Morphological and functional brain changes in chronic cancer-related pain : a systematic review

Morphological and functional brain changes in chronic cancer-related pain: a systematic review

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Abstract

Purpose

To perform a systematic review of the available literature on morphological and functional brain changes measured by modern neuroimaging techniques in patients suffering from chronic cancer-related pain.

Methods

A systematic search was conducted in PubMed, Embase and Web of Science using different keyword combinations. In addition, a hand search was performed on the reference lists and several databases to retrieve supplementary primary studies. Eligible articles were assessed for methodological quality and risk of bias (RoB) and reviewed by two independent researchers.

Results

The search yielded only four studies, three of which used MRI and one PET-CT. None of the studies measured longitudinal morphological (i.e., gray or white matter) changes. All studies investigated functional brain changes and found differences in specific brain regions and networks between patients with chronic cancer-related pain and pain-free cancer patients or healthy volunteers. Some of these alterations were found in brain networks that also show changes in non-cancer populations with chronic pain (e.g., the DMN and SN). However, specific findings were inconsistent, and there was substantial variation in imaging methodology, analysis, sample size, and study quality.

Conclusions

There is a striking lack of research on morphological brain changes in patients with chronic cancer-related pain. Moreover, only a few studies investigated functional brain changes. In the retrieved studies, there is some evidence that alterations occur in brain networks also involved in other chronic non-cancer pain syndromes. However, the low sample sizes of the studies, finding inconsistencies, and methodological heterogeneity do not allow for robust conclusions.

Introduction

In the last few decades, incredible progress has been made in the way cancer is detected and treated, with over 40% of cancer survivors now living longer than ten years (1). Unfortunately, of the patients with stable disease and those that may have beaten cancer, many continue to experience a range of long-term symptoms that can substantially impact their quality of life(2, 3).

Besides fatigue, chronic cancer-related pain is one of the most common and debilitating long-term symptoms, affecting up to half of the cancer survivors(4-7). Chronic cancer-related pain is pain caused by the primary cancer itself, by metastases, or by the treatment(8). However, as this is not the primary focus of the cancer treatment and follow-up, cancer-related pain is often underrecognized and undertreated(9, 10). It can persist for months, years, or even a lifetime(9) and is generally considered chronic if it lasts longer than three months(11).

The tumor itself, or its metastases, can cause damage to surrounding non-neural tissues (e.g., muscle, bone, joints, tendons, skin, etc.) and activate peripheral nociceptors(8). In addition, the somatosensory system can also be damaged, leading to a neuropathic pain state(8). However, in most patients with pain due to the cancer itself, a mix of nociceptive and neuropathic pain is thought to be present(8, 12).

Cancer treatment can also cause damage to the somatosensory system, with similar neuropathic pain phenotypes(8). For instance, chronic polyneuropathies are commonly reported after chemotherapy treatment i.e., chronic chemotherapy-induced polyneuropathy (CIPN)(7). In addition, invasive procedures such as surgery or radiotherapy can cause further damage to the somatosensory system (e.g., post-mastectomy pain syndrome)(7, 13-15). Even novel cancer treatments, like hematopoietic stem cell transplants (HSCTs) or treatment with monoclonal antibodies, have been associated with chronic pain syndromes of nociceptive and neuropathic origin (16, 17).

Fortunately, in the past few decades, substantial progress has also been made in our understanding of underlying pain chronification mechanisms. For instance, we now

know that underlying nociceptive and neuropathic mechanisms do not fully explain the chronic pain state(18). In a subset of patients, underlying nociplastic mechanisms may also be involved, with sensitization of the somatosensory system and altered pain modulation, but no clear evidence of actual or threatened tissue damage(18).

