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Abstract

Pain is one of the most frequent and persistent side effects of breast cancer treatment. Besides pain, breast cancer survivors (BCS) are prone to experience a myriad of other signs and symptoms related to altered somatosensory function, including e.g., hypoesthesia, allodynia, and hyperalgesia, both at the local site of cancer and in remote body parts. Different breast cancer treatments can have a direct effect on somatosensory functioning, resulting in a wide range of these signs and symptoms.

To our knowledge, currently no comprehensive overview exists on altered somatosensory functioning and resulting signs and symptoms in BCS with persistent pain. Investigating altered somatosensory functioning in this population could provide more insights in the underpinning pathophysiological mechanisms and consequently improve prevention and treatment in the future. Therefore, in this paper, first, normal somatosensory functioning is described. Second, quantitative sensory testing (QST) is presented as the recommend method to evaluate somatosensory functioning. Third, existing evidence on altered somatosensory functioning in BCS with persistent pain is summarized. Altered somatosensory functioning related to the most common cancer treatment modalities, including surgery and radiotherapy, hormone therapy and chemotherapy are discussed. In addition, evidence on the presence of nociplastic pain as pain resulting from altered somatosensory functioning without evidence for nociception and/or neuropathy in BCS is summarized. At last, a discussion on this available evidence, limitations, and perspectives for clinical practice and for research are made.

1. Somatosensory functioning

The somatosensory nervous system (SNS) is part of our complex sensory nervous system. Without the SNS one would not experience the sense of touch, pressure, temperature, vibration and also pain. The SNS informs us of our surroundings and provides us with signals to react in certain situations. Somatosensory processing of noxious or other sensory signals is usually divided in four stages: *transduction, transmission, modulation, and perception.*

Transduction is the conversion of a physical signal (such as a heat, pressure, touch, vibration) to an electrical signal. Different types of receptors and free nerve endings are able to detect different types of stimuli. *Physical stimuli* such as light touch can be detected by mechanoreceptors in the skin. *Noxious stimuli* or stimuli that are damaging or threaten to damage normal tissues are detected by afferents such as mechano-heat nociceptors, cold nociceptors, polymodal nociceptors sensitive to heat, pinch, and cold, and wide-dynamic range afferents. [1] Whenever a stimulus is strong enough, voltage-gated ion channels in the cell membrane will become activated, causing depolarization. When depolarization is sufficient it can induce an electrical signal (i.e. action potential). [2]

Transmission happens when the axon of the primary afferent (nociceptor) transmits a (nociceptive) signal from the periphery to the spinal cord (or medulla). Nociceptive primary afferents can be divided into two groups, based on their axon conduction velocity: Aδ and C fibers. Aδ fiber afferents are myelinated fast conducting neurons and are predominately heat-, cold- and or mechanosensitive. C fiber afferents are unmyelinated slow conducting, polymodal neurons which are also sensitive to mechanical, chemical, and thermal stimuli. In the dorsal horn, the primary afferent nociceptors terminate near second-order nerve cells where synaptic transmission takes place. [3,4] Once the nociceptive signal reaches the terminal of the primary afferent nociceptor, it releases chemical transmitter substances into the synapse between the terminus of the primary afferent nociceptor and adjacent second-order afferent neuron. [3] Synaptic transmission is mediated in large part by glutamate and peptides (e.g., substance P, CGRP). Second-order afferent neurons decussate and ascend in the anterolateral quadrant of the spinal cord's white matter to reach the brainstem and thalamus (Figure 1).

