.³⁹ Thus, total sample sizes for these analysis ranged from *N* = 80 to *N* = 112. Differences in mean threshold values for children with leukemia vs other diagnoses were evaluated using 2-sided *t* tests for independent samples in line with standard procedures. Effect sizes are reported as Cohen's *d* and were defined as *d* = 0.2 small, *d* = 0.5 medium, and *d* = 0.8 large.¹⁴

2.5.5. Examination of risk factors

The relationships between sensory thresholds and clinical and psychological factors were tested using Pearson correlations. Following the same convention described for the z-scores above, the sign of the correlation was reversed for CDT, WDT, MDT, and MPT such that positive correlations represent more sensitivity, and negative correlations represent less sensitivity.

2.5.6. Sensitivity power analysis

A sensitivity power analysis was performed using G*Power 3.1²² to determine the minimum detectable effect size (expressed as Cohen's *d*) for differences in QST parameters between the childhood cancer survivor group and the reference values. Given $\alpha = 0.05$ and $\beta = 0.8$ for 2-tailed independent *t*-tests, the lower bound of effect sizes required to achieve significance was of medium size and ranged from *d* = 0.47 (for *N* = 112) to *d* = 0.56 (for *N* = 80).

3. Results

3.1. Study participants

Of the 156 potential participants who were sent introductory letters, 57 (37%) consented to participate. Reasons for non-participation included the following: not eligible (n = 21), unable to reach by telephone (n = 18), not interested (n = 42), distance too far (n = 12), and scheduling conflict (n = 6). One child declined to complete all QST tasks, opting only to complete the questionnaires. This participant's data were not used in the analysis. The final sample comprised 56 survivors of childhood cancer.

Most participants opted to complete all tests, although 22% of participants declined to participate in the pinprick-related tasks because of fear and anxiety. Overall, 1 participant declined to participate in MPT testing, 9 declined to participate

in MPS testing, 10 declined to participate in WUR testing, and 4 declined to participate in DMA testing. One participant declined to participate in the heat pain task, and another was unable to complete any thermal tasks because of equipment failure. The flow of participants through the study is depicted in **Figure 1**.

3.2. Demographic characteristics and questionnaires

Children ranged in age from 8 to 17 years ($M_{age} = 13.5$, $SD = 3.2$), and 48% were female. The 3 most common cancer diagnoses were acute lymphoblastic leukemia (42.9%), Wilms tumour (12.5%), and neuroblastoma (10.7%). On average, children were diagnosed at 4.9 years of age ($SD = 3.2$) and at the time of participation, had been off treatment for 7.1 years ($SD = 4.1$). Almost all (92.9%) children identified as White. None