Multiple studies indicate that chronic pain is in fact a brain disease state(19, 20), associated with maladaptive neuroplasticity, i.e. abnormal morphological and functional changes occurring in corticolimbic brain regions, across a variety of chronic pain syndromes(21-29). More specifically, in the acute phase of pain, peripheral nociceptive input causes spinal and central reorganization of regions associated with nociceptive circuitry (thalamus, insula, anterior cingulate cortex (aCC), etc.), which then tends to shift towards emotional-motivational circuits in the chronic phase (medial prefrontal cortex (mPFC), amygdala, hippocampus, etc.)(30, 31). Certain predispositions and the way these emotional-motivational circuits respond to the inciting event are believed to determine the maintenance of the chronic pain state(20). It is not clear, however, to what extent the reorganization summarized above also occurs in the brain of cancer patients or survivors with chronic cancer-related pain.

Brain changes are often quantified using modern non-invasive brain imaging techniques like magnetic resonance imaging (MRI). For instance, cortical reorganization is most commonly studied using voxel-based morphometry (VBM), a technique that segments and compares the local concentration of gray matter (GM) between two groups of subjects(32). Changes in brain activity are commonly investigated with hemodynamic techniques like functional MRI (fMRI) or positron emission tomography (PET)(33-35). Resting-state fMRI (rs-fMRI) is a task-free technique that measures spontaneous low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal and is often used in chronic pain studies to quantify functional connectivity between regions and investigate functional networks(36).

The present systematic review summarizes the available evidence on morphological and functional brain changes in cancer patients or survivors with chronic cancer-related pain, using modern neuroimaging techniques. We hypothesize that structural and functional alterations occur in brain circuits that have been associated with other chronic non-cancer pain syndromes. However, considered the unique characteristics and heterogeneity of chronic cancer-related pain, possible differences might be encountered.

Methods

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines(37), and was prospectively registered in Prospero, under the registration number CRD42022306909.

Search strategy

A systematic search of the literature, based on the PICO-framework(38), was conducted in the period from January until February 2022, using online databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com) and Web of Science (http://webofknowledge.com). In addition, relevant journals and databases were hand-searched for any supplementary primary studies.

The following search terms were entered in PubMed: (chronic pain AND (neoplasms[MeSH Terms] OR carcinoma[MeSH Terms] OR cancer OR carcinoma OR neoplasm)) AND (neuroimaging[MeSH Terms] OR neuroimaging OR brain imaging OR magnetic resonance imaging[MeSH Terms] OR MRI OR tomography, xray computed[MeSH Terms] OR "computed tomography" OR positron emission tomography[MeSH Terms] OR "positron emission tomography" OR PET OR "voxel-based morphometry" OR VBM OR "gray matter" OR "grey matter" OR "white matter"). A detailed summary of keywords for Embase and Web of Science can be found in Supplementary material.

Study selection

The following inclusion criteria were used to retrieve eligible articles: (1) only human studies were included, (2) patients had to be between 25 and 65 years old and diagnosed with cancer, or survived cancer, and have chronic pain (defined as pain lasting longer than 3 months(8)), without any other pain syndrome or major concomitant neurological or psychiatric disorder (P, patient population), (3) one or more neuroimaging techniques had to be used (I, diagnostic intervention), (4) patients had to be compared to healthy volunteers or pain-free cancer patients (C, comparison)

(5) morphological (i.e., GM) and/or functional changes (i.e., activation or functional connectivity) had to be described between the pain and the pain-free group (O) (6) articles had to be written in English or Dutch, between 2002 and 2022 and (7) had to be full texts of original research. Articles not fulfilling these criteria were excluded.

All articles were uploaded into an online software tool (i.e., Covidence, https://www.covidence.org). In a first phase, the uploaded articles were screened by two independent researchers (T.VdV. and A.D.) and selected based on title and abstract. Eligible articles were retrieved in full text. In a second phase, the full text articles were evaluated on meeting inclusion criteria. In case of uncertainty about inclusion or exclusion, a decision was made based on consensus. If no consensus was found, a decision was made by adjudication of a third reader (M.M.).

