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REVIEW

Advances in Neuroimaging of Breast Cancer Pain: An Overview

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Abstract: Breast cancer is currently the most common malignant tumor, primarily affecting women, and it frequently leads to chronic pain that significantly impairs physical and mental health. Neuroimaging studies have demonstrated that breast cancer-related pain is associated with specific brain alterations, including changes in activation, connectivity, and structure of pain-processing regions. This review synthesizes findings on functional and structural brain changes related to chronic pain in breast cancer and compares them with non-cancer chronic pain patterns. By integrating recent evidence, it proposes a conceptual framework to advance the understanding of pain mechanisms and supports personalized pain management strategies to improve quality of life.

Keywords: breast cancer, chronic pain, brain function, resting-state fMRI, diffusion tensor imaging

Introduction

Breast cancer is currently the most prevalent cancer among women worldwide, with incidence rates continuing to rise, especially among younger populations.[1,2] Patients commonly face cognitive decline, chronic pain, and psychological distress.[3,4] Despite improvements in treatments such as surgery and radiotherapy,[5] survivors remain susceptible to a wide range of complications - physical, psychological, and medical.[6] Quality of life assessments consistently show that prognosis and treatment modality significantly affect outcomes for survivors.[7]

According to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[8] In patients with advanced cancer, up to 90% report moderate to severe pain, highlighting its high clinical relevance in this population.[9] A systematic review spanning 40 years found that 59% of cancer patients undergoing treatment and 64% with metastatic disease experienced pain, while 33% of cancer survivors reported persistent pain.[10]

Bone metastasis, a common occurrence in advanced breast cancer, is often associated with severe pain,[11] and current therapies - analgesics, radiation, and surgery - often provide insufficient relief.[12] Researchers commonly use functional MRI (fMRI) to study pain-related brain alterations in these patients, detecting neuronal activity via changes in blood oxygenation levels (BOLD signals).[13,14]

Another important technique, Diffusion Tensor Imaging (DTI), evaluates the movement of water molecules along nerve fibers to assess white matter integrity and identify pain-related damage to neural pathways.[15,16] Additionally, psychological tests like the Emotional Stroop Task help investigators understand how pain affects cognitive and emotional functioning in cancer survivors.

This review focuses on how chronic pain related to breast cancer affects brain function, specifically examining neural activation patterns, functional connectivity, and white matter integrity. Despite the high prevalence of breast cancer-related pain, critical gaps remain in the systematic characterization of its neuroimaging signatures, the distinction from non-cancer chronic pain mechanisms, and the clinical translation of neuroimaging findings. This review aims to bridge these gaps by analyzing current evidence to enhance the clinical understanding of the underlying neural mechanisms and

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to support the development of personalized pain management strategies. In addition, these findings may offer translational insights for understanding pain mechanisms in other cancer types.

The methodological framework of this review aligns with standard neuroimaging workflows used in chronic pain research among breast cancer survivors. Figure 1 illustrates the key components of this framework, including participant classification, imaging modalities, and analytical approaches.

Breast Cancer Pain

Pain affects most breast cancer patients during their illness,[17] with more than 40% developing persistent pain that continues after treatment ends.[18] Patients describe this pain in various ways - as dull aches, sharp stabbing sensations, or vague discomfort - which may be limited to the breast area or spread to nearby regions like the shoulders and arms.[19] When cancer metastasizes, additional pain symptoms frequently appear, including spinal pain from bone metastases, pelvic discomfort, or chronic headaches.[20]

Cancer-related pain develops through several mechanisms: the primary tumor invading surrounding tissues, metastatic spread to distant sites, or nerve compression. Treatment interventions like surgery, chemotherapy, and radiation can also induce pain by damaging tissues or nerves.[21] Clinically, cancer pain is categorized by duration as either acute (short-term) or chronic (lasting more than three months).[22] This review primarily examines chronic cancer-related pain, the most frequently reported type, which develops from either the primary tumor, metastatic spread, or therapeutic interventions.[23]

The ICD-11 classification system identifies seven chronic pain subtypes, including chronic cancer-related pain, chronic neuropathic pain, and chronic post-surgical pain.[24] It also updated that persistent or recurrent pain continuing