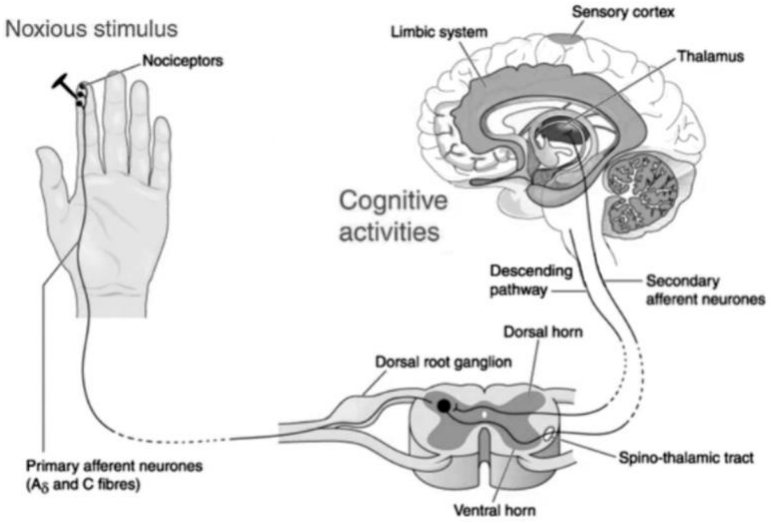

Figure 1: A schematic overview of somatosensory processing of a noxious stimulus.

The thalamus is responsible for the strict segregation of place- and modality-specific responses, acting as a relay station. Information that has been processed by the thalamus is transmitted to the somatosensory cortex (postcentral gyrus) and associated brain regions such as the anterior cingulate cortex, prefrontal cortex, insula, amygdala, hippocampus, cerebellum and the mesolimbic reward circuit. [1,2,5] These regions, termed the (pain) neuromatrix, are not exclusively activated by nociception or solely restricted to pain perception. [6] The areas defined as the pain neuromatrix also serve other neurological functions including cognition, emotion, motivation and sensation which are functionally connected in the context of nociception and influence the experience of pain.[7]

Modulation of these incoming sensory or noxious signals can happen in both the peripheral and central SNS through top-down (descending) and bottom-up (ascending) mechanisms. [2] *At the level of the dorsal horn*, sensory signals can be facilitated or inhibited, respectively increasing or decreasing the intensity of the incoming signal via presynaptic and postsynaptic modulation. [2] In addition, plasticity in synaptic strength, which is the ability to increase homosynaptic and heterosynaptic connections is important considering somatosensory modulation. [2] At this level, the gate control theory, first discovered by Mellzack & Wall, which is based on presynaptic inhibition, could be seen as a form of ascending inhibition. Non-noxious stimulation can suppress the noxious stimulus by 'closing the gate' at the level of the spinal cord via an inhibitory interneuron, hindering the noxious

signal to reach the thalamus. [8] In case of descending inhibition, primary afferent terminals are inhibited largely due to release of norepinephrine in the dorsal horn. [9] Descending facilitation may occur via serotonergic mechanisms intensifying incoming signals and/or lowering the threshold for transmitting signals from the dorsal horn to the thalamus. [7,10]

At the level of the brain, modulation can also occur. Different brain regions, or as mentioned above, the (pain) neuromatrix receive sensory input and contribute to the processing of an incoming (noxious) signal. The evaluation of signals by the brain will determine the degree of modulation in the brain as well as in the spinal cord (descending inhibition or facilitation of (noxious) signals). Psychosocial factors such as stress and fear are associated with the pain neuromatrix and therefore can have an influence on the processing and modulation of those signals. [8,11] Two examples of somatosensory modulation are temporal summation (TS) and conditioned pain modulation (CPM). These paradigm will be discussed later on.

All these processes help us to *perceive* sensory and noxious input. **Perception** entails the synthesis of multiple incoming signals into something coherent. Perception is a multi-step process including numerous factors such as attention, expectation, and interpretation. [12] Additionally, in therapeutic settings, context-related factors such as beliefs and therapy expectations, and the use of placebo (e.g., effects due to a positive healthcare context) and nocebo (e.g., effects 6due to a negative healthcare context) are known to influence the perception of pain.[13]

The thalamus and cortex are thought to be involved in the processes that underpin pain perception. [4]

Damage to tissues and neurons (e.g. due to different cancer treatment modalities) cause **peripheral and central sensitization** via products of tissue inflammation and neuronal processes respectively. [14] Peripheral sensitization is defined as a reduction in threshold, a gain in responsiveness, and occasionally spontaneous activation of peripheral endings of nociceptors, reflecting overall increased transduction and transmission. [15] It emerges from the activity of inflammatory chemicals generated at the damaged tissue site by both sensory nerve fibers and inflammatory cells. [15] Some of these inflammatory chemicals (such as protons, ATP, and serotonin) can directly trigger peripheral nociceptors, whereas others have a more regulating role, resulting in increased nerve ending responsiveness (transduction and transmission). [15] A clinical manifestation of peripheral sensitization is

primary hyperalgesia which consists of a painful response to stimuli that are not normally painful within the area of injury and/or inflammation. [15]