Study Characteristics

Relevant characteristics of included studies were extracted and presented in an evidence table (Table 2), containing the following items: author, sample size, main cancer diagnosis, cancer treatment type, inclusion and exclusion criteria, age and sex of the pain and pain-free patient group(s) or healthy control group, pain characteristics (if described), pain assessment, imaging modality and characteristics, and main findings of the study.

Risk of bias and level of evidence

Methodological study quality and risk of bias were assessed using the Newcastle-Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) for risk of bias and independently reviewed by two researchers (T.VdV and A.D.). Results were compared, and disagreements were resolved by consensus.

The NOS contains 8 items within 3 domains (selection, comparability, outcome) and a total maximum score of 9. In line with the agency for healthcare research and quality (AHRQ) standards, studies with 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome domain were considered good quality. Studies with 2 stars in the selection domain and 1 or 2 stars in the

comparability domain and 2 or 3 stars in the outcome/exposure domain were considered fair. Studies with 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 star in the outcome/exposure domain were considered poor quality. Each study was also given a level of evidence, according to the 2005 classification system of the Dutch Institute for Healthcare Improvement (CBO, http://www.cbo.nl). Given the low number of identified studies, no studies were excluded based on quality. Moreover, since no meta-analysis could be performed, we reviewed the results in a narrative way, taking the low number of studies and variable quality into consideration.

Qualification of searchers

Articles were searched, screened, selected, and assessed for quality independently by T.VdV., a postdoctoral researcher working on brain imaging, independently from A.D., a PhD candidate working on chronic pain, under supervision of M.M. and A.D.G., two senior researchers with extensive experience in chronic pain research and conducting systematic reviews.

Results

Study selection

A total of 2,152 studies were identified from the three databases. After removing duplicate records, 1,991 unique articles remained. No eligible extra articles were identified from the reference list. One article was identified through handsearching. After the full-text screening phase, four studies were considered eligible and were included in the review. A detailed flowchart can be found in Figure 1.

Study Characteristics

Three studies used a cross-sectional study design(39-41) and one study was a prospective longitudinal study(42). Three studies used MRI(40, 42), one study used PET-CT imaging(39). Three studies investigated chronic pain in a specific type of cancer (i.e., breast cancer or multiple myeloma)(40-42), while one study included chronic pain patients with different types of cancer(39). Two studies investigated only women(41, 42), while the other studies investigated both men and women(39, 40). Three studies compared cancer patients with and without pain(39, 41, 42), two studies compared cancer patients with healthy volunteers(40, 41). The number of patients in the pain group was quite low for two studies (n = 11 and 12)(39, 40), and reasonable in the other studies (n > 20)(41, 42). Three studies looked at brain activation or perfusion differences(39, 40, 42), while one study investigated functional connectivity changes(41). One study investigated morphological changes, but only in the acute phase(42) and was included because functional changes were assessed up until one year after chemotherapy. One study used neurophysiological testing in addition to self-reporting pain(40), while the other studies mainly relied on self-reports. Only two studies reported median or mean pain scores in the different groups(39, 42). For each study, the main study characteristics can be found in the evidence table (Table 2).

Risk of bias and level of evidence

Results of the risk of bias (RoB) and quality assessment using the NOS can be found in Table 1. Low scores were encountered for the comparability and exposure section because pain is often only measured through self-report. In addition, it was not always clear whether adjustment for confounders was performed in the analysis. Only one study actively matched for age(41) and two studies included only women (41, 42). Good agreement was found between the two raters (28/36; 78%) for the quality assessment. Differences were resolved by consensus. All studies were assigned a level of evidence B, given that they are all case-control or cohort studies, lacking the criteria of randomized controlled trials (A2), and having relatively small sample sizes.