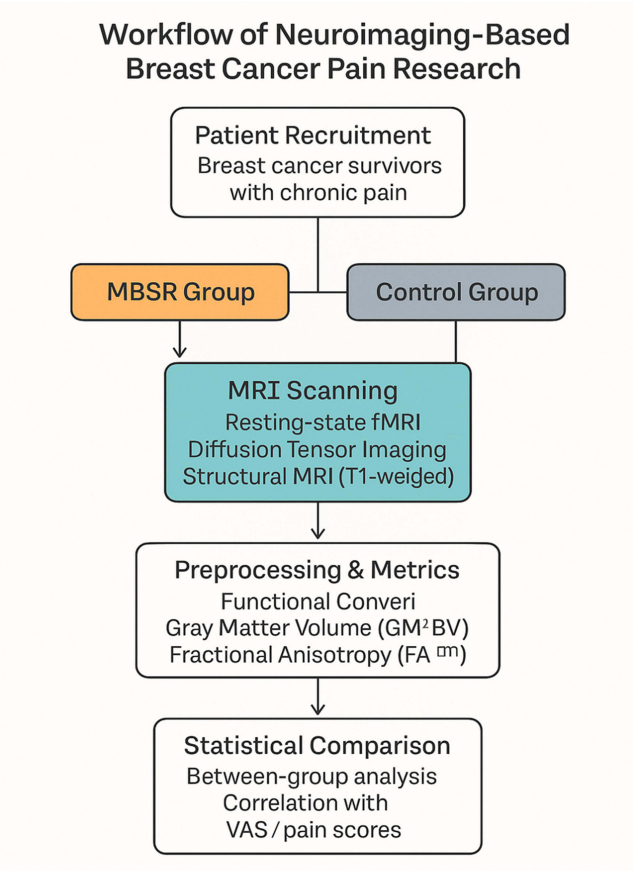

Figure 1 Illustrates the study design framework commonly used in neuroimaging investigations of chronic pain among breast cancer survivors. The workflow includes participant recruitment and group allocation (MBSR vs control), neuroimaging acquisition (resting-state fMRI, DTI), data preprocessing, and multi-level analysis of functional connectivity, gray matter volume (GMV), and white matter integrity (FA).

beyond three months qualifies as chronic pain. Therefore, we want to study chronic cancer pain, ie, related to studying chronic pain. From a pathophysiological perspective, pain is divided into three mechanistic types: nociceptive pain (from tissue damage), neuropathic pain (from nerve injury), and nociplastic pain (from sensitized pain pathways).[25] Each category has distinct diagnostic features and requires specific treatment approaches.

Chronic Pain and Brain Function

Brain Activation

Pain is a complex, conscious experience involving both sensory processing and emotional appraisal, as described by Baliki et al.[26] Neuroimaging studies have consistently identified a distributed network of brain regions - commonly termed the "pain matrix" - that respond to nociceptive stimuli, including the thalamus, primary/secondary somatosensory cortices (S1/S2), insula, anterior cingulate cortex (ACC), and prefrontal cortex.[27] However, current understanding suggests these regions are not exclusive to pain processing but rather form part of a broader salience detection system that responds to various significant stimuli.[28,29] Notably, in chronic pain conditions, sustained hyperactivation of this network has been well-documented,[30] suggesting maladaptive plasticity.

Mioduszewski & Hatchard's fMRI study[31] investigated 21 female breast cancer survivors (≥1 year post-treatment) with chronic neuropathic pain using a rigorously designed protocol. Participants underwent pain specialist consultation and maintained stable pharmacotherapy for ≥2-week before randomization to either an 8-week Mindfulness-Based Stress Reduction (MBSR) program or waitlist control group, with stratification by pain severity (moderate ≤6 vs severe 7–10) and blinded assessment.

The MBSR intervention produced significant neural changes, including reduced activation in visual (precuneus, lingual gyrus), temporal (middle temporal gyrus), frontal (middle/inferior frontal gyri), and sensory (postcentral gyrus) processing areas, along with decreased activity in left hemisphere pain-modulation regions (ACC (the anterior cingulate cortex), MCC (middle cingulate cortex)). These findings, measured pre-intervention and 2-week post-intervention while controlling for medication effects through the stabilization period, demonstrate MBSR's capacity to induce beneficial functional reorganization in pain-processing circuits. The study's optimized minimization randomization and blinded design strengthen the evidence for these intervention-specific neural changes in breast cancer survivors with treatment-resistant neuropathic pain.

Functional Connection

Chronic pain involves significant central nervous system reorganization. Functional magnetic resonance imaging (fMRI) studies consistently show altered functional connectivity (FC) in chronic pain patients, which can be broadly categorized into intra-network and inter-network changes.[32] Intra-network alterations, such as increased FC within the default mode network (DMN), suggest maladaptive internal processing, potentially leading to pain catastrophizing.[33] Similarly, changes within the sensorimotor network (SMN) indicate impaired sensory processing.[34] Inter-network reorganization is also critical. For instance, modified interactions between the salience network (SN), DMN, and central executive network (CEN) reveal shifts in attention and cognitive control, often biasing individuals towards pain and impeding effective pain modulation.[35] These connectivity changes collectively highlight the brain's complex adaptation to persistent pain, reflecting both adaptive and pathological processes that contribute to the chronic pain experience.