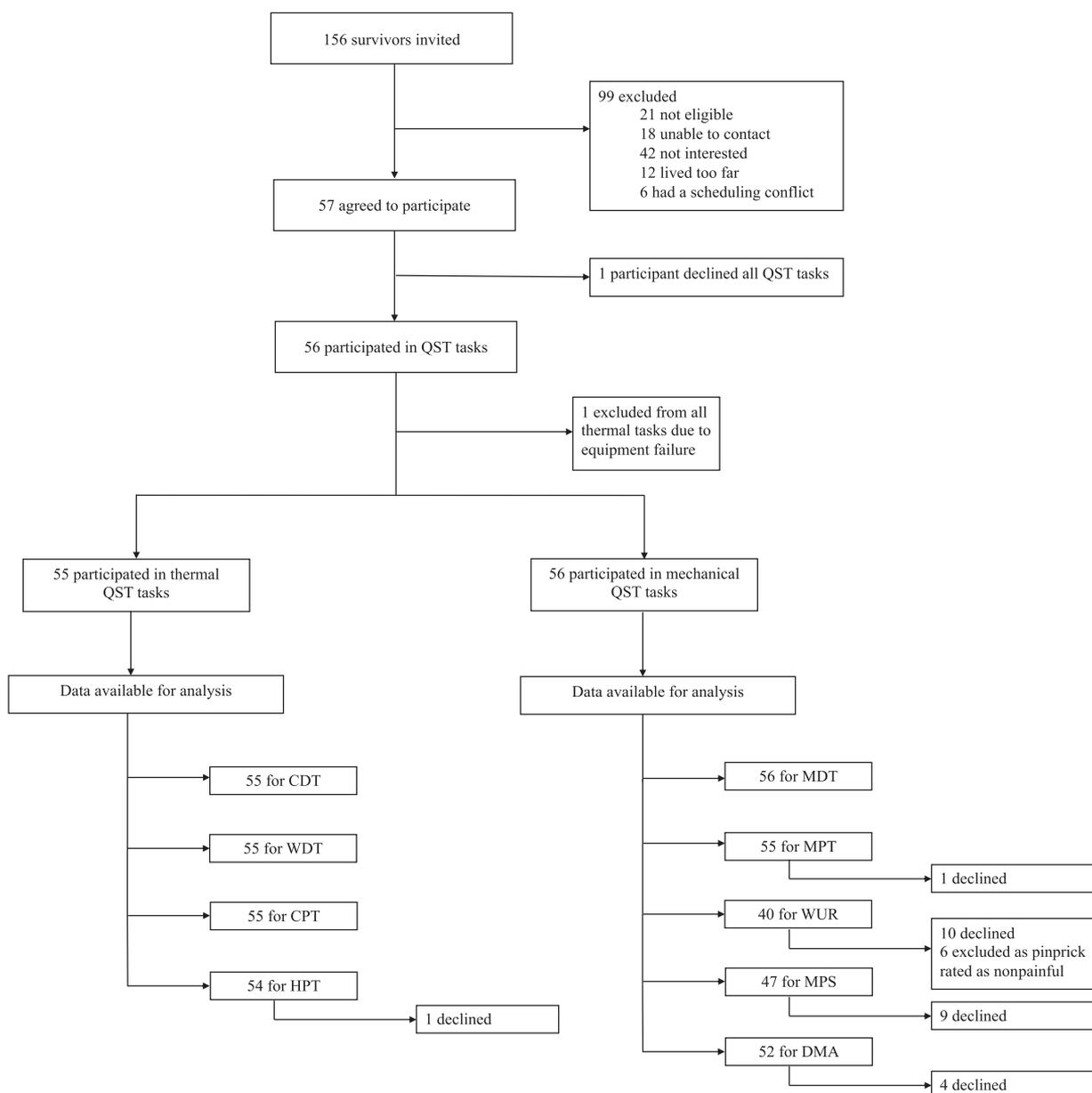


Figure 1. Flow of participants through the study. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; QST, quantitative sensory testing; WDT, warm detection threshold; WUR, wind-up ratio.

Table 1
Demographic characteristics.

Characteristics	Total (N = 56)	Leukemia (N = 29)	Other diagnosis (N = 27)	P*
Age at participation, mean (SD) range, y	13.5 (3.2) 8.4-17.9	13.5 (3.1) 8.5-17.8	13.5 (3.3) 8.4-17.9	0.99
Sex, no. female (%)	27 (48.2)	15 (51.7)	12 (44.4)	0.61
Age at diagnosis, mean (SD) range, y	4.9 (3.2) 0.2-13.8	5.0 (2.9) 0.3-11.3	4.9 (3.6) 0.2-13.8	0.89
Time since treatment completion, mean (SD) range, y	7.1 (4.1) 1.2-16.5	6.3 (3.5) 1.3-14.5	7.9 (4.6) 1.2-16.5	0.12
Race no. (%)				0.80
White	52 (92.9)	27 (93.1)	25 (92.6)	
Native/Aboriginal	3 (5.4)	2 (6.9)	1 (3.7)	
Other	1 (1.8)	0 (0)	1 (3.7)	
Diagnosis, no. (%)				
Leukemia	29 (51.8)	29 (100)	0 (0)	
Wilms tumor	7 (12.5)	0 (0)	7 (12.5)	
Neuroblastoma	6 (10.7)	0 (0)	6 (10.7)	
Lymphoma	5 (8.9)	0 (0)	5 (8.9)	
Sarcoma	5 (8.9)	0 (0)	5 (8.9)	
CNS tumor	2 (3.6)	0 (0)	2 (3.6)	
Other†	2 (3.6)	0 (0)	2 (3.6)	
Chemotherapy, no. (%)	55 (98.2)	29 (100)	26 (96.3)	0.48
Platinum agents	11 (19.6)	1 (3.4)	10 (37)	<0.01
Glucocorticoids	31 (56.4)	24 (82.8)	7 (25.9)	<0.001
Vincristine	47 (83.9)	24 (82.8)	23 (85.2)	0.71
Cumulative dose, mean (SD), range, mg/m ²	38.5 (25.3) 2.0-79.5	59.5 (15.1) 22.5-79.5	16.5 (11.0) 2.0-45	<0.001
Radiation, no. (%)	15 (26.8)	4 (13.8)	11 (40.7)	<0.05
CNS-directed	4 (7.1)	3 (10.3)	1 (3.7)	<0.05
Surgery, no. (%)	27 (48.2)	1 (3.4)	26 (96.3)	<0.001
Resection (tumor or organ)	22 (39.3)	0 (0)	22 (81.5)	<0.001
Open biopsy	14 (25)	1 (3.4)	13 (48.1)	<0.001
Other‡	4 (7.1)	0 (0)	4 (14.8)	<0.001
Bone marrow or stem cell transplant, no. (%)	8 (14.3)	2 (6.9)	6 (22.2)	0.14
Intensity of treatment, mean (SD) range	2.7 (0.90) 1-4	2.8 (0.7) 2-4	2.6 (1.0) 1-4	0.50

*Independent samples t-test or Fisher's exact test.