Morphological brain changes

Morphological changes were investigated in only one of the four studies we identified(42). More specifically, GM changes were quantified up to one month after chemotherapy in patients with breast cancer and were correlated longitudinally with perfusion changes one year later. Cancer patients with a greater decrease in GM density from baseline (i.e., after surgery) to one month post-chemotherapy in the right superior frontal gyrus (SFG), mPFC and left cingulate gyrus did not show increased perfusion, or did not report increased pain symptoms, compared to cancer patients with pain(42). However, these differences were not present at one year follow-up. The authors did not report any GM analysis at one year after chemotherapy, which did not allow us to perform a full assessment of GM density changes in the chronic phase.

Functional brain changes

Brain activation

One study found increased activation (i.e., increased regional cerebral glucose metabolism) in the bilateral PFC (including SFG and mPFC) in patients with moderate to severe chronic cancer pain (i.e. NRS >= 4), compared to pain-free cancer patients (p=0.001)(39). Two studies found increased activation of the precuneus(39, 40). More specifically, Buvanendran et al. reported precuneus hyperactivity in patients with spontaneous moderate to severe chronic cancer pain versus pain-free cancer patients (p=0.001), using task-free PET-CT imaging. Boland et al. also reported precuneus activation in MM-CIPN patients versus healthy volunteers (p = 0.001) in response to heat-pain stimulation(40). In addition, they found increased activity in the operculo-insular cortex and decreased activation in the SFG in response to heat-pain stimuli (40).

Functional connectivity

One study used rs-fMRI to investigate functional connectivity in breast cancer patients after cancer treatment(41). They found that patients who developed post-mastectomy pain syndrome showed decreased functional connectivity between the mPFC and inferior frontal gyrus *(*IFG, $p = 0.003$), inferior temporal gyrus *(*ITG, $p = 0.007$), and the amygdala *(*$p = 0.046$), compared to pain-free breast cancer patients. In addition, they also found decreased connectivity between the mPFC and regions of the salience network (SN) *(*$p = 0.009$), and increased connectivity between the mPFC, the left cerebellum *(*$p = 0.003$) and occipital pole ($p = 0.029$).

Discussion

The main aim of this study was to systematically review the literature on morphological and functional brain changes in patients with chronic cancer-related pain. Our search resulted in only four studies, which prevented us from conducting any overall or subgroup meta-analysis. A narrative summary of the results is discussed below and compared to what is known from other chronic pain syndromes in non-cancer patients.

Morphological brain changes

Of the four studies we identified, one study investigated morphological changes, but only before and immediately after chemotherapy (i.e., one month). Although this does not comply with the definition of chronic pain, the changes they encounter are worth discussing. More specifically, they found that breast-cancer patients with chemotherapy-induced pain showed a larger GM decrease in the cingulate cortex, the sFG and mPFC compared to pain-free cancer patients that didn't receive chemotherapy (42). Interestingly, Baliki et al. found that patients transitioning from a subacute low back pain (cLBP) state to a persistent pain state show larger GM decreases compared to recovered patients(43), which complicates these findings. In non-cancer patients there is also substantial evidence for a characteristic decrease in GM in the chronic phase of pain, either in total GM volume(24, 28, 44), or in specific regions (e.g., the dorsolateral prefrontal cortex (dlPFC)(28, 44-50), anterior cingulate cortex (aCC)(46, 48, 51-53), primary somatosensory cortex (S1)(48, 54), insular cortex (IC)(46, 48, 49, 51, 54, 55), etc.(56)). Nevertheless, inconsistencies about GM decreases in chronic pain have been reported (55, 57, 58), and the underlying physiological mechanisms that govern these changes are not yet fully understood. Studies have shown that a decrease in GM is not necessarily attributed to neuronal degeneration, but could be related to a decrease in tissue water content(59), glial death(60), inflammation (i.e. IL-6)(61), changes in local microvasculature due to metabolic changes in glutamate and γ-aminobutyric acid (GABA)(62) or synaptic-dendritic spine remodelling(63, 64). In recovered or successfully treated chronic pain patients, localized GM decreases tend to normalize(47, 65, 66), indicating that these underlying physiological processes are reversible.