Central sensitization is defined by The International Association on the Study of Pain (IASP) as the "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input." [16] Rather than reflecting the presence of peripheral noxious stimuli, pain is perceived due to alterations centrally in the SNS (dorsal horn or supraspinal)**.** This sensitization is characterized by a variety of different mechanisms such as increased facilitation (ascending and descending) and decreased descending inhibition. [15] In the long term changes in microglia, astrocytes, gap junctions, membrane excitability, and gene transcription might occur, all of which contribute to the maintenance of central sensitization. [15] **Secondary hyperalgesia** and **tactile allodynia** in non-affected tissue are common clinical symptoms of central sensitization. [17] Tactile allodynia is a painful reaction due to a tactile stimulus that does not normally provoke pain (e.g., feather). [17]

2. Evaluation of somatosensory functioning

Quantitative sensory testing (QST) has shown to be useful to assess alterations of somatosensory function (loss or gain of somatosensory function) in different populations, and has helped to gain insight in the pathophysiological mechanisms involved in somatosensory dysfunction. [18] Quantitative sensory testing consists of multiple psychophysical tests assessing the different properties of the SNS by evaluating the function of nerve Aβ, Aδ and C fibers, as well as central pathways. [19–21] Quantitative sensory testing protocols can be divided into a static and dynamic part. The static QST part typically includes the assessment of detection and pain thresholds: warm and cold detection, heat and cold pain, mechanical detection and pain, pressure pain, and vibration detection. [19–21] A gain in somatosensory functioning (primary hyperalgesia and/or allodynia) or a loss in somatosensory functioning (hypoalgesia, meaning a loss of feeling in response to a noxious stimulus) can be evaluated using detection thresholds. When altered central somatosensory processing is suspected, increased sensitivity can also be present in more remote, or distal areas (secondary hyperalgesia). The dynamic QST protocols assesses spinal and supraspinal processes by evaluating the response to several stimuli instead of one static sensory threshold. Dynamic QST protocols such as temporal summation (TS) and conditioned pain modulation (CPM) are used to assess spinal and supraspinal processes respectively. [22]

Temporal summation refers to the bottom-up wind-up phenomenon (or as mentioned above, ascending facilitation) in which repetitive activation of C and Aδ fibers produces a progressive increase in evoked responses of dorsal horn neurons. [23] In case of altered somatosensory processing, neuronal activity due to wind-up is exaggerated in amplitude and duration (e.g., TS of pain). [22,24] Conditioned pain modulation is the human counterpart of diffuse noxious inhibitory control in animals. [25] Conditioned pain modulation explores the top-down inhibitory effect of the SNS using the 'pain inhibits pain' principle in which a noxious stimulus exerts inhibitory effects over subsequent noxious stimuli. In case of altered somatosensory processing, an increase in pain is reported, rather than a decrease, due to the impaired inhibitory effects. [22,24,26]

Given that QST protocols assess somatosensory functioning, they can be used to evaluate differences in somatosensory processing which may be associated with the presence of one or more pain mechanisms (nociceptive, neuropathic, nociplastic and mixed). [27] Quantitative sensory testing paradigms using heat, cold, touch, vibration and pinprick sensation can be used to confirm the suspicion of *neuropathic pain*. [20,28,29] Neuropathic pain, defined as pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system resulting in somatosensory abnormality (e.g. loss or gain in sensory function), can therefore be evaluated by QST. [20,28,29]

Nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". [30] Before the term nociplastic pain was introduced, 'central sensitization' or 'central sensitization pain' was broadly used as a term for persistent, widespread pain. Even though central sensitization is more considered as a normal neurophysiological process after tissue injury or inflammation at present times, it is still thought to be the mean contributor to the development of nociplastic pain. [15,31] Whereas the mechanisms underlying *neuropathic pain* are more apparent, the mechanisms underlying nociplastic pain are not yet fully understood. It is hypothesized that increased facilitation of sensory and noxious input, as well as altered modulation of pain (e.g. decreased inhibition) in the central nervous system, play important roles in the mechanisms underlying nociplastic pain. [31,32] Nociplastic pain can be ascribed when the following clinical criteria are present in a patient: (1) pain duration

longer than three months, (2) regional (rather than discrete) in distribution, (3) no evidence that nociceptive pain (a) is present or (b) if present, is entirely responsible for the pain; and (4) no evidence that neuropathic pain (a) is present or (b) if present, is entirely responsible for the pain. [30] In addition, (hyper)sensitivity to one of the following stimuli in the region of pain can be indicative for the presence of nociplastic pain: (5) mechanical allodynia, (6) heat or cold allodynia, (7) painful after-sensations following (5) and/or (6). [30] Other symptoms related to the excitability of the central nervous system, such as fatigue, cognitive problems (memory, concentration) and sleep problems can be observed. [30] Quantitative sensory testing paradigms can be used to assess somatosensory (hyper)sensitivity in terms of static or dynamic mechanical allodynia, heat or cold allodynia and painful after-sensation. In addition, secondary hyperalgesia, which is a clinical manifestation of central sensitization can be evaluated using QST at a distant body region. Whereas there are guidelines and clinical criteria to assess neuropathic [28] and nociplastic pain [30,33], there are currently no guidelines or clinical criteria described to evaluate *nociceptive pain* (pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors) and mixed pain (a mixture of different pain mechanisms).

3. Altered somatosensory functioning in breast cancer survivors with pain

Most research on pain in BCS utilized a symptom-orientated classification (e.g., post-mastectomy pain syndrome[34], aromatase inhibitor associated musculoskeletal symptoms[35]) or a pain classification based on intensity (e.g., moderate vs. severe pain)[36,37]. With research evolving from the musculoskeletal field and with increasing knowledge on the presence of nociplastic pain in breast cancer survivors (BCS), it might be helpful for research and clinic to utilize a mechanism-based classification system as mentioned above (nociceptive pain, neuropathic pain, nociplastic pain). Up until now, only chemotherapy-induced peripheral neuropathy could be seen as a mechanism-based class. Unfortunately, this does not explain all the side effects related to altered somatosensory functioning in cancer survivors. This narrative review aims to give overview of these side effects in relation to the SNS from a mechanism-based approach, in BCS experiencing pain. For this narrative review, the SANRA checklist was used.[38]

We therefore performed a literature search on the 16th of May 2022 in databases PubMed and Embase using search terms 'pain', 'breast cancer', 'aromatase', 'chemotherapy-induced peripheral neuropathy', 'phantom pain', 'post-mastectomy pain syndrome', 'intercostobrachial', 'nociplastic pain', 'central sensitization', 'nociplastic pain' and 'neuropathic pain'. In addition, hand searching and checking the reference lists of the retrieved studies were also performed. For the scope of this paper, evidence on altered somatosensory functioning in breast cancer survivors with persistent pain was summarized in four groups: 1) Post-Mastectomy Pain Syndrome (PMPS); 2) Aromatase Inhibitor Associated Musculoskeletal Symptoms (AIMS); 3) Chemotherapy-induced peripheral neuropathy (CIPN).