†Other diagnoses included the following: retinoblastoma and hepatoblastoma.

‡Other surgeries included the following: enucleation, solid organ transplant, thoracotomy, and vaginoplasty.

CNS, central nervous system.

of the children had taken any analgesics or adjuvant pain medications 24 hours before participation. Almost all children reported that they were right handed ($n = 48$, 85.7%), whereas 10.7% ($n = 6$) were left handed and 3.6% ($n = 2$) were ambidextrous. See **Table 1** for complete demographic characteristics.

Results of the child-reported questionnaires are displayed in **Table 2**. Sensory deficits were reported in 25.5% of participants, functional deficits in 34.5%, and autonomic deficits in 56.4%, as

measured by the Ped-mTNS. Seven participants (12.7%) indicated having parts of their body that hurt: $n = 4$ (7.3%) reported pain above the knee or elbow, $n = 2$ (3.6%) reported pain extending to the knee or elbow, and $n = 1$ (1.8%) reported pain limited to the fingers or toes. Although the average level of anxiety in the sample was low, 12 participants (21.4%) exhibited scores above the clinical cutoff. On average, participants reported moderate levels of pain catastrophizing with 11 participants (19.6%) exhibiting high levels (score ≥ 26).

Table 2
Self-report measures.

	Total (N = 56)		Leukemia (N = 29)		Other diagnosis (N = 27)	
	Mean (SD), range	% With deficit	Mean (SD), range	% With deficit	Mean (SD), range	% With deficit
Ped-mTNS items						
Sensory symptoms	0.67 (1.35), 0-4	25.5	0.69 (1.31), 0-4	31.0	0.68 (1.44), 0-4	20
Functional symptoms	0.56 (0.92), 0-4	34.5	0.55 (0.95), 0-4	34.5	0.48 (0.77), 0-2	32
Autonomic symptoms	1.22 (1.26), 0-4	56.4	1.07 (1.36), 0-4	44.8	1.36 (1.15), 0-3	68
Anxiety symptoms	9.32 (7.14), 0-30		8.55 (5.95), 0-29		9.59 (7.89), 1-30	
Pain catastrophizing	15.07 (10.40), 0-43		15.36 (11.22), 0-43		14.26 (9.47), 3-39	

Deficit refers to a score >0 on the ped-mTNS.

Ped-mTNS, pediatric-modified Total Neuropathy Score.

3.3. Somatosensory profile of survivors of childhood cancer

Almost all participants (n = 48, 85.7%) showed at least one abnormal QST parameter. Of those with abnormalities, n = 29 (60.4%) had 2 or more, n = 11 (22.9%) had 3 or more, and n = 7 (14.6%) had 4 abnormal parameters.

3.3.1. Spectrum of sensory abnormalities at the individual level

The proportion of participants at the individual level that showed normal, loss of, and gain of sensitivity across the QST parameters is shown in **Figure 2**.

Decreased sensitivity was observed for thermal detection and pain perception in 20 (35.7%) participants overall (CDT: n = 7, 12.7%; WDT: n = 1, 1.8%; CPT: n = 10, 18.2%; HPT: n = 9, 16.7%). For mechanical detection and pain perception, loss of sensitivity was observed in 26 (46.4%) total participants (MDT: n = 6, 10.7%; MPT: n = 24, 43.6%).

Increased sensitivity was observed for thermal pain sensitivity in 2 (3.6%) participants overall, n = 1 participant each in CPT (1.8%) and HPT (1.8%). A total of 24 (42.9%) participants displayed gain of sensitivity for mechanical sensitivity (MPT: n = 2, 3.6%; MPS: n = 21, 44.7%; DMA: n = 10, 19.2%). Temporal summation, as measured by WUR, was within normative ranges for all participants who completed the parameter (**Table 3** for group means).