Pre-existing GM density in the above-described regions may also interfere with the development of chronic pain. For instance, increased pre-existing GM in certain regions prevented the transition to a chronic pain state in patients with cLBP and knee osteoarthritis(67, 68). Lower pre-existing GM in brain regions associated with specific cognitive and affective predispositions, like pain-related worrying, have also shown complex interaction with pain-driven GM changes(69).-

Understanding which neuroanatomical regions show GM changes is essential, because it could lead to fundamental knowledge about cancer-related pain and lead to more targeted treatments. For instance, if we can pinpoint the exact regions that are associated with chronic pain, this could be used to monitor and assess treatment efficacy. Moreover, it could possibly also inform the development and optimalization of non-invasive neurostimulation techniques, like transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS)(70).

To conclude, only information about the acute phase of GM changes has been studied in cancer patients with pain, with inconsistent results. The lack of identified studies therefore does not allow us to make inferences about morphological GM changes in patients with chronic cancer-related pain.

Functional brain changes

All four studies we identified investigated functional brain changes and found alterations in regions of the medial parietofrontal network, or the so-called default mode network (DMN)(71). This functional network is associated with emotional processing, relating external information to the self, and remembering prior experiences(72). Interestingly, disruption of DMN dynamics have also been found in acute and chronic non-cancer pain syndromes(73).

One of the main functional nodes of the DMN is the mPFC. It receives ascending inputs from regions such as the thalamus, hippocampus, amygdala, and the anterior cingulate cortex (aCC)(74), and is believed to be involved in endogenous descending pain modulation via projections to the periacquaductal gray (PAG)(75, 76).

From studies in animal models and human fMRI studies, a typical hypoactivation of the mPFC is found in chronic non-cancer pain syndromes(74, 77). Surprisingly, Buvanendran et al. report increased activation in the mPFC in patients with moderate-to-severe chronic cancer-related pain(39). Increased activity in these regions is uncommon in chronic pain and has been associated with acute sustained levels of spontaneous pain(78), or pain with underlying nociplastic mechanisms(79). This finding was also not repeated in the other two studies we identified. Possible explanations for this inconsistency include the small sample size of the study, substantial variation in neuroimaging methods or differences in underlying etiology.

Another essential functional node of the DMN is the precuneus(71), located in the posteromedial parietal cortex. Two studies in our review showed hyperactivation in this region. More specifically, Buvanendran et al. showed an increase in activation in cancer patients with moderate to severe pain compared to pain-free cancer patients, and Boland et al. in MM patients with CIPN compared to healthy controls, using a heat-pain stimulation protocol. The precuneus has been associated with monitoring the external environment(80), retrieval of remembered episodes, first-person perspective taking and experience of agency(81). Interestingly, mindfulness-based stress reduction techniques (MBSR) in breast cancer patients with chronic neuropathic pain seem to decrease precuneus activity, along with decreases in the primary somatosensory cortex (S1) and the dorsolateral prefrontal cortex (dlPFC), which results in a reduction in pain severity(82).

Apart from activity changes in the DMN in the above-described studies, Bukkieva et al. also report decreased functional connectivity between the mPFC, a primary functional node of the DMN, and other networks in breast cancer patients with post-mastectomy pain syndrome(41). More specifically, they report a functional disruption between the mPFC and nodes of the midcingulo-insular network, or the so-called salience network (SN), a finding that is also commonly encountered across a wide range of chronic non-cancer pain syndromes(73, 79, 83-85). The anterior insular cortex and the anterior cingulate cortex (aCC) are principal nodes of the SN and limbic system. They have been associated with processing emotional-affective aspects of painful attention-demanding stimuli and play a role in regulating adaptive behavioral

changes(55, 86, 87). Sustained increased activation in the SN has been associated with deactivation of regions in the DMN in chronic pain(88). Moreover, DMN-SN disruptions also tend to correlate with pain sensitivity(89). Interestingly, these findings of Bukkieva et al. also correspond to animal studies of chronic cancer-related pain, where functional reorganization of the prefrontal and cingulate cortices have been reported(90, 91).