3.1 Post-mastectomy pain syndrome

Post-mastectomy pain syndrome is defined as pain located in the area of the chest, axilla, shoulder and/or medial upper arm. Approximately 25-50% of BCS reported having PMPS with 20% experiencing moderate to severe pain. [39–41] Even though PMPS suggests a status after mastectomy, the term has been used to encompass a broader state and therefore also includes persistent pain after mastectomy, lumpectomy, lymph node dissection and reconstruction, as well as chemotherapy and radiation. [42] Although the pathophysiology is not fully understood, PMPS has been related with a lesion to the SNS and sensory signs in the same anatomical logical distribution, fulfilling the definition of possible (but not definite) neuropathic pain. [28] Indeed, PMPS is usually described as a neuropathic and persisting pain (> 3 months from surgery). Signs and symptoms reported are burning pain, shooting pain, pressure sensation and/or numbness. [39] The contribution of the resected intercostobrachial nerve (ICBN) with axillary lymph node dissection resulting in hypoesthesia/anesthesia together with static mechanical allodynia or persistent pain has been evaluated multiple times in surgical studies for breast cancer. [41,43–46] A recent systematic review by Dams et al. concluded that BCS with persistent pain in the surgical area showed local disturbances in thermal detection and increased TS of pain. [47] In addition, pressure pain thresholds (PPTs) at the same area were significantly lower in comparison to women without a history of breast cancer. [47] These findings were strengthened by Mustonen and colleagues who also found sensory loss in thermal and mechanical detection thresholds and sensory gain reflected by reduced PPTs in the affected area. [48] However, evidence is conflicting whether surgical

handling and the resulting lesion of the ICBN has an influence on the development of PMPS. [34,41]. At this stage, it remains unclear whether the surgical handling of the ICBN can explain all the proposed neuropathic aspects of PMPS. Local positive signs and symptoms, such as gain of function, appear to have less value towards the probability of neuropathic pain when there is no neuroanatomical distribution present. [28] In addition, gain of function can be present in patients presenting with inflammatory pain, pain of unknown origin, anxiety, and sleep deprivation. [28] Also, negative signs and symptoms such as sensory loss is a not prerequisite for a neuropathic pain state as other conditions can present as local sensory loss (subgroups of patients with, e.g., peripheral nerve injury, touch-evoked allodynia or thermal hyperalgesia). [28] It could also be possible that sensitization of the peripheral and central nervous system contribute to the development and the chronicity of PMPS. [48] This is illustrated by the presence of widespread pressure hyperalgesia, enhanced TS of pain, decreased CPM effects and general altered somatosensory findings, also in non-affected areas, suggesting the presence of secondary hyperalgesia in BCS. [47–53] Nociplastic pain can therefore be suspected in some cases. Earlier research investigated the presence of 'central sensitization pain' using of the Central Sensitization Inventory (CSI), a questionnaire to assess self-reported signs of central sensitization. [54–56] The use of solely questionnaires for the evaluation of somatosensory functioning to unravel 'central sensitization pain' lacks correlation with existing QST protocols in BCS and chronic musculoskeletal pain. [57,58] Even though not all studies identified the location and/or type of pain, they did find presence of 'central sensitization pain' in BCS experiencing persistent pain. [55,56]

No guidelines exist on the clinical criteria of nociceptive pain, therefore it is not possible to exclude nociceptive pain in PMPS. Surgical interventions and radiotherapy can induce scar tissue and fibrosis, possibly contributing to the development of nociceptive pain in the treated area of the axilla and chest. [33,59,60] It is possible multiple pain mechanisms are present concurrently in BCS experiencing PMPS.

3.2 Aromatase Inhibitor Associated Musculoskeletal Symptoms

Aromatase inhibitors (Ais) are increasingly used as the standard adjuvant endocrine therapy for hormone receptor–positive, postmenopausal breast cancer providing increased survival rates in comparison to tamoxifen. [61,62] Aromatase inhibitors are associated with AIMS which

are often described as symmetrical pain and soreness in the joints (arthralgia), musculoskeletal pain or myalgia and joint stiffness, predominantly involving the hands, wrists, and ankles. [61] Around half of BCS on Ais experience AIMS, significantly impacting their quality of life [63] In addition, AIMS decreases adherence rates to AI therapy in approximately half of BCS, in turn compromising survival rate. [64,65]

Although the specific pathophysiology of AIMS remains unclear, current theories point to estrogen deprivation as a crucial element contributing to bone and cartilage degeneration and the development of musculoskeletal symptoms. [63,66] Estrogen reduces osteoclast maturation and lifespan, and increases osteoblast maturation and lifespan. Estrogen is also involved in the maintenance of joint integrity inhibiting breakdown of cartilaginous extracellular matrix. In addition, estrogen seems to influence somatosensory processing due to pro- and anti-nociceptive properties involved in transmission and modulation of noxious stimuli. [66,67] It also has an anti-inflammatory function decreasing the synthesis of inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin 1ß), but also increasing C reactive protein (CRP). [63] In addition, TNF-α increases C fiber activity causing an increase in the wind-up phenomenon at the dorsal horn and hyperalgesia to cold and pressure in rats. [68,69] In addition, increased levels of high sensitivity CRP has been associated with increased sensitivity to cold during cold pressor testing in the general population. [70,71]

