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ORIGINAL RESEARCH

Right Hemispheric Neuronal Dysfunction in Cancer Pain: A Resting-State fMRI Exploratory Study

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Background: This exploratory study investigated the neurobiological mechanisms of cancer pain by examining functional brain alterations using resting-state functional magnetic resonance imaging (fMRI), aiming to characterize neural network changes and identify potential neuroimaging biomarkers.

Methods: A cross-sectional study was conducted from October 2021 to October 2022, involving 20 cancer pain patients and 20 age-, sex-, and education-matched healthy controls. Participants underwent comprehensive clinical assessments and 3.0T resting-state fMRI scanning. Inclusion criteria were patients aged ≥18 years with pathologically confirmed malignant neoplasms experiencing moderate to severe pain (NRS ≥ 4). Functional connectivity and low-frequency amplitude analyses were performed using the right nucleus accumbens as a seed region.

Results: Significant neuroplastic changes were observed in cancer pain patients, primarily in the right hemisphere. Low-frequency amplitude analysis revealed reduced spontaneous neural activity in critical brain regions, including the right medial prefrontal cortex (T = −4.36), right superior/middle frontal gyrus (T = −5.21), and right precuneus (T = −4.15). Functional connectivity analysis showed substantially decreased connectivity between the right nucleus accumbens and bilateral medial prefrontal cortex (T = −4.86), left temporal pole (T = −5.62), and right superior temporal gyrus (T = −5.05).

Conclusion: The study provides preliminary evidence of right hemispheric neuronal dysfunction in cancer pain, highlighting altered functional connectivity in emotion regulation and pain processing neural circuits. These findings offer insights into the neurobiological mechanisms of cancer pain and potential objective assessment approaches.

Keywords: fMRI, negative emotion, cancer pain, cross-sectional study

Introduction

Chronic pain represents one of the most prevalent and distressing symptoms encountered in cancer patients, presenting a complex clinical challenge that transcends traditional assessment methodologies. Conventional pain evaluation tools, such as Visual Analog Scale (VAS) and Numerical Rating Scale (NRS), despite their widespread application, exhibit significant limitations. These assessment methods are inherently subjective, profoundly influenced by individual emotional states, cognitive functions, and cultural backgrounds. In patient populations with compromised consciousness, cognitive impairment, or communication barriers, these tools become critically unreliable. Furthermore, the absence of objective assessment indicators impedes clinicians' ability to precisely evaluate analgesic treatment efficacy, consequently hindering timely therapeutic interventions.[1]

Functional Magnetic Resonance Imaging (fMRI) emerges as an advanced neuroimaging technology offering unprecedented insights into the intricate neural mechanisms underlying cancer-related pain. By detecting blood-oxygen-level-dependent (BOLD) signal dynamics, fMRI enables non-invasive, high-resolution real-time observation of cerebral functional activities. Recent neuroscientific investigations have demonstrated that pain stimuli activate a complex neural

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network encompassing primary somatosensory cortex, anterior cingulate cortex, and insula, forming a characteristic pain processing circuit.[2] Beyond capturing pain-related brain activation patterns, fMRI provides a comprehensive exploration of pain's profound implications for emotional processing and cognitive functionality.[3]

Comparative analysis of functional neuroimaging characteristics between cancer pain patients and healthy controls presents a promising avenue for identifying cancer pain-specific neuroimaging biomarkers.[4] These objective indicators potentially offer clinicians more precise pain assessment tools, facilitating optimized personalized treatment strategies and ultimately enhancing cancer pain patients' quality of life. However, despite the increasing application of functional neuroimaging technologies in neuroscientific research, systematic investigations focusing on brain functional alterations in cancer pain patients remain remarkably scarce. Existing research predominantly concentrates on general chronic pain mechanisms, with minimal exploration of the neurobiological foundations specific to cancer-induced pain.