3.3.2. Comparison between survivors and the reference values

As a group, loss of sensitivity was found for all thermal detection and pain perception modalities CDT $t(108) = 5.08, P < 0.001, d = 0.97$, WDT $t(108) = 3.21, P < 0.01, d = 0.61$, CPT $t(108) = 3.45, P < 0.001, d = 0.66$, HPT $t(106) = 2.07, P =$

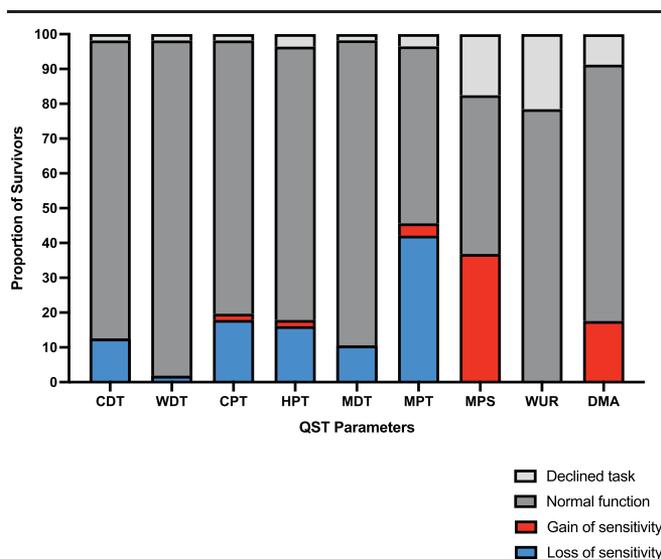


Figure 2. Patterns of sensory abnormalities in childhood cancer survivors. The proportion of individual z-scores above the upper bound of the 95% CI of the reference data (ie, > 1.96) is represented in red, and the proportion of individual z-scores below the lower bound of the 95% CI of the reference data (ie, < -1.96) is represented in blue. The proportion of children who declined to complete each task is shown in light grey. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; QST, quantitative sensory testing; WDT, warm detection threshold; WUR, wind-up ratio.

0.04, $d = 0.40$ compared with the reference data. Similarly, loss of sensitivity was found for mechanical detection and pain perception: MDT $t(110) = 2.20, P = 0.03, d = 0.42$, MPT $t(108) = 6.70, P < 0.001, d = 1.28$, and WUR $t(78) = 2.65, P = 0.01, d = 0.59$ compared with the reference data. Gain of sensitivity was limited to MPS $t(92) = 7.60, P < 0.001, d = 0.42$ compared with the reference data (**Fig. 3**).

3.3.3. Comparison between survivors with leukemia vs other diagnoses

Participants with a history of leukemia exhibited decreased sensitivity to noxious cold stimuli (ie, lower CPT) $t(53) = 2.35, P < 0.05, d = 0.65$ and increased sensitivity to noxious mechanical stimuli (ie, lower MPT) $t(53) = 2.22, P < 0.05, d = 0.61$, compared with children with other cancer diagnoses. Thresholds for the other QST parameters did not vary significantly between groups (**Fig. 4**).

3.4. Correlation with risk factors

The relationships between key demographic, clinical, and psychosocial factors and the QST parameters are shown in **Figure 5**. See supplementary material for complete correlation table (available at <http://links.lww.com/PAIN/B496>).

3.4.1. Demographic correlates

Younger age at the time of study was associated with increased sensitivity to heat pain (HPT: $r = -0.32, P < 0.05$) and higher mechanical pain scores (MPS: $r = -0.47, P < 0.01$).

Sex was significantly correlated with mechanical detection (MDT: $r = -0.30, P < 0.05$), with boys showing less sensitivity than girls (male and female absolute geometric means \pm SD: 0.33 ± 0.14 vs 0.63 ± 0.63).

Similar to the relationship between participant age and sensitivity to heat pain, children who were off treatment for longer showed less sensitivity to heat pain (HPT: $r = -0.32, P < 0.05$). However, there was no relationship between age at diagnosis and any QST parameters (P 's > 0.05).

3.4.2. Clinical correlates

Reduced sensitivity to cold pain was associated with having received a greater cumulative dose of vincristine (CPT: $r = -0.31, P < 0.05$). Conversely, participants with a history of major surgery during treatment exhibited heightened sensitivity to cold pain (CPT: $r = 0.34, P < 0.05$).

Similarly, participants who underwent major surgery had higher thresholds for mechanical pain (MPT: $r = 0.24, P < 0.05$). Participants who received higher cumulative doses of vincristine displayed greater sensitivity (ie, lower thresholds) to mechanical pain (MPT: $r = -0.29, P < 0.05$).

Participants who received a bone marrow or stem cell transplant exhibited greater DMA scores compared with those who did not (ie, allodynia; $r = 0.37, P < 0.01$).

Overall intensity of treatment was not associated with any QST parameters, nor was receipt of platinum agents, glucocorticoids, or radiation therapy (P 's > 0.05).

3.4.3. Psychosocial correlates

Children who scored higher on measures of pain catastrophizing and anxiety displayed increased sensitivity across certain

Table 3

Quantitative sensory testing (QST) absolute values for childhood cancer survivors.