The posterior cingulate cortex (PCC) is a key hub of the default mode network (DMN), critical for cognitive integration and consciousness regulation.[36] Its anatomical connections align closely with widespread functional connectivity across the brain.[37] In this rigorously controlled study of breast cancer survivors (BPI (Brief Pain Inventory) >4 at baseline with ≥6 months CNP duration), the 8-week MBSR intervention produced distinct connectivity changes: enhanced coupling between PCC and key DMN regions (ACC, mPFC, angular gyri) correlated with pain reduction,[38] while weakened PCC-motor area connectivity (precentral/superior frontal gyri) was linked to greater pain intensity.[39] These differential effects were identified through pre-post intervention fMRI scans conducted after a ≥2-week medication stabilization period, with pain levels systematically tracked using validated BPI measurements (severity α=0.85, interference α=0.88).

The findings demonstrate MBSR's capacity to selectively modulate PCC connectivity patterns, ie, strengthening integration within cognitive-emotional networks while reducing sensorimotor system coupling. This dual mechanism may underlie its therapeutic effects in treatment-resistant neuropathic pain, with the stratified randomization (moderate vs severe pain) and blinded assessment ensuring robust detection of these intervention-specific neural changes.

The precentral gyrus, which houses the primary motor cortex, is involved in motor planning, emotion-driven behavior, and inhibitory control. Its inverse relationship with DMN activation indicates that weaker integration between sensorimotor and default-mode systems may underlie persistent pain. Based on these findings, Smith et al and Mioduszewski et al hypothesized that altered FC may reflect disrupted coordination between motor control and pain processing circuits. However, the precise neural mechanisms remain unclear, warranting further research into dynamic network interactions. Recent resting-state studies have reported both increases and decreases in FC within the DMN and salience network (SN) during chronic pain states. Figure 2 illustrates these connectivity shifts, emphasizing enhanced PCC–mPFC coupling and reduced sensorimotor integration as core patterns of change.

Recent brain imaging studies are helping us understand how chronic pain changes brain connections. One rs-fMRI study examined 46 women with post-mastectomy pain compared to 20 pain-free controls. The scans revealed important differences, ie, patients showed weaker communication between the MPFC and two right brain regions (the inferior frontal and temporal areas). Interestingly, while the MPFC had stronger links to visual and cerebellar areas, its connections to attention and salience networks were weaker.[40] These findings connect to what we know about how the brain processes pain, but the functional significance of the changes in MPFC-occipital and MPFC-cerebellar connectivity, including whether they represent a compensatory mechanism, remains to be determined by future studies.

The S1 region, which often shows changes in chronic pain patients, works closely with S2 to identify pain location, intensity, and type, ie, what scientists call sensory discrimination.[41,42] This helps explain why altered S1 function might contribute to ongoing pain. Building on this, another team compared 20 breast cancer survivors (with at least 3 months of nerve pain following treatment) to 20 healthy women. They discovered the survivors had unusual thalamus connections: stronger links to sensory areas (S1 and parietal lobe) that increased with longer pain duration, but weaker connections to the cerebellum.[43] Together, these studies paint a picture of how chronic pain can reorganize brain networks over time.

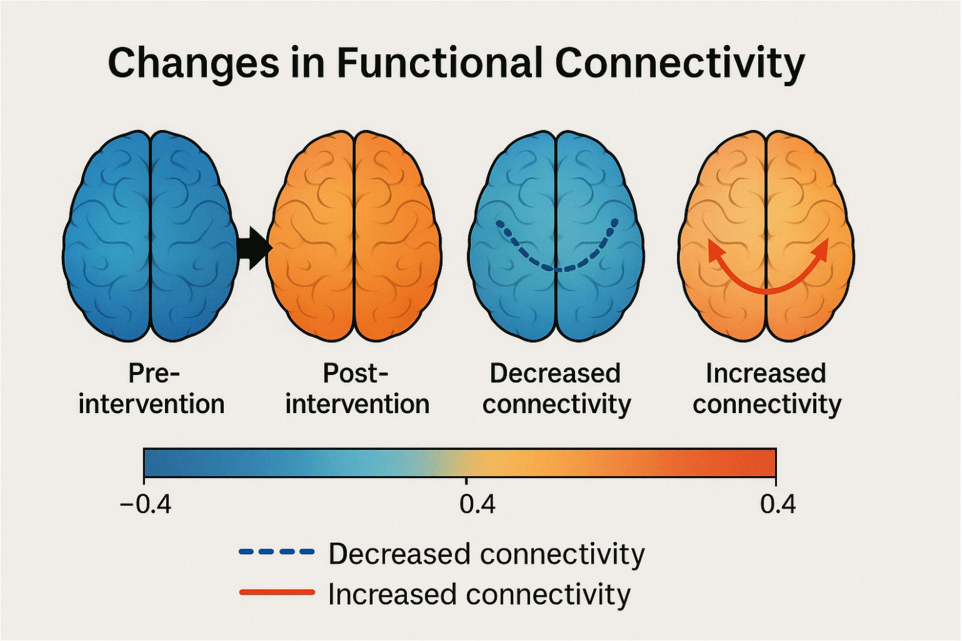

Figure 2 Depicts alterations in functional connectivity (FC) observed before and after mindfulness-based stress reduction (MBSR). Increased connectivity is represented with solid red lines (eg, between PCC and mPFC), while decreased connectivity is marked with dashed blue lines (eg, between PCC and sensorimotor regions). The color gradient bar quantifies connectivity strength. (Self-plotted in this study).