Grounded in this critical research landscape, our study employs advanced resting-state functional MRI techniques to systematically investigate functional brain alterations in cancer pain patients. Theoretical framework supporting hemispheric lateralization in pain processing suggests that the right hemisphere plays a dominant role in emotional processing and pain regulation. The right hemisphere possesses specialized functions for emotional processing and pain-related affective components. Moreover, accumulating evidence demonstrates that the right hemisphere shows preferential activation during negative emotional states and pain experiences, with the right amygdala exhibiting lateralized dominance in pain processing circuits. This evolutionary conserved lateralization pattern suggests that cancer-related pain, with its significant emotional and psychological burden, may preferentially affect right-hemispheric neural networks involved in emotion-pain integration. Through a comprehensive comparative analysis of 20 cancer pain patients and 20 age- and sex-matched healthy controls, primary objective: To characterize right hemispheric neuronal dysfunction patterns in cancer pain patients using resting-state fMRI compared to healthy controls. Secondary objectives: (1) To identify potential neuroimaging biomarkers for cancer pain assessment; (2) To explore functional connectivity alterations in emotion regulation and pain processing circuits. This investigation not only promises to offer novel perspectives on the neural mechanisms underlying cancer pain but also aspires to provide scientific foundations for personalized pain management and treatment strategies. By elucidating the impact of cancer pain on brain functional networks, particularly within emotion regulation and cognitive function-related neural circuits, we anticipate establishing groundwork for developing more precise and objective pain assessment methodologies.

Method

Study Design

We conducted a prospective, cross-sectional study to track functional brain network alterations in cancer pain patients. The research was implemented from October 1, 2021, to October 21, 2022. The research protocol was approved by the Institutional Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (approval No: BF2020-277-01) and registered with the Chinese Clinical Trial Registry (ChiCTR) (identifier: ChiCTR2100050935). The study cohort comprised 20 pathologically confirmed cancer pain patients and 20 age-, sex-, and education-level-matched healthy controls, all of whom provided fully informed, voluntary written consent. The study rigorously adhered to the ethical principles of the Declaration of Helsinki, ensuring maximal protection and respect for participants' rights and personal privacy.

Participants

Inclusion criteria encompassed patients aged ≥18 years with pathologically confirmed solid malignant neoplasms at stage II or above (according to TNM classification system) experiencing moderate to severe pain (Numerical Rating Scale, NRS ≥ 4) directly attributable to either tumor progression or cancer treatment interventions. To reflect real-world clinical scenarios and maximize generalizability, no restrictions were imposed on specific solid tumor types, allowing inclusion of patients with any pathologically confirmed solid malignancies including but not limited to lung, breast, colorectal, liver, gastric, pancreatic, and other solid organ cancers. Pain assessment was conducted using both NRS for pain intensity evaluation and the Douleur Neuropathique 4 Questions (DN4) screening questionnaire to differentiate neuropathic pain components (DN4 ≥ 4) from predominantly nociceptive pain (DN4 < 4). Pain severity was assessed daily for one week

prior to scanning, with average scores recorded to ensure stability and reliability of pain measurements. All participants provided voluntary, informed written consent following comprehensive explanation of the study protocol.

Exclusion criteria: pregnant or lactating women; patients with abnormal coagulation profiles; localized dermatological lesions; inability to cooperate with assessments; severe life-threatening comorbidities; primary or metastatic brain tumors that could directly affect brain functional imaging results; and any condition deemed unsuitable by investigators.

Concurrently, we recruited 20 age-, sex-, and education-matched healthy volunteers as a control group. All participants underwent comprehensive screening to ensure compliance with the predefined inclusion and exclusion criteria, and completed comprehensive clinical assessments using the Edmonton Symptom Assessment Scale (ESAS)[5,6] and Hamilton Anxiety Scale (HAMA) prior to study enrollment, thereby establishing a rigorous and methodologically robust comparative framework for neuroimaging analysis.

Data Collection

Resting-state functional magnetic resonance imaging magnetic resonance imaging (fMRI) data were acquired using a 3.0T Siemens Prisma MR scanner (Siemens, Munich, Germany) equipped with a 64-channel head and neck coil at the Imaging Department of Guangdong Provincial Hospital of Traditional Chinese Medicine. The imaging protocol comprised three optimized sequences to capture comprehensive brain imaging data.

Structural imaging was performed using a three-dimensional spoiled gradient recalled (3D-SPGR) sequence. Sequence parameters were precisely calibrated: repetition time (TR) of 2200 ms, echo time (TE) of 2.48 ms, flip angle (FA) of 8°, and slice thickness of 1.0 mm. The field of view (FOV) was standardized to 230 mm × 230 mm with a matrix of 256 × 256, yielding high-resolution images with a voxel size of 0.98 × 0.98 × 1 mm^3. A total of 160 slices were acquired to comprehensively cover the entire brain volume.