QST parameter	Units	n	Mean	SD	95% CI	
					Low	High
Cold detection threshold (CDT)	Δ°C	55	1.82	0.96	1.55	2.01
Warm detection threshold (WDT)	Δ°C	55	2.03	0.70	1.84	2.21
Cold pain threshold (CPT)	°C	55	12.65	8.92	10.24	15.06
Heat pain threshold (HPT)	°C	54	43.33	5.0	41.97	44.69
Mechanical detection threshold (MDT)	mN	56	0.47	0.47	0.35	0.60
Mechanical pain threshold (MPT)	mN	55	167.50	144.34	128.45	206.49
Mechanical pain sensitivity (MPS)	NRS	47	9.52	14.29	5.33	13.71
Wind-up ratio (WUR)	Ratio	40	1.79	0.79	1.54	2.04
Dynamic mechanical allodynia (DMA)	NRS	52	0.34	1.09	0.04	0.65

C, celsius; mN, millinewtons; NRS, numerical rating scale.

parameters. Specifically, higher pain catastrophizing scores were correlated with increased sensitivity to cold pain (CPT: $r = 0.38$, $P < 0.01$), and higher anxiety scores were associated with greater sensitivity to mechanical pain (MPT: $r = 0.27$, $P < 0.05$) and wind-up (WUR: $r = 0.41$, $P < 0.01$).

4. Discussion

This study examined the somatosensory profiles of survivors of childhood cancer using a standardized QST protocol. The sensory profiles revealed pervasive changes in somatosensation present years after treatment completion. In this study, over 85% of survivors of childhood cancer survivors (mean time off treatment >7 years) had at least 1 sensory abnormality compared with age- and sex-matched reference data.

Generally, participants in this study demonstrated increased thresholds (ie, reduced sensitivity) across the QST parameters examined. A significant proportion also exhibited pain sensitization, evidenced by gain in sensitivity for MPS and DMA. Examination beyond the group-level data revealed variation across participants in the pattern of sensory abnormalities, with some participants experiencing loss and others experiencing gain of sensitivity across parameters. These findings are in line with past qualitative work suggesting that pain is a changed experience after cancer with some survivors reporting increased pain, others reporting decreased pain, and some reporting no change.⁶⁶ The heterogeneity in the somatosensory phenotype is expected given the complexity of diagnoses, painful procedures, treatment exposures, and psychosocial profiles inherently characteristic of the cancer experience.

Although almost all participants had at least 1 QST-measured sensory abnormality, only 26% self-reported sensory deficits and only 35% self-reported functional deficits on the Ped-mTNS. It is possible that the sensory differences observed via QST were subclinical and had not progressed to a severity that would cause clinically significant symptoms to be reported, but may, nevertheless, confer risk for this later outcome. Alternatively, survivors may have adapted to sensory changes that occurred and, therefore, not recognize them as abnormal. Many survivors were treated at an age too young to recall what their sensory processing was like before cancer, thus limiting their ability to identify changes. Baseline sensory testing before the initiation of treatment may provide an opportunity for the individualized assessment of sensory changes after childhood cancer. The results of this study

may help inform conversations between clinicians and patients about typical expected sensory changes that may occur after treatment.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common neurologic effect of cancer treatment, predominately in survivors of ALL. Sensory abnormalities that accompany the presentation of CIPN can include negative (eg, hypoesthesia) or positive (eg, hyperalgesia) signs,⁴⁷ and both were observed in this study. Although a diagnosis of CIPN cannot be made based on QST alone, hypoesthesia was present in 13% of participants for thermal and 10% for mechanical stimuli, which may reflect the deafferentation of small- and large-fibres secondary to neurotoxic treatments. Pain sensitization was observed in 45% of participants. This value is likely an underestimation given that 22% of participants declined to participate in pinprick tasks.

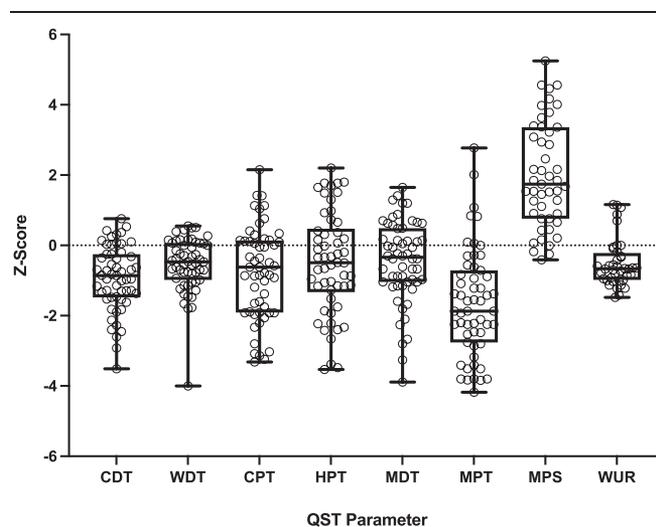


Figure 3. Quantitative sensory testing results in childhood cancer survivors. Data for the QST parameters are presented as z-scores. Single dots represent individuals' mean scores. Box and whisker plot illustrates the group median, IQR, and range. Z-scores outside the 95% confidence interval of the reference data were considered abnormal, with scores >1.96 indicating gain of sensitivity and scores <-1.96 indicating loss of sensitivity. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; QST, quantitative sensory testing; WDT, warm detection threshold; WUR, wind-up ratio.