In addition to changes in DMN-SN dynamics, Bukkieva et al. report functional connectivity changes between the mPFC and other regions in breast cancer patients after treatment. For instance, they show decreased functional connectivity between the mPFC, inferior frontal gyrus, middle temporal gyrus and amygdala, all regions that have also been associated with impaired pain modulation. In non-cancer patient populations with chronic pain, mPFC-amygdala functional connectivity is typically increased and has been related to pain-related worrying (92-95).

In conclusion, the studies we retrieved provide some evidence of functional brain reorganization in patients with chronic cancer-related pain. Changes seem to occur in brain networks that have also been reported in non-cancer chronic pain syndromes (i.e., the DMN and SN) and add to the evidence that a set of core functional networks are involved in chronic pain, whether cancer-related or not. The inconsistencies we encountered between our studies and studies performed in other pain syndromes do require further investigation.

Limitations and suggestions for future research

For the interpretation of the findings, it is important to consider that most of the studies we identified had small sample sizes and were of variable quality. We also found inconsistent results for activation in certain brain regions, which could be attributed to the small sample sizes, differences in study design, different patient populations or differences in underlying pain mechanisms (i.e., neuropathic versus non-neuropathic(96, 97)). Moreover, although these studies investigated functional brain changes, it is difficult to synthesize the results or make solid conclusions about the findings because of the low number of studies and the heterogeneity in terms of used paradigms and analysis methods. For instance, even though PET-CT and fMRI investigate changes in blood flow, activity during heat-pain stimulation cannot be directly compared to activity during a task-free study. In addition, even though PET-CT, rs-fMRI, and arterial spin labeling (ASL) fMRI are methods that measure task-free brain activity based on blood flow or perfusion, they are inherently different and use different analyses, which can introduce substantial variability. Nevertheless, these methods are complementary and can provide some evidence of functional changes in specific anatomical regions and networks. To make a robust meta-analysis of studies that can help us understand the pathophysiology of chronic pain in these patients, more neuroimaging studies with larger sample sizes, similar paradigms, and analysis methods are needed.

In addition to the variability in imaging and imaging analysis methodology, chronic pain was also not always well-defined and mostly measured using different subjective self-reporting scales. A more standardized way of measuring pain would also improve quality and allow for more solid conclusions.

Future research should take these limitations into account, and, as our study also shows, a focus on longitudinal assessment of GM, WM, and brain connectivity is urgently needed. Investigating whole-brain and regional GM changes over time and mapping the structural and functional connectome could help us better understand pain chronification and the effects that cancer and cancer treatment can have on the brain. For instance, such approaches could lead to specific biomarkers, similar to the ones found in studies of patients with chronic low back pain (cLBP), where an increase

in mPFC-NAcc connectivity was able to predict the development of chronic pain with reasonable accuracy(98). In addition, disentangling differences between chronic cancer pain and post-cancer treatment pain would also be interesting, as chronic cancer pain (i.e., pain caused by the cancer itself) is believed to be a separate pain state(99).

Conclusion

Our study shows that, in contrast to studies in non-cancer pain populations, there is a striking lack of non-invasive neuroimaging studies investigating maladaptive neuroplasticity in the chronic cancer-related pain population. The few studies we identified mainly looked at functional changes and found differences in regions and networks that have also been associated with pain chronification in non-cancer chronic pain syndromes (e.g., the DMN and SN). This indicates that also in cancer patients, a common set of functional brain networks appears to be involved in developing chronic pain. Nevertheless, some findings were inconsistent, and because of the low number of studies, the variable quality, and the heterogeneity in terms of paradigms and analysis methods used, no solid conclusions could be drawn. More longitudinal studies with larger sample sizes and more standardized pain measurements are therefore urgently needed.

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