Functional imaging utilized a T2-weighted gradient echo-echo planar imaging (T2-EPI-GRE) sequence for resting-state functional imaging. After iterative optimization, the final sequence parameters were: TR of 2000 ms, TE of 30 ms, FA of 90°, and slice thickness of 3.6 mm. Balancing temporal and spatial resolution, the FOV was set to 230 mm × 230 mm with a matrix of 64 × 64, resulting in a voxel size of 3 × 3 × 3.5 mm^3. Thirty-seven slices were acquired to capture comprehensive brain functional activity.

Neuroimaging Acquisition

Data processing was performed using MATLAB 2018b with a systematic approach to ensure robust functional magnetic resonance imaging (fMRI) data analysis. Original DICOM data were converted to NIFTI format using specialized MRI Convert software, maintaining data integrity and compatibility. To optimize signal quality, the initial preprocessing involved removing the first 10 time points to account for magnetic field stabilization. Subsequent preprocessing steps included precise slice-timing correction to address inter-slice acquisition differences and rigorous head motion correction using a six-parameter rigid body alignment method.

Artifact detection was rigorously implemented using the Artifact (ART) toolbox, with strict quality control criteria: volumes with global signal intensity exceeding three standard deviations or head motion displacement >0.5 mm were systematically excluded. Following artifact removal, all images were precisely co-registered to the Montreal Neurological Institute (MNI) standard space and spatially smoothed using a Gaussian kernel with 6 mm full-width at half-maximum to enhance signal-to-noise ratio. Resting-state fMRI preprocessing incorporated bandpass filtering (0.01-–0.08 Hz) to isolate relevant neuronal oscillations, linear trend removal, and regression of potential confounding white matter and cerebrospinal fluid signals.

Functional connectivity analysis utilized the widely recognized Automated Anatomical Labeling (AAL116) atlas, focusing on key brain regions critical to emotional regulation and pain processing. Regions of interest (ROIs) included the medial prefrontal cortex (mPFC), amygdala, hippocampus, nucleus accumbens, and ventral tegmental area. Mean time series were extracted from these ROIs, and functional connectivity was quantified through Pearson correlation coefficients, enabling comprehensive assessment of inter-regional neural interactions.

Complementary analyses included fractional amplitude of low-frequency fluctuations (fALFF), calculated by determining the energy ratio within the 0.01–0.08 Hz frequency band, providing insights into local spontaneous neural activity

intensity. To establish clinical relevance, comprehensive correlation analyses were performed between functional metrics and clinical scores, including ESAS pain scores and HAMA. Two-way repeated measures analysis of variance was employed to examine group differences and interaction effects.

Statistical Analysis

Statistical analysis adhered to stringent methodological standards, applying voxel-level ($P < 0.001$) and cluster-level ($P < 0.05$) significance thresholds. Multiple comparison corrections were implemented using Family-Wise Error (FWE), False Discovery Rate (FDR), or Gaussian Random Field (GRF) methods to ensure robust and reliable statistical inference, thereby minimizing potential type I error and maintaining high scientific rigor.

Quality Control

The fMRI scans were uniformly performed by two dedicated professional technicians from the Imaging Department of Guangdong Provincial Hospital of Traditional Chinese Medicine using the same scanning equipment. Prior to scanning, a comprehensive patient preparation protocol was implemented to ensure data quality and minimize potential physiological variations. Participants were thoroughly briefed about the MRI procedure to alleviate anxiety and psychological tension associated with neuroimaging examinations.

Strict pre-scanning guidelines were established to standardize participant preparation. Subjects were instructed to abstain from intense physical activities for 2 hours before the scan and mandated to rest for a minimum of 30 minutes prior to the imaging session. Meticulous attention was paid to metal object removal, with careful screening of both personal belongings and clothing to prevent potential magnetic interference.

During the scanning procedure, participants were positioned supine on the scanning bed with specific measures implemented to optimize image quality. Foam padding was strategically utilized to minimize head movement, while earplugs were provided to reduce scanner noise and potential auditory-induced stress. Participants were explicitly instructed to maintain a relaxed, awake state with eyes closed, avoiding active cognitive processing and minimizing voluntary head movements.

The scanning environment was carefully controlled to maintain a quiet, stable atmosphere, with the primary objective of reducing inter-individual variability caused by scanning-related operational procedures and external environmental factors. These comprehensive preparation and scanning protocols ensured standardized data acquisition and enhanced the overall reliability of the neuroimaging results.