Morphological Changes in the Brain

Cancer-related neuropathic pain (CNP), including chemotherapy-induced polyneuropathy (CIPN), arises from mechanisms such as paraneoplastic activity, tumor progression, or neurotoxic effects of chemotherapy.[44] In preclinical models, neuropathic pain following chemotherapy has been associated with heightened activation in pain-processing areas like the thalamus, periaqueductal gray (PAG), and anterior cingulate cortex (ACC).[45]

Translating these findings to humans, breast cancer patients with CIPN exhibit dynamic brain changes. The study cohort included 47 female patients (24 receiving standard chemotherapy and 23 without chemotherapy), all with non-metastatic disease (stage 0-III). In the acute phase (one month after chemotherapy), arterial spin labeling (ASL) MRI detected detected increased cerebral blood flow in regions including the bilateral superior frontal gyri, cingulate cortex, and left medial/middle frontal gyri. Interestingly, those with greater gray matter (GM) loss in the left cingulate and right superior frontal gyrus showed smaller increases in blood flow, implying a link between structural degeneration and vascular response. However, these changes were not evident at one-year follow-up (n=18 chemotherapy, n=19 no chemotherapy), possibly due to the lack of longitudinal symptom tracking beyond the first month.[46]

In terms of chronic phase intervention, Hatchard et al[47] applied voxel-based morphometry (VBM) to assess the effects of MBSR on brain morphology in 23 female breast cancer survivors (13 in the MBSR group, 10 controls) with chronic neuropathic pain (≥6 months duration, BPI>4). The 8-week MBSR intervention group exhibited increased GM volume in regions such as the right parahippocampal gyrus, left angular gyrus, and right cuneate lobe, whereas waitlist controls showed GM reductions in areas including the left parahippocampal gyrus, precuneus, and middle temporal gyrus. These differential morphological changes, observed through pre-post MRI assessments with rigorous blinding procedures, suggest MBSR may exert neuroprotective effects against pain-related degeneration in this carefully characterized patient population.

Beyond these functional and volumetric changes, chronic pain is increasingly linked to broader neuroanatomical alterations, involving both gray and white matter degeneration. Figure 3 summarizes these morphological changes, including GMV increases and fractional anisotropy (FA) reductions in corpus callosum tracts, underscoring the brain-wide impact of prolonged pain.

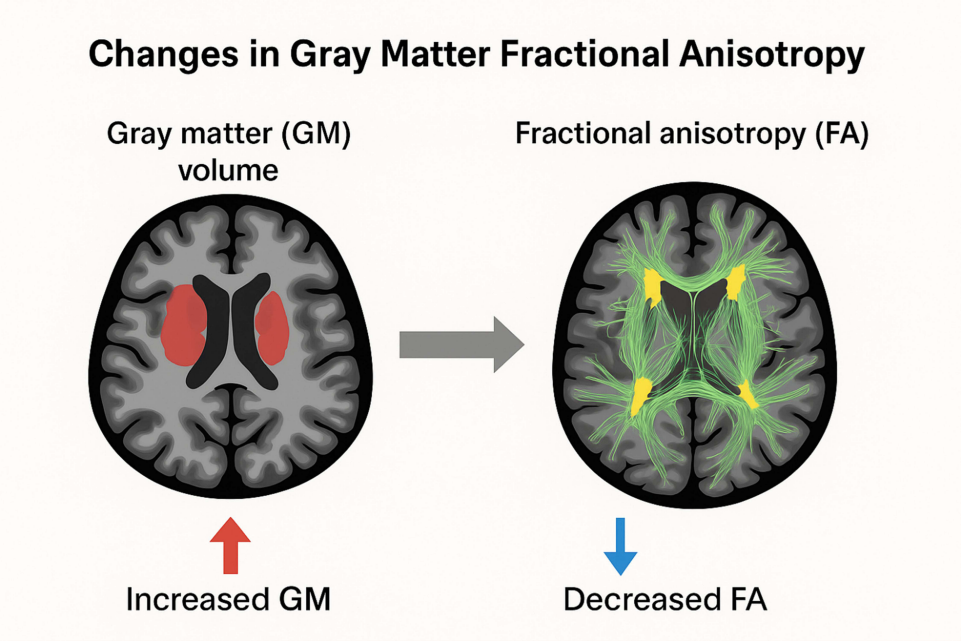

Figure 3 Shows structural brain differences in chronic pain patients. The left panel displays increased gray matter (GM) volume in regions such as the parahippocampal gyrus and angular gyrus (highlighted in red). The right panel illustrates decreased fractional anisotropy (FA) in major white matter tracts, such as the corpus callosum (highlighted in yellow), reflecting compromised white matter integrity.