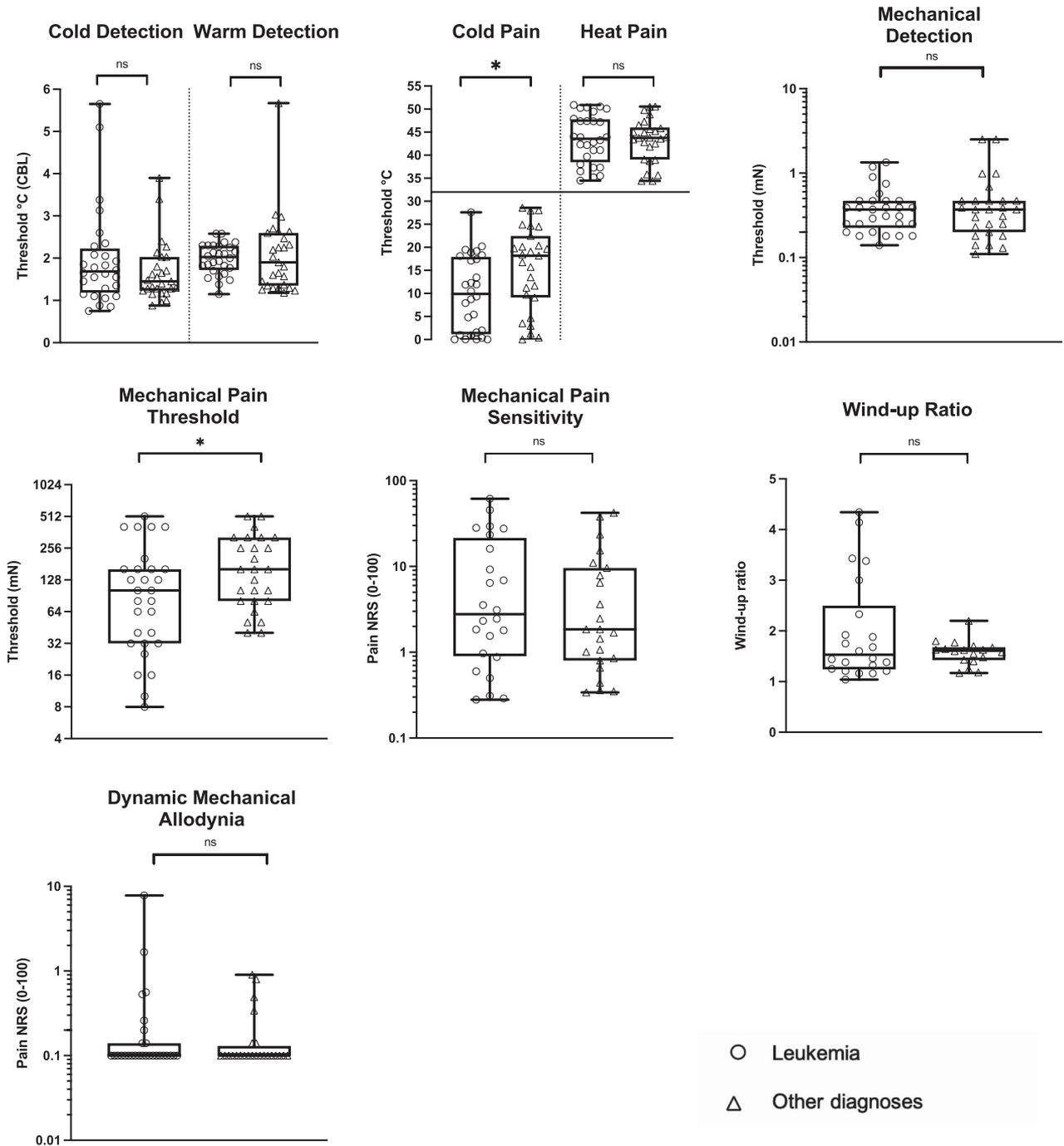


Figure 4. Comparison of somatosensory profiles between children with histories of leukemia (circles; n = 29) vs other diagnoses (triangles; n = 27). Children with a history of leukemia had less sensitivity to cold pain and greater sensitivity to mechanical pain. Single dots represent individuals' mean scores on each parameter. Box and whisker plots illustrate the group median, IQR and range. CBL, change from baseline; mN, millinewtons; NRS, numerical rating scale. **P* < 0.05.