To the best of our knowledge, no studies have assessed somatosensory functioning using QST in BCS experiencing AIMS. It can be hypothesized that BCS on Ais will demonstrate lowered PPTs, lowered mechanical pain thresholds and possibly increased TS of pain at the painful and/or stiff joints. Aforementioned neurophysiological changes in the SNS could in term induce nociplastic pain presenting as enhanced facilitation (enhanced TS of pain), decreased inhibition (maladaptive CPM) and (hyper)sensitivity to stimuli locally and at distant regions (secondary hyperalgesia). Specific evidence confirming these hypotheses lack, however studies investigating pain in BCS included BCS actively taking Ais. [54–56] Therefore, it remains unclear whether 'central sensitization pain' or nociplastic pain was ascribed due to AI related symptoms, or symptoms related to PMPS. Local nociceptive pain mechanisms could also be present due to the decrease of estrogen production and possibly, but less likely, changes in cartilaginous tissue within the joint. [72–74] Just as PMPS, it remains difficult to single out one factor underlying AIMS. It is probable that multiple peripheral and central factors within the SNS contribute to the development or maintenance of AIMS.

3.3 Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy is a frequent dose-limiting toxicity that affects 10-60% of cancer patients, and has mostly been associated with microtubule-targeting agents such as taxanes (e.g. paclitaxel and docetaxel), platinum, vinca alkaloids, and bortezomib. [75,76] Chemotherapy-induced peripheral neuropathy is usually present in the hands and feet, following a 'glove and stocking' distribution as chemotherapy-induced nerve damage first occurs in the longest axons in distal nerves. [77] Numbness, tingling, burning, paresthesia/dysesthesia and/or hyperalgesia/allodynia have been described as such sensory signs and symptoms. [77] Other symptoms such as cramps in feet, limb loss of strength, reduced vibration perception threshold and reduced proprioception can be present. [75] The severity and patient experience of CIPN can be variable. Cancer patients can experience CIPN in an acute phase, but it can also persist for several months or even years after treatment discontinuation. [75,77]

Multiple mechanisms have been validated with the most widely accepted mechanism being a "dying back" process with axonal degeneration of sensory neurons, leading to loss of intra-epidermal nerve endings. [78] Other mechanisms such as irreversible cell injury due to mitochondrial vacuolization and production of reactive oxygen species, changes in the excitability of peripheral nerves (e.g., increased transmission), and neuroinflammation involving the activation of macrophages in both the dorsal root ganglion and peripheral nerve, and activation of microglia cells within the spinal cord are mentioned. [77] Taken together, the literature emphasizes the biological intricacy that underpins CIPN.

Prior research has found loss of function in both the large Aβ/Aδ fibers and the small C fibers. [79–81] Damage to Aβ/Aδ fiber results in dysesthesia, paresthesia, and loss of position sense. Multiple studies suggest the presence of increased mechanical detection thresholds and vibration thresholds due to reduction in Aβ fibers. [82–84] Assessing the peripheral SNS, mechanical pain sensitivity, dynamic mechanical allodynia and PPTs do not seem to be altered in BCS experiencing CIPN. [84] Some studies suggest the presence of increased thermal detection (for cold) and increased thermal pain thresholds due to reduced Aδ and C fiber function. [84] Allodynia and hyperalgesia, such as cold hyperalgesia are clinical presentations of damage to small C fibers. [81] The study by Hammond et al. however, was not able to confirm a loss of Aδ and C fibers. [85] Temporal summation measured in painful regions,

contralaterally or between hands and feet, did not seem to be affected by CIPN. [84] The absence of increased TS of pain does not exclude the presence of nociplastic pain as the presence of decreased inhibition (maladaptive CPM) has not been investigated thoroughly within this population. If nociceptive pain were to be expected in BCS experiencing CIPN it would probably be induced during the infrequent cramps in hand and/or feet.