Results

A total of 40 participants underwent functional magnetic resonance imaging (fMRI), comprising 20 cancer pain patients and 20 healthy volunteers (Figure 1). Demographic characteristics demonstrated robust comparability between groups. The cancer pain group comprised 11 males (55.0%), while the control group included 12 males (60.0%), with no statistically significant difference in gender distribution ($P = 0.71$). Mean ages were 60.6 ± 13.47 years for cancer patients and 58.15 ± 8.73 years for controls ($P = 0.49$), with comparable educational backgrounds ($P = 0.27$), predominantly characterized by high school-level education (40.0% in both groups).

Low-frequency amplitude analysis revealed intricate alterations in spontaneous neural activity among cancer pain patients (Figure 2). Notably, significant reductions in local brain functional dynamics were observed across multiple cortical regions, including the right mPFC ($T = -4.36$, $Z = -3.87$, cluster size = 27), right superior/middle frontal gyrus ($T = -5.21$, $Z = -4.46$, cluster size = 82), left middle frontal gyrus ($T = -4.68$, $Z = -4.10$, cluster size = 31), right precuneus ($T = -4.15$, $Z = -3.71$, cluster size = 37), right inferior parietal lobule ($T = -4.52$, $Z = -3.98$, cluster size = 26), and right angular gyrus ($T = -4.94$, $Z = -4.28$, cluster size = 39). All statistical comparisons underwent rigorous correction methods (voxel-level $P < 0.001$, cluster-level $P < 0.05$, using Family-Wise Error, False Discovery Rate, and Gaussian Random Field corrections), ensuring robust and statistically validated neuroimaging findings.

Functional connectivity analysis centered on the right nucleus accumbens unveiled substantial alterations in brain network dynamics among cancer pain patients (Figure 3). Compared to healthy controls, cancer pain individuals demonstrated significant reductions in functional connectivity across critical brain regions, encompassing bilateral mPFC ($T = -4.86$, $Z = -4.22$, cluster

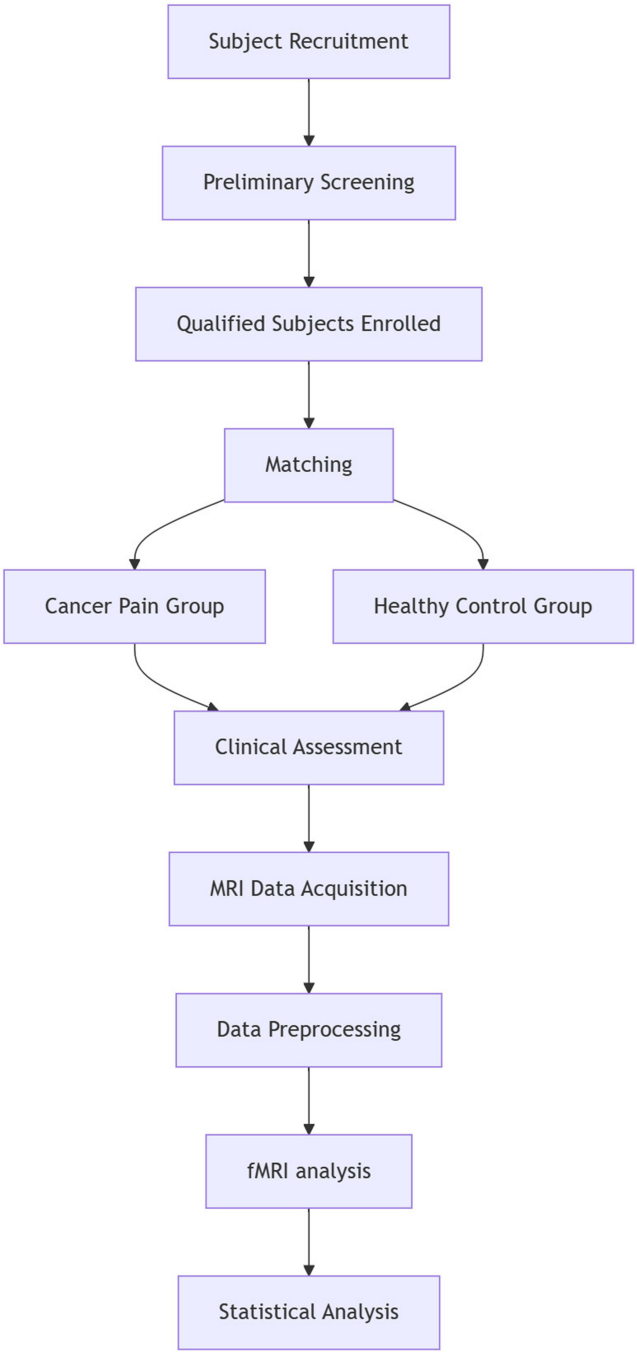

Figure 1 Study flow.

size = 97), left temporal pole (T = −5.62, Z = −4.71, cluster size = 32), right superior temporal gyrus (T = −5.05, Z = −4.35, cluster size = 25), and right supplementary motor area (T = −4.78, Z = −4.16, cluster size = 13).