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Functional Brain Changes in the Acute Phase

Two key brain networks—the salience network (SN) and dorsal attention network (DAN)—play vital roles in the experience and regulation of pain. The salience network, anchored in the anterior cingulate cortex and anterior insula, facilitates the detection and integration of pain-related sensory and emotional signals. It also mediates dynamic switching between the default mode and central executive networks, enabling flexible responses to noxious stimuli.[48] The dorsal attention network, involving regions such as the intraparietal sulcus and frontal eye fields, is engaged in top-down attentional control and sensory selection.[49] Disruptions in these networks during the acute phase of breast cancer pain may reflect altered salience attribution and impaired attentional regulation, which together contribute to pain amplification and emotional distress.

Chronic Pain and Cerebral White Matter

The brain operates as an interconnected system where white matter plays a crucial role in information processing and interregional communication.[50] Specialized neural pathways, supported by distinct structural components, enable efficient data transfer across regions, essential for maintaining network integration and functional coordination.[51]

Early research by Melzack and Casey emphasized that pain processing engages limbic structures, particularly the hippocampus and amygdala.[52] Building on this, Gustin et al[53] found significant correlations between white matter structural changes and chronic pain development, suggesting that altered connectivity may underlie persistent pain states. Recent studies have highlighted the basolateral amygdala (BLA) as a key nociceptive processing hub. Elevated BLA activity is observed during chronic pain, reflecting its role in triggering automatic, emotionally laden pain responses.[40] Importantly, experimental interventions have shown that reducing neural activity in the BLA selectively diminishes the emotional impact of pain, while the sensory dimension remains unchanged.[54] This dissociation indicates that the BLA modulates the affective - not sensory - aspect of pain experience.

Mindfulness-based interventions, such as MBSR, appear to influence this pain-affective network. In a study of 23 female breast cancer survivors (13 in MBSR group, 10 controls) with chronic neuropathic pain (BPI>4 for >6 months post-treatment), Mioduszewski et al[52] reported increased fractional anisotropy (FA) in several white matter tracts following 8-week MBSR training, particularly in left-hemisphere regions including the external capsule, uncinate fasciculus, amygdala, and hippocampal cingulate gyrus. Notably, the left sagittal stratum - housing tracts like the inferior fronto-occipital fasciculus and posterior thalamic radiation - also showed FA increases that correlated with reduced pain interference and lower pain intensity, suggesting a neuroprotective effect of this standardized mindfulness intervention in carefully selected patients who had undergone prior pain medication optimization and stabilization.

To further illustrate these structural and functional changes, Table 1 presents a neuroimaging-based comparison between MBSR participants and non-intervention controls.

Finally, supporting these findings, Bukkieva et al[40] compared brain connectivity patterns in post-mastectomy patients. Those experiencing persistent pain showed reduced functional connectivity between the medial prefrontal cortex (MPFC)

Table 1 Neuroimaging Comparison Between MBSR and Non-Intervention Groups

Region / Metric	MBSR Group Mean	Control Group Mean	Statistic (t/Z)	p-value
Prefrontal Functional Connectivity (FC)	0.68	0.45	2.83	0.006
Hippocampal Gray Matter Volume (GMV)	2.45 cm^3	2.12 cm^3	2.15	0.036
Corpus Callosum Fractional Anisotropy (FA)	0.52	0.48	1.98	0.048
Default Mode Network Activation	↑up	↓down	3.21	0.002
Pain Score Change (VAS)	−2.1	−0.5	2.91	0.005

Notes: Table 1 summarizes the differences in functional connectivity, structural brain metrics, and clinical pain outcomes between MBSR and control groups. These findings highlight the potential of MBSR in modulating both brain function and structure.

and right amygdala, relative to pain-free controls. This reduction suggests a disruption in emotional regulation circuits in chronic pain syndromes.

Chronic Pain and Emotions

Human pain is a complex experience composed of two primary components: the sensory/somatic aspect and the affective/distress aspect.[54] The sensory component of pain is processed in regions such as the posterior insula, the neighboring suprasylvian operculum, the S1, the primary motor cortex, and the posterior parietal cortex. These areas receive afferent signals that transmit nociceptive (pain) information from the periphery to the central nervous system, primarily through the spinal-thalamic tract. This information is relayed via the ventral posterolateral and ventral posteromedial nuclei of the thalamus, which are crucial relay centers in processing sensory pain signals.[55]

On the other hand, the emotional or affective dimension of pain is processed in a different neural pathway. The central thalamic nuclei, particularly the mediodorsal nucleus, play a key role in generating the emotional response to pain. From here, information is sent to several brain regions involved in emotional regulation and pain perception, including the amygdala, dorsal ACC, anterior insula, lateral prefrontal cortex, and posterior parietal regions. These regions integrate the sensory and emotional aspects of pain, leading to a unified experience.[56,57]