Nonetheless, the high level of sensitization observed links with existing research and may be due to both peripheral and central mechanisms.

Peripherally, mechanical hypersensitivity to pinprick and light touch may reflect the hyperexcitability of peripheral neurons due to neural damage caused by chemotherapy and repeated exposure to noxious stimuli during treatment. Vincristine is believed to cause peripheral hyperexcitability, secondary to distal axonopathy (ie, nerve degeneration beginning at the terminal of peripheral fibres) and Wallerian degeneration (ie, self-destructive

retrograde degeneration of an axon resulting from a nerve lesion).⁷² In this study, participants with a history of leukemia displayed greater sensitivity to noxious mechanical stimuli (eg, lower MPT). Children with leukemia received significantly greater cumulative doses of vincristine compared with children with other diagnoses (**Table 1**), which was associated with increased sensitivity to mechanical pain (**Fig. 5**). This finding is in line with translational work that has found mechanical pain hypersensitivity in animal models exposed to vincristine⁵⁷ and clinical studies with vincristine-treated adult cancer survivors.¹⁸

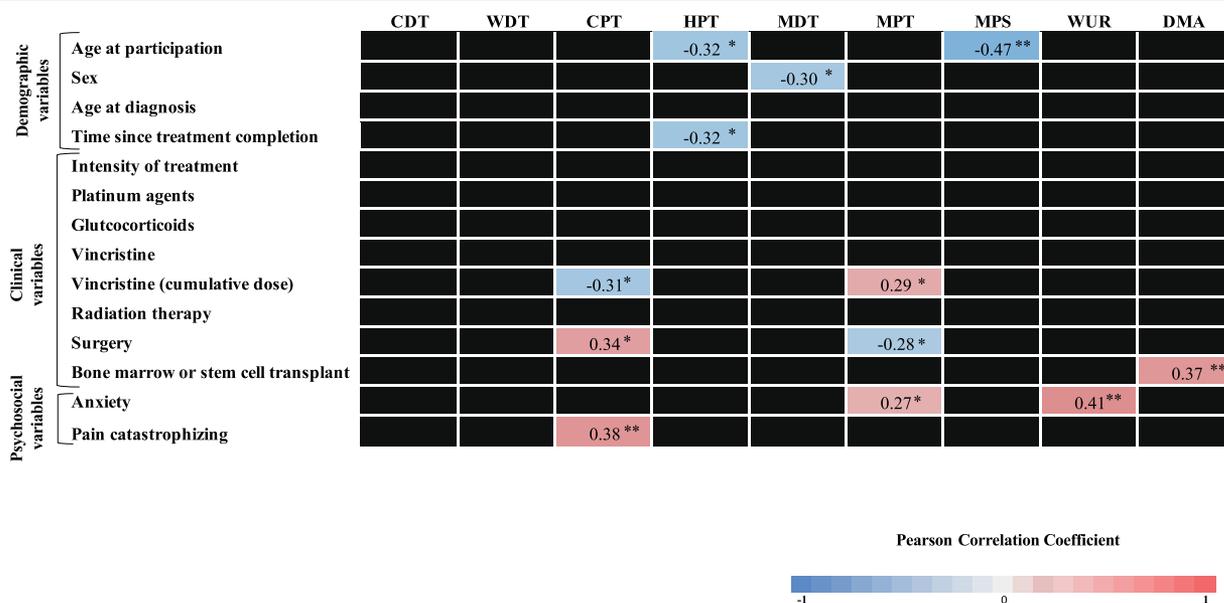


Figure 5. Relationship between demographic, clinical, and psychosocial variables and QST parameters in survivors of childhood cancer. The heat map depicts Pearson correlation coefficients. Significant correlations are colored red (positive relationship) or blue (negative relationship). See supplementary material for complete correlation table (available at <http://links.lww.com/PAIN/B496>). CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; WDT, warm detection threshold. **P* < 0.05; ***P* < 0.01.