These observed functional connectivity modifications implicate complex neural circuits integral to emotional regulation, pain perception, and motor control, underscoring the profound neuroplastic consequences of chronic cancer-related pain. The disrupted connectivity patterns provide compelling neurobiological evidence of the extensive neurological impact induced by persistent pain experiences, revealing intricate alterations in brain functional architecture beyond traditional neuroimaging perspectives.

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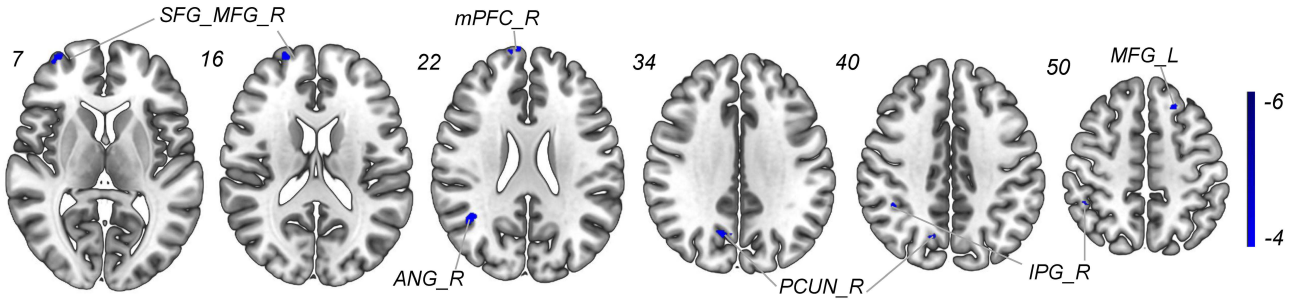

Figure 2 Low-frequency amplitude analysis.
Abbreviations: R, Right; L, Left; mPFC, Medial prefrontal cortex; SFG, Superior frontal gyrus; MFG, Middle frontal gyrus; PCUN, Precuneus; IPG, Inferior parietal gyrus; ANG, Angular gyrus.

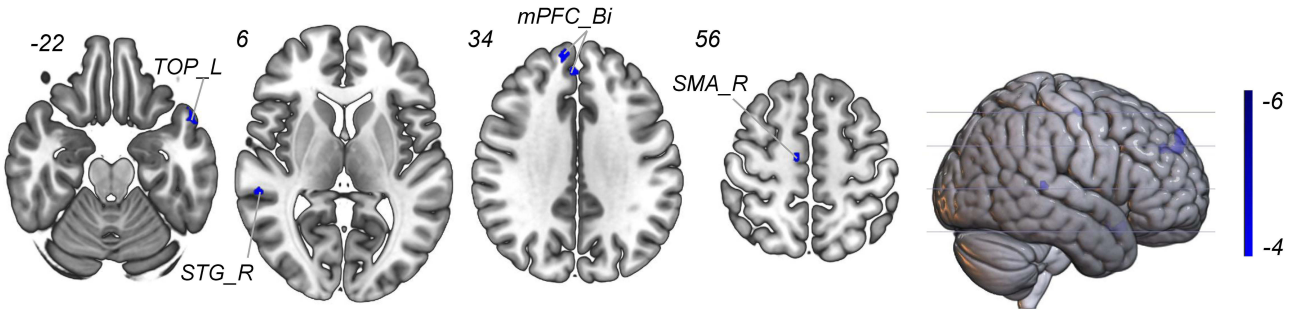

Figure 3 Functional connectivity analysis.
Abbreviations: mPFC_Bi, Bilateral medial prefrontal corte; TOP_L, Left temporal pole; STG_R, Right superior temporal gyrus; SMA_R, Right supplementary motor area.

Notably, these neuroplastic alterations predominantly manifest in the right cerebral hemisphere, suggesting that cancer-related pain may induce asymmetric functional reorganization of brain networks. These findings provide critical objective neurobiological evidence for understanding the complex neural mechanisms underlying cancer pain, simultaneously laying a foundational framework for developing image-based pain assessment methodologies.