Research has highlighted the significance of functional brain connectivity in the perception of pain, particularly in how the somatic and affective pain pathways interact. When either of these pathways is disrupted, it can result in decreased connectivity within important pain-processing networks, potentially impairing the overall pain experience.[58]

Following MBSR, Hatchard et al[31] observed decreased activation of the Left precuneus, left S1, and left prefrontal cortex in breast cancer survivors with CNP. This suggests a decreased executive control over emotions, pain perception.[59] Emotional components of pain have been related to the limbic system, which includes the amygdala, anterior cingulate gyrus, subcallosal area, parahippocampal gyrus, hippocampus, and dentate gyrus.[56] To process pain, these brain regions collaborate, are structurally and functionally linked, and are not individually active. Cognitive, emotional, motivational, and sensory-related neurofunctional areas all contribute to the sensation of pain,[26] in other words, pain and emotion are strongly intertwined. In their study of upstream pathway deficits in patients with CNP who had breast cancer, Liu et al[43] discovered that the FC between the thalamus and S1 influenced the level of anxiety and depression. Not only that, but it was more grave in the breast cancer group compared to the control group. They also confirmed that FC between the thalamus and S1 is associated with the effect of pain duration on depression, with pain duration positively correlating with the degree of anxiety and depression. Based on these findings, they hypothesized that pain duration could contribute to depression through thalamus-S1 connections.

Bukkieva et al[40] discovered that patients with depressive symptoms showed less connection between the MPFC and the fusiform gyrus in their investigation of FC in breast cancer individuals. Besides, this investigation revealed that FC between the MPFC and para-hippocampal gyrus was altered in patients with mild depression. However, this study solely looked at the functional connections of the brain in relation to depression and pain in individuals with breast cancer; it did not combine breast cancer survivors with depression and pain symptoms to observe the brain's functional activities. Nevertheless, there was an overlap between the two groups of pain and depression, so it has some reference value.

Breast Cancer Bone Metastasis Pain and Brain Function Connections

Bone metastasis pain represents a chronic pain condition that includes neuropathic, inflammatory, and injury-related components.[60] Pain is believed to be largely caused by osteoclast-mediated bone resorption, which can be avoided by using osteoprotegerin to block osteoclast differentiation.[61] To better understand chronic pain brought on by bone metastases of breast cancer, researchers looked at a mouse model. They used longitudinal resting-state functional MRI (rs-fMRI) to compare the model's brain activity with that of Sham-Vehicle animals. Alterations in the relationships between the cingulate cortex and two distinct hippocampal regions: ventral and dorsal areas. Additionally, researchers observed modified interactions between striatal areas and sensory processing regions, including motor and parietal cortices. The investigation also identified changes in neural networks connecting the opposite side thalamus with somatosensory areas. The brain becomes less connected as a result of these disturbances. Moreover, the study also revealed that the cingulate, piriform, and prefrontal cortices exhibited the largest effect sizes in FC alterations, while the

ventral striatum and dorsal hippocampus showed the smallest effects. Reductions in FC were primarily observed in the cingulate cortex, prefrontal cortex, ventral striatum, and dorsal hippocampus. Not only that, but the experiment demonstrated that mice treated with zoledronic acid (ZA) (Tumor-ZA group) experienced significantly smaller declines in within-network connectivity changes in the ventral striatum, prefrontal/ACC, and cingulate cortex compared to the Tumor-Vehicle group.[62] A comparative study of the ZA-treated group (Tumor-ZA) versus the untreated group (Tumor-Vehicle) provides important insights into the translational treatment of bone metastatic pain. ZA significantly attenuated the decline of FC in the aforementioned pain-critical brain regions, suggesting its protective effect against chronic pain-induced CNS remodelling. Since ZA preserves FC by inhibiting osteoclast-mediated bone resorption, a major driver of pain signalling, its FC-preserving effect may stem from the inhibition of peripheral inflammatory and neuropathic pain inputs.[63] These findings suggest that ZA may synergise with anti-Nerve Growth Factor (anti-NGF) therapies targeting central pain sensitisation to form a "dual mechanism" strategy, ie, ZA mitigates bone destruction while anti-NGF blocks central adaptation to maladaptive remodelling. In clinical practice, ZA in combination with neuromodulatory drugs (eg, gabapentin, ketamine) may optimise analgesia by simultaneously interfering with peripheral and central pain pathways.[64] Future validation of whether the stabilising effect of ZA on FC is associated with long-term pain improvement in patients is needed to establish its value in multimodal analgesia for metastatic bone disease.