The existing literature suggests that 30% to 52% of survivors of pediatric ALL experience pain sensitization measured by QST.^{36,56} However, these studies were conducted in samples comprised exclusively of survivors of ALL and were unable to examine the potential impact of vincristine on sensory outcomes, nor the differences between children with leukemia vs other diagnoses. This study builds on this existing work and lends support to the hypothesis that survivors of childhood leukemia may be a high-risk group for somatosensory changes after cancer, perhaps because of the type (eg, vincristine) and amount (eg, cumulative dose) of neurotoxic treatments received. That said, the cumulative dose of vincristine has been inconsistently related to neurotoxicity^{30,62} and requires further examination. Children with hematologic malignancies also receive other drugs with known neurotoxic effects, including those administered intrathecally,^{35,46} and undergo repeated invasive procedures (eg, lumbar punctures) over many years of treatment. It is possible that these factors cumulatively and uniquely prime children with a history of leukemia to sensory changes. Nevertheless, somatosensation is a complex biopsychosocial process, particularly in the context of cancer survivorship. In line with proposed conceptual models,^{1,59} it is likely that a range of factors beyond those that are treatment related (eg, sleep, physical activity, and other late effects of treatment) contribute to pain and sensory processing in this population.

Pain sensitization may also reflect the involvement of central mechanisms. Hyperactivity in injured peripheral nerves can lead to the sensitization of central nociceptive pathways via synaptic facilitation in the dorsal horn.⁴³ Central sensitization is believed to be a key mechanism underpinning the development and maintenance of chronic pain.²⁷ Chronic pain in survivors of childhood cancer is increasingly recognized as a potential late effect of cancer treatment.^{1,59} Although only 13% of participants in this study reported having pain on the Ped-mTNS, as many as 45% exhibited pain sensitization on QST. These

results may reflect early sensory changes that precede future chronic pain pathology. That said, overall reduced sensory sensitivity has also been hypothesized as a risk factor for the development of persistent widespread pain.⁴⁴ Prospective longitudinal studies would be valuable to elucidate the trajectory of symptoms over time and their relationship with QST parameters.

In this study, several demographic, clinical, and psychosocial variables were associated with somatosensation in survivors of childhood cancer. The overall treatment intensity was not correlated with any QST parameters. However, the relationships of QST parameters identified with intrathecal chemotherapy, history of major surgery, and higher cumulative dose of vincristine suggest that specific examination of the cumulative neurotoxic risk may be more informative as opposed to a global rating of treatment intensity. Children who received a bone marrow or stem cell transplant displayed higher DMA scores. This finding builds on data from Ruscher and colleagues,⁵⁶ highlighting this subgroup as potentially high risk for sensitization.

Interestingly, albeit not unexpectedly, children with greater self-reported pain catastrophizing and anxiety displayed increased sensitivity across different parameters. Similar findings have been noted in adult cancer survivors²¹ and children with other chronic illnesses (eg, sickle cell disease⁴ and arthritis¹⁵). Anxiety and catastrophizing are known to modulate pain sensitivity in healthy children,^{7,10,67} through supraspinal mechanisms (eg, attention, memory, and coping).²⁰ Anxiety sensitivity is another key construct underpinning the sensory experience,⁶⁵ which should be examined in future studies.

The relationship between emotional processing and pain sensitivity may be particularly relevant for survivors of childhood cancer. Children with cancer often receive inadequate analgesia for painful procedures,⁵² which can lead to a cycle of increased distress and pain in future procedures.^{13,71} This study demonstrates that the relationship between pain catastrophizing, anxiety, and increased pain sensitivity persists in long-term

survivors and underscores the necessity of adequately managing pain during treatment and into survivorship. A significant proportion of survivors may continue to experience significant anxiety and distress about needle procedures, which has implications for the lifelong follow-up care required after childhood cancer.

This study has many strengths, including the inclusion of survivors of various forms of childhood cancer, use of a standardized QST protocol, and the comprehensive examination of risk factors. There are some limitations to be acknowledged. Although a standardized QST protocol for children was used, there may be contextual differences between the data in this study and reference data collected at a different laboratory. Furthermore, multiple modalities were evaluated using a comprehensive QST protocol but did not include vibration or pressure pain, which may yield important insights into the function of deeper nociceptors. In addition, QST was performed at 1 body site to allow for optimal comparison with reference values, and results may differ when examined at other sites across the body. Finally, although the diverse sample of childhood cancer survivors in this study allowed us to overcome the limitations of past research examining only survivors of ALL, the current sample was quite heterogeneous with regard to clinical variables, which may limit the generalizability of the findings. Conversely, race was relatively homogeneous. Future multisite studies with more demographically diverse and larger numbers of subjects and longitudinal data collected after treatment will be important in leading to prevention and intervention measures related to pain in this population.

In conclusion, this study demonstrated that somatosensory abnormalities are prevalent in survivors of childhood cancer years after the completion of treatment. These findings may guide clinical conversations about pain and sensory changes after cancer and add to the growing body of literature pointing to the need for personalized approaches for survivorship care.⁴² Future research is needed to understand long-term implications of altered somatosensation in this complex population.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B496>.

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