Discussion

This study used resting-state functional magnetic resonance imaging technology to compare 20 cancer pain patients and 20 healthy controls, revealing the characteristic changes in brain functional activity in cancer pain patients. The study found that cancer pain patients showed significant neural functional reorganization patterns, which were mainly reflected in two key aspects:

First, low-frequency amplitude (fALFF) analysis showed that cancer pain patients showed significantly reduced spontaneous neural activity in multiple important brain regions, including the right medial prefrontal cortex, bilateral frontal lobes (mainly on the right side), right precuneus, right inferior parietal lobule, and right angular gyrus. These affected brain regions constitute a complex functional network, participating in important functional processes such as advanced cognitive functions, multimodal information integration, and attention networks.[7–9]

Secondly, functional connectivity analysis based on the right nucleus accumbens further revealed that cancer pain patients had significant functional connectivity abnormalities in the neural circuits related to emotion regulation and pain processing. Specifically, the functional connectivity strength with the bilateral medial prefrontal cortex, left temporal pole, right superior temporal gyrus, and right supplementary motor area was significantly reduced. This change in functional connectivity pattern suggests that cancer pain may lead to functional reorganization of emotion regulation and pain perception pathways by affecting the limbic-cortical network.[10,11]

The changes in brain function revealed by low-frequency amplitude and functional connectivity analysis in this study have important neurobiological significance. First, in terms of low-frequency amplitude, cancer pain patients showed

reduced spontaneous neural activity in multiple brain regions, mainly in the right hemisphere. Among them, the significant reduction in mPFC activity (T = −4.36) is particularly noteworthy because this region is a key hub for emotion regulation and cognitive control. This weakening of functional activity may reflect the decreased emotion regulation ability of cancer pain patients, which is consistent with their higher anxiety levels (HAMA score: 13.45 ± 6.64). At the same time, the reduced activity in the right superior and middle frontal gyri (T = −5.21) suggests impaired executive control network function, which may explain the difficulties of cancer pain patients in pain coping and emotion regulation.

In terms of functional connectivity, the analysis results with the right nucleus accumbens as the seed point are particularly striking. As an important component of the limbic system, the nucleus accumbens is closely related to reward processing and emotion regulation. The study found that its functional connectivity with the bilateral medial prefrontal cortex was significantly reduced (T = −4.86), which suggests that the functional integration of the emotion-cognitive network is impaired.[12,13] In particular, the functional connectivity with the left temporal pole (T = −5.62) and the right superior temporal gyrus (T = −5.05) was weakened, reflecting the reorganization of the emotion-memory network during the chronicity of pain. This change in functional connectivity pattern may be the neural basis for the abnormal emotion regulation caused by chronic cancer pain.

It is worth noting that these functional changes showed obvious right hemisphere dominance, and this asymmetric change has special clinical significance. The right hemisphere plays a more important role in emotion processing and pain regulation.[14–16] The right hemisphere possesses a relatively independent dominant role in emotion processing and pain regulation. Ji et al demonstrated[17] that the lateralized predominance of the right amygdala in pain processing is consistent with the right hemisphere's dominant position in negative emotions. Ross et al's Right Hemisphere Hypothesis further supports the right hemisphere's dominant role in emotional processing, indicating that this lateralization represents an intrinsic characteristic of brain functional organization.[18] The right hemispheric functional abnormalities observed in our study suggest that cancer pain produces specific neural functional reorganization patterns by affecting these evolutionarily conserved emotion-pain regulation circuits. However, it should be acknowledged that handedness information was not collected in this study, which represents a limitation of our research. Although existing theories support the independence of right hemispheric emotional processing dominance, future studies should include handedness assessment to further validate the generalizability of these findings.

In addition, the weakening of the functional connectivity between the right supplementary motor area and the nucleus accumbens (T = −4.78) suggests that the motor control network is also affected, which may be related to the decreased mobility caused by chronic pain, further confirming the extensive impact of cancer pain on brain function. There is a potential correlation between these changes in neurological function and the patients' clinical manifestations, especially significant pain symptoms (ESAS pain score: 4.8 ± 1.64), which provides an important basis for the development of objective assessment methods based on imaging.

The abnormalities in mPFC function found in this study provide important insights into the neural mechanisms of cancer pain. Through systematic comparison with previous studies, our findings not only validate existing theories but also provide new perspectives. First, in terms of functional activity, the significant decrease in mPFC activity we observed (T = −4.36) is highly consistent with the latest research findings.[19,20] According to a study published in Nature Scientific Reports in 2024,[21] there are significant changes in the functional activity of the prefrontal cortex in patients with chronic pain, especially the reorganization of functional connectivity patterns in the resting state. This functional change may reflect an important feature of brain plasticity changes during the chronicity of pain.[22] Our study further confirmed that this functional change is more significant in cancer pain patients and shows a unique right hemisphere dominance.