4. Commentary

Breast cancer survivors can experience a multitude of side effects related to altered somatosensory functioning after breast cancer treatment. One side effect does not exclude the other and it is possible, and also probable that some BCS experience multiple side effects at the same time. [55,86] It is apparent that all the aforementioned conditions (PMPS, AIMS and CIPN) affect the quality of life and return to work. [86]

Overall, there is still a limited understanding of the pathophysiological mechanisms underpinning conditions such as PMPS, AIMS and CIPN. This lack of knowledge is again confirmed in the lack of effective treatment modalities for each of these conditions resulting in prolonged symptoms and in turn decreased quality of life. [87,88]

Investigating these conditions using comprehensive QST protocols could provide more insights in the alteration of somatosensory functioning after cancer treatment and consequently improve treatment in the future. A mechanism-based approach has been key in the management of different medical conditions (e.g., diabetes, peptic ulcers) since a condition could be addressed accordingly after the discovery of its mechanism. With a mechanism-based approach towards altered somatosensory functioning, we hope that research can fulfill the same hiatuses medical conditions such as diabetes once had. There are, however, a few hurdles to overcome regarding the assessment of somatosensory functioning in this population. First, research must recognize the complexity of cancer, cancer treatment and pain as their own entity and combined resulting in even a more sophisticated puzzle with multiple psychosocial factors possibly influencing each other and other systems. For example, fatigue, sleep disorder and cognitive problems are other well-known side effects of cancer treatment but were not covered in this review. [89] Second, these symptoms and other psychosocial factors are known to be associated with nociplastic

pain, and are able to influence the processing of sensory and noxious stimuli within the peripheral and central SNS. [30,31] Quantitative sensory testing protocols do not assess these psychosocial factors, even though it is known that they can influence somatosensory functioning and therefore QST results. [18,90,91] Third, although some guidelines have been formulated on the use of QST protocols for the assessment of somatosensory functioning in a non-cancer population, universal and standardized QST protocols are still lacking for the cancer population. [92]

A mechanism-based classification of pain has extensively been researched in non-cancer populations. With this mechanism-based classification signs and symptoms are used to ascribe a pain mechanism being either nociceptive, neuropathic, nociplastic or a mixture of these. [30,31] Despite the proposed clinical and research advantages for the use of such classification system in non-cancer population, it still lacks reliability and validity in the non-cancer population, and it has certainly not yet been investigated thoroughly in the (breast) cancer population.

It could be hypothesized that all three aforementioned conditions would be able to fall under the mixed pain state. Post-mastectomy pain syndrome could present as a mixture of nociceptive, neuropathic and nociplastic pain; AIMS presumably nociceptive and nociplastic pain; CIPN presumably neuropathic and nociplastic pain. It is therefore possible that this classification system becomes less specific within a breast cancer population as mixed pain states are likely to be present. Therefore, within a mixed pain state, it is necessary to mention what types of pain mechanisms are present. Even though QST and a mechanism-based approach towards pain after breast cancer treatment has its limitations, research suggests it can be useful to assess somatosensory functioning as it can provide information towards diagnosis, prognosis and finally management or treatment. [18,93] Future research is warranted to investigate clinical QST alternatives in cancer survivors. Studies on clinical bedside QST in patients suffering from neuropathic pain[94–96] or osteoarthritis[97,98] have emerged but we have yet to see data in a cancer population with persistent pain. In addition, more data is required to investigate the effect of a mechanism-based approach on diagnosis, prognosis and treatment of painful symptoms after cancer.[99]

Conclusion

Altered somatosensory functioning is commonly present in breast cancer survivors experiencing painful side effects such as PMPS, AIMS and CIPN either separately or in combination, affecting the quality of life of this population. Pathophysiological mechanisms underpinning these conditions are still unclear, making it difficult to improve prevention and treatment. Comprehensive QST protocols can aid in the identification of altered somatosensory functioning and improve mechanism-based classification after breast cancer treatment, but limitations are present and need to be considered. Mechanism-based classifications of pain, often used in non-cancer population, have not been investigated thoroughly in a cancer population.

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