Another prospective study investigated the effects of anti-nerve growth factor therapy on FC in mice with cancer-induced bone pain following mammary carcinoma tumor cell implantation. The results showed that the interaction between the amygdalar and thalamic regions, as well as midbrain areas, was most significantly disrupted. FC changes in midbrain structures were mainly observed in motor-related regions and the PAG. Additionally, alterations were found in the connectivity between cortical areas, particularly between the temporal associative/insular regions and the cingulate cortex. Changes were also noted in the FC between striatal regions and both midbrain and thalamic areas. The study further revealed significant FC impacts in the amygdalar regions opposite the tumor site, as well as in the thalamic, dorsal hippocampus, and S1 regions. In the Tumor+Vehicle group, notable FC changes were observed between the ipsilateral motor-related epithalamus and the amygdala, the anterior PAG and S2, and the posterior PAG and limbic cortex. These changes were characterized by a consistent decline in FC across all the mentioned brain regions.[65] Although the current data are derived from animal models, they provide a foundation for clinical imaging research.

Discussion

Pain associated with breast cancer is often chronic,[66] and studies have shown that approximately 37.5% of patients continue to suffer from pain 24 months after surgery.[67] The current pharmacological regimens are associated with dependence risks and adverse effects, while non-pharmacological interventions are often not as effective as they should be.[68] In recent years, non-invasive brain stimulation techniques (eg, transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS)), which are able to precisely modulate the function of pain-associated brain regions, have provided a breakthrough therapeutic option for this kind of intractable pain.[69] This review systematically compiles the latest neuroimaging research results and reveals for the first time that breast cancer-related chronic pain is different from non-cancer chronic pain in terms of brain functional networks and structural reorganisation, which not only elucidates the underlying neurobiological mechanisms but also lays a theoretical foundation for the development of individualised pain management strategies based on neuroimaging markers.

Our comprehensive analysis of neuroimaging studies investigating breast cancer pain reveals the involvement of multiple functional brain networks, with the SN, frontoparietal network (FPN), and DMN demonstrating significant structural and functional alterations. The DMN, comprising core regions such as the MPFC, PCC, and precuneus, plays a crucial role in higher-order cognitive functions, including self-referential processing, autobiographical memory retrieval, and prospective thinking.[70] The SN, involving the ACC and anterior insula, helps detect and respond to important stimuli.[71] Notably, SN dysfunction has been implicated in the pathophysiology of various neuropsychiatric disorders, including schizophrenia spectrum disorders and autism spectrum conditions.[72] These networks interact dynamically, with the SN regulating shifts between internal and external focus by influencing the DMN and FPN. This interaction is supported by the inhibitory relationship between the DMN and FPN, which helps switch between introspective and task-focused states.[73,74]

Several studies on chronic non-cancer pain have shown changes in the SN and the DMN.[75] For example, chronic back pain is associated with disrupted DMN activity, particularly in the MPFC and PCC. The connection between these regions correlates with pain duration.[76] Patients with chronic low back pain show reduced connectivity between the ventral tegmental area and regions like the rostral ACC and MPFC.[77] In summary, recent studies on chronic non-cancer pain have highlighted several brain regions that undergo structural and functional changes. These include the prefrontal cortex, ACC, amygdala, hippocampus, thalamus, nucleus accumbens, and somatosensory areas. The development of chronic pain is linked to synaptic plasticity, changes in the central nervous system, and alterations in multiple brain regions involved in pain regulation.[78] The MPFC, a key part of the DMN, plays a role in executive function and pain processing. Its connections to areas like the thalamus, hippocampus, and amygdala influence how pain is perceived.[79–81] Unlike the increased MPFC activation observed by Buvanendran et al[82] in patients with moderate to severe chronic cancer-related pain, studies have shown that chronic non-cancer pain is associated with only mild MPFC activity.[83] This inconsistent result may be due to the small sample size of the study, the small number of disease types, and systematic error. Buvanendran et al[82] did not clarify whether their study population included patients with breast cancer-related pain. In contrast, Mioduszewski et al[84] studied breast cancer patients before and after MBSR therapy, finding reduced MPFC activation post-treatment. However, the lack of a healthy control group makes it unclear if MPFC activity differs between patients and healthy individuals.

The MPFC is also involved in psychiatric conditions often seen with chronic pain.[85] Animal and clinical studies support this finding.[86–90] Quidé et al[90] found weaker connections between the right amygdala and MPFC in breast cancer patients with chronic pain compared to healthy individuals. Depression levels were linked to stronger amygdala-MPFC activity, suggesting that depression may alter how chronic pain affects emotional processing. Bukkieva et al[40] also found weaker amygdala-MPFC connectivity in post-mastectomy pain patients but did not explore the role of depression in long-term pain. This gap highlights the need for further research on how chronic pain and depression interact in breast cancer patients.