In terms of functional connectivity networks, this study found that the functional connectivity strength between the mPFC and the nucleus accumbens was significantly reduced (T = −4.86), a finding that echoes the latest neuroimaging studies. A recently published preliminary study on cancer pain patients showed that cancer pain can cause significant changes in brain functional activity and connectivity patterns, especially between key nodes in the emotion-cognition network.[23] This change in functional connectivity may be the neural basis for the abnormal emotion regulation caused by chronic cancer pain.

Of particular note, a recent large-scale meta-analysis study provides a new perspective for understanding the role of mPFC in chronic pain. By integrating literature review, meta-analysis, and functional connectivity analysis, the study found that mPFC is not only involved in the regulation of pain perception but also plays a key role in pain-related emotional processing. This provides theoretical support for the association between mPFC dysfunction and patient anxiety levels (HAMA score: 13.45 ± 6.64) that we observed.

From a neuroscience perspective, recent studies reveal that cancer-related neural changes are becoming an emerging research direction.[24] Our study provides new evidence in this field by identifying the characteristic change of mPFC dysfunction. In particular, the right hemisphere dominance changes we found suggest that cancer pain may affect emotional and cognitive functions through specific neural circuits.

In addition, recent studies have also emphasized the potential value of brain stimulation in the treatment of chronic pain, in which the mPFC is considered an important therapeutic target. A study used transcranial direct current stimulation to place the anode at the Fz site (corresponding to the mPFC region), which showed good pain relief effects.[25] This finding is consistent with our observation of mPFC functional abnormalities, suggesting that this region may be a potential target for cancer pain treatment.

Our results also showed that changes in mPFC function were associated with abnormal functional connectivity in multiple brain regions, forming a complex functional network change pattern. This systematic functional reorganization may explain the common multidimensional symptoms of cancer pain patients, including changes in pain perception, emotional regulation disorders, and impaired cognitive function. This finding provides an important basis for the development of neuroimaging-based cancer pain diagnosis and treatment evaluation methods.

This study showed many advantages and characteristics in the design and implementation process. The study adopted a rigorous prospective observational study design, which was approved by the ethics committee. A prospective cross-sectional study method was used to ensure that the two groups of subjects were well matched in terms of demographic characteristics such as gender, age and educational background. On the technical level, the study used the advanced Siemens Prisma 3.0T superconducting magnetic resonance scanner and adopted a carefully optimized multi-sequence scanning scheme, including a three-dimensional fast spoiled gradient echo sequence and a T2-weighted gradient echo-planar imaging sequence, to ensure the high-quality acquisition of image data. The study established a complete image quality monitoring system, with fixed professional technicians completing the scan on a unified device, and taking a variety of measures to reduce interference factors during the scanning process, such as using earplugs to reduce noise interference and using sponge pads to reduce the impact of head movement. In terms of data processing, the study adopted a systematic processing process, including strict head motion correction, standardized processing and multiple comparison correction, to ensure the reliability and scientificity of the results. It is particularly worth mentioning that this study explored the characteristics of brain function changes in patients with cancer pain and found characteristic changes with right hemisphere dominance, which provided new ideas for the construction of an objective assessment system for cancer pain. The study also collected clinical scoring data, and by establishing the relationship between imaging changes and clinical symptoms, it deepened the understanding of the neural mechanism of cancer pain and laid an important foundation for the development of imaging-based cancer pain assessment methods. These findings not only have important theoretical value but also provide an objective basis for the future development of individualized treatment plans and evaluation of treatment effects, showing significant prospects for clinical translation and application.

As an exploratory cross-sectional study, this study has the following limitations: First, as a cross-sectional study, we can only collect data on cancer pain clinical scales and brain functional imaging at the same time point. Therefore, it is difficult for us to determine the time sequence of the two and determine the causal relationship. Second, this study is a single-center study with a relatively small sample size (20 cases per group), which may limit the extrapolation and statistical power of the results and make it difficult to fully reflect the characteristics of different subgroups. At the clinical level, the heterogeneous characteristics of cancer pain patients (such as primary tumor type, pain nature, pain duration, tumor stage, etc.) represent an important limitation regarding their impact on brain functional change patterns. While our inclusive inclusion criteria enhanced external validity, they also increased the complexity of result interpretation. Different tumor types may produce pain through distinct mechanisms, including direct tumor invasion, inflammatory responses, and treatment-related side effects, potentially leading to different neural network adaptive changes.