The precuneus, another key DMN region, regulates emotions and pain processing. Research conducted by Buvanendran et al[82] demonstrated that individuals experiencing moderate-to-severe chronic cancer-related pain exhibited heightened neural activity in the right precuneus region. Compared to healthy individuals, patients with multiple myeloma-CIPN (12) showed higher activity in the left precuneus after heat stimulation.[91] Similar increased precuneus activity appears in other chronic pain conditions. These include nerve pain after shingles and long-term lower back pain,[92,93] which is consistent with the findings of the two earlier investigations on chronic cancer pain. Together, the research points to a possible link between pain intensity and precuneus activity levels. Hatchard et al[31] observed reduced precuneus, S1, and dorsolateral prefrontal cortex activity in breast cancer patients with chronic nerve pain after MBSR therapy, along with improved pain relief. These findings provide additional support for our hypothesis. However, larger studies are needed to confirm the connection between precuneus activity and pain intensity.

The ACC is involved in both the DMN and SN, playing a role in pain and emotional processing.[94,95] It is particularly important for the emotional aspects of pain, which are often linked to anxiety and depression.[96] Animal studies using male mice show that overactive circuits between the ACC and amygdala increase the risk of chronic pain-related depression.[97] While mindfulness training has been shown to strengthen ACC-PCC connections in breast cancer patients, more research is needed to understand how the ACC affects emotional processing in these patients.

The anterior insula and ACC are key regions in the SN and limbic systems, involved in emotional pain processing and sensory integration.[98–100] This paper shows that only two articles currently exist on how chronic pain from bone metastases in breast cancer affects brain-related regions. Both articles found that the tumor-vector group in a mouse model of chronic pain experienced a reorganization of FC due to pain. They observed changes in FC within the limbic system and SN, noting a decrease in both cases. These findings do not fully align with the previously reported changes in FC in brain regions related to chronic pain in breast cancer. Additionally, they did not investigate whether a connection exists between the DMN and the SN. To improve the prognosis for breast cancer patients, we need to increase the number of experiments and sample sizes. This will help us investigate changes in FC in brain regions affected by bone metastases. Additionally, it is important to understand the molecular mechanisms of tumor cell invasion and metastasis, as well as to explore new therapeutic targets.

Reduced DMN activity is linked to increased SN activity in chronic pain,[101,102] and DMN-SN disruption is also frequently linked to pain sensitivity.[103] Bukkieva et al[40] found weaker connections between the MPFC and SN in post-mastectomy pain patients, but mindfulness training restored these connections and reduced pain.[38,52] Similar disruptions

are seen in other chronic pain conditions.[104–107] Bukkieva et al[40] also found that breast cancer patients experienced decreased FC of the MPFC with the right inferior frontal gyrus, right inferior temporal gyrus, and amygdala after treatment. In contrast, patients with chronic non-cancer pain usually exhibited increased connectivity between the MPFC and the amygdala.[42,108,109] This discrepancy in the outcomes of MPFC-amygdala connectivity related to tumors necessitates further investigation to clarify the underlying mechanisms.

Research on brain structure changes in breast cancer pain is limited. Nudelman et al,[46] found reduced GM density in breast cancer survivors with post-chemotherapy pain, particularly in the superior frontal gyrus, MPFC, and ACC. Hatchard et al[47] observed increased GMV in breast cancer patients with chronic nerve pain after MBSR therapy. These findings suggest that cytotoxic treatments may alter pain-processing brain regions. However, GM changes in chronic pain vary, with some studies reporting volume reductions and others reporting increases.[110–118] This inconsistency highlights the need for larger, more standardized studies to clarify the relationship between chronic pain and GM changes.

Moreover, emerging evidence suggests neuroanatomical changes in chronic pain may be reversible. Studies show GM normalization in treated patients, including breast cancer patients with CNP after MBSR therapy.[119,120] These findings suggest pain-related GM changes reflect dynamic, reversible neuroplasticity, not permanent damage, offering new treatment directions.

Conclusions

While functional MRI (fMRI) and diffusion tensor imaging (DTI) have advanced significantly, research on breast cancer-related chronic pain still faces several key limitations. Current studies face multiple methodological challenges, including a lack of controlled experiments to verify core findings, small sample sizes, inconsistent research methods, and an overreliance on subjective pain assessments (eg, VAS and NRS scales).[121] These issues significantly undermine the reliability of research outcomes. The most pressing problems are the absence of standardized objective pain assessment methods and insufficient investigation into spinal cord-brain interactions. These fundamental shortcomings greatly hinder the identification of precise treatment targets.

Nevertheless, existing evidence, though limited, has uncovered distinct functional abnormalities in key brain networks (including the default mode network and salience network) of breast cancer pain patients. These abnormalities show remarkable similarities to neural mechanisms observed in non-cancer chronic pain conditions, providing valuable insights into the complex pathophysiology of breast cancer pain.

Moving forward, research must prioritize well-designed controlled experiments and incorporate advanced multimodal techniques like cortico-spinal imaging.[122] Such approaches will enable systematic examination of spinal cord-brain circuit dynamics in pain processing, facilitating the development of personalized treatment strategies that could substantially improve clinical outcomes.

Generative AI Statement

The authors declare that no Generative AI was used in the creation of this manuscript.

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Disclosure

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