Additionally, pain duration and severity may also influence the extent and patterns of brain plasticity. The observed right hemispheric low-frequency amplitude reduction may represent common neuropathological features of cancer pain patients, but its manifestation across different cancer subtypes may vary. Due to sample size limitations, we were unable to perform adequate subgroup analyses to explore the specific impacts of these factors, limiting our understanding of brain functional change specificity across different cancer subgroups. At the same time, the analgesic treatment (such as opioids) received by patients may have an impact on brain function, and this treatment effect is difficult to completely separate. Furthermore, different classes of analgesic medications may produce distinct neurobiological effects that could potentially confound our findings. Opioid medications, commonly used in cancer pain management, are known to affect dopaminergic reward pathways and opioid receptors distributed throughout limbic and cortical regions, including the nucleus accumbens and medial prefrontal cortex - key regions identified in our analysis. Similarly, adjuvant analgesics such as anticonvulsants and antidepressants can modulate neurotransmitter systems and neural plasticity. The heterogeneity of analgesic regimens among our participants represents an important confounder that limits our ability to definitively attribute observed neural alterations solely to cancer pain pathophysiology. Future research would benefit from systematic documentation of medication details and potentially stratified analyses based on analgesic classes to better delineate pain-specific versus medication-related neural changes.

In addition, common complications in cancer patients (such as anemia, malnutrition, etc.) may also become confounding factors affecting brain function. In terms of research methods, although functional magnetic resonance imaging technology can reflect the state of brain function, resting state scanning is susceptible to multiple factors, such as emotional state and attention level. Functional connectivity analysis only selected a single seed point (right nucleus accumbens), which may not fully reveal the changes in brain functional networks related to cancer pain. At the same time, the lack of integrated analysis of multimodal imaging data limits the in-depth understanding of the relationship between brain structure and functional changes.

Conclusion

As an exploratory study, this investigation provides preliminary evidence for understanding the neural mechanisms of cancer pain, with particular emphasis on the critical importance of right hemispheric dominance. Our findings demonstrate that cancer pain patients exhibit predominantly right hemispheric neuronal dysfunction, which aligns with the established Right Hemisphere Hypothesis for emotional processing and pain regulation. The observed right-lateralized alterations in low-frequency amplitude and functional connectivity patterns support the evolutionarily conserved role of the right hemisphere in emotion-pain circuits. These neurobiological findings not only validate theoretical models of hemispheric specialization but also establish a foundation for developing objective, neuroimaging-based assessment approaches for cancer pain. However, these findings require confirmation through larger sample, multicenter validation studies.

Future research should prioritize several methodological and conceptual advances to extend our findings. First, longitudinal follow-up studies are essential to characterize the temporal dynamics of cancer pain-related neural plasticity, tracking how brain functional alterations evolve with disease progression, treatment responses, and pain chronification processes. Such studies could identify critical time windows for therapeutic intervention and biomarkers predictive of pain trajectory outcomes. Second, multimodal neuroimaging integration represents a crucial next step, combining our functional connectivity findings with structural MRI to assess gray matter volumetric changes, diffusion tensor imaging to evaluate white matter integrity alterations, and molecular imaging techniques such as PET to examine neurotransmitter system dysfunction. This comprehensive approach would provide mechanistic insights into the neurobiological substrates underlying our observed functional alterations. Third, large-scale multicenter collaborations are imperative to enhance statistical power, improve population generalizability, and enable adequately powered subgroup analyses stratified by cancer type, treatment regimen, and demographic variables. Fourth, intervention studies targeting the identified neural circuits—particularly right hemispheric emotion-pain networks—should be developed, potentially incorporating neuromodulation techniques such as transcranial magnetic stimulation or deep brain stimulation directed at specific anatomical targets. Finally, integration with precision medicine approaches could leverage individual neural signatures to develop personalized pain management strategies, potentially revolutionizing cancer care through neuroimaging-guided therapeutic decision-making.

Data Sharing Statement

Due to the involvement of sensitive medical information of cancer patients in this study, and considering that the ethics committee approval and participants' informed consent did not include data sharing provisions, along with strict requirements of relevant Chinese laws and regulations for medical data management and the need for participant privacy protection, individual participant data from this study will not be publicly shared. Scholars with specific research needs may contact the corresponding author to discuss potential academic collaboration opportunities.

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