Volume 1

Journal of Clinical and Medical Case Reports of Oncology

Laboratory Investigation of Neuroplasticity Markers in Chronic Pain: Correlating Pain Severity with Functional

Abstract

Chronic pain, persisting beyond the expected period of healing, leads to significant neuroplastic changes in the brain's structure and function. This study explores the relationship between chronic pain severity and brain alterations, focusing on gray matter atrophy and altered functional connectivity within pain-related regions. Using structural MRI and functional MRI (fMRI), we evaluated 80 patients with chronic pain and 40 control participants. Significant gray matter atrophy was observed in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and thalamus in chronic pain patients, with atrophy severity correlating with higher pain intensity scores. Functional connectivity analysis revealed increased connectivity between the insula and ACC, associated with heightened emotional pain processing, and decreased connectivity between the PFC and brainstem, indicating impaired descending pain modulation. These findings suggest that chronic pain severity is strongly linked to neuroplastic changes, affecting both sensory and emotional aspects of pain. The results highlight the need for clinical interventions targeting pain-related brain circuits.

Keywords: Chronic Pain; Neuroplasticity; Gray Matter Atrophy; Functional Connectivity; Brain Structure; Pain Modulation; Prefrontal Cortex; Anterior Cingulate Cortex.

***Corresponding Author(s):** Syed Basit Ali Shah

Founder & Clinical Laboratory Technologist Medi Health Labs, Islamabad, Pakistan.

Email: faiza.naseer@ymail.com

Tayyab Iqbal[1]; Abdullah[1]; Marryam Naseer[2]; Syed Basit Ali Shah[3]*

[1]Department of Neurology, Chongqing Medical University (General Medicine), China.

[2]Department of Neurology, Sahiwal Medical College, Sahiwal, Pakistan.

[3]Founder & Clinical Laboratory Technologist Medi Health Labs, Islamabad, Pakistan.

Received: Jul 24, 2025

Accepted: Sep 04, 2025

Published Online: Sep 11, 2025

Journal: Journal of Clinical and Medical Case Reports of Oncology

Online edition: https://www.cancercasereports.org/

Cite this article: Tayyab I, Abdullah1; Marryam Naseer, Syed Basit Ali S. Laboratory Investigation of Neuroplasticity Markers in Chronic Pain: Correlating Pain Severity with Functional. J Clin Med Case Rep Oncology. 2025; 1(1): 1003.

Introduction

Chronic pain is a complex condition that affects millions of people worldwide, often persisting for months or even years after the original injury or illness has healed. Unlike acute pain, which is a direct response to injury and serves a protective role, chronic pain is considered maladaptive, leading to long-lasting discomfort and disability. The brain plays a pivotal role in pain perception, and recent studies have shown that chronic pain can induce profound neuroplastic changes that alter both the structure and function of key pain-processing regions [1-5].

Neuroplasticity refers to the brain's ability to adapt and reorganize itself in response to various stimuli, including chronic pain. However, in the context of chronic pain, these changes are often maladaptive, contributing to the persistence and exacerbation of pain. Previous research has identified significant alterations in gray matter volume, cortical thickness, and functional connectivity in individuals with chronic pain, particularly in regions such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, thalamus, and somatosensory cortex [5-10].

The objective of this study is to investigate the relationship between chronic pain severity and structural and functional changes in the brain, focusing on gray matter atrophy and altered connectivity. We hypothesize that more severe chronic pain will be associated with greater gray matter atrophy and disrupted functional connectivity, particularly in pain-modulating networks.

Methods

Study Population

- **Patients**: 80 individuals diagnosed with chronic pain for more than six months were recruited for this study. The chronic pain conditions included musculoskeletal pain, fibromyalgia, neuropathic pain, and post-surgical pain.
- **Control Group**: 40 healthy individuals matched for age and gender were included as controls.

Inclusion criteria:

- Age: 18–65 years.
- Chronic pain lasting for at least six months.
- No history of neurological or psychiatric disorders unrelated to chronic pain.

Exclusion criteria:

- Neurological disorders unrelated to pain.
- History of brain surgery or significant head trauma.

Pain Severity Assessment

- **Visual Analog Scale (VAS)**: A 10-point scale used to quantify current pain severity.
- **Brief Pain Inventory (BPI)**: This inventory assessed the impact of pain on daily life activities, including mood, sleep, and work.

Cognitive and Emotional Assessments

- **Montreal Cognitive Assessment (MoCA)**: Evaluated cognitive performance, including memory, attention, and executive function.
- **Hospital Anxiety and Depression Scale (HADS)**: Measured anxiety and depression symptoms in the study participants.
- **Imaging Protocols**
- **Structural MRI**: High-resolution MRI was used to measure gray matter volume and cortical thickness. Regions of interest included the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, thalamus, and hippocampus.
- **Functional MRI (fMRI)**: Resting-state functional MRI (rs-fMRI) was employed to assess functional connectivity between key brain regions involved in pain processing and modulation. Seed-based correlation analysis was used to map functional connectivity patterns, with seeds placed in the PFC, ACC, and insula.

Data Analysis

- **Voxel-based morphometry (VBM)**: Used to assess gray matter atrophy in the regions of interest.
- **Cortical thickness analysis**: Performed using the FreeSurfer software to measure cortical thinning in chronic pain patients.
- **Functional connectivity analysis**: Conducted using seed-based correlation techniques to map changes in brain network activity.

Statistical analyses were performed using SPSS and MATLAB software. Correlations between pain severity and brain changes were calculated using Pearson's correlation coefficients (r-values), and significance was established at $p < 0.05$.

Results

Table 1: Brain Structure and Connectivity Changes in Chronic Pain Patients.

Brain Region / Network	Observed Changes	Chronic Pain Patients (Compared to Controls)	Correlation with Pain Severity (r-value)	p-value
	Gray Matter Volume			
Prefrontal Cortex (PFC)	Significant gray matter atrophy	-12.5% gray matter volume reduction	r = -0.62 (VAS score)	p < 0.001
Anterior Cingulate Cortex (ACC)	Gray matter atrophy	-9.8% gray matter volume reduction	r = -0.48 (VAS score)	p = 0.005
Thalamus	Moderate gray matter atrophy	-7.4% gray matter volume reduction	r = -0.38 (VAS score)	p = 0.02
Hippocampus	Gray matter atrophy	-8.1% gray matter volume reduction	r = -0.55 (MoCA score)	p = 0.003
	Cortical Thickness			
Prefrontal Cortex (PFC)	Significant cortical thinning	0.75 mm reduction in thickness	r = -0.62 (VAS score)	p < 0.001
Somatosensory Cortex	Cortical thinning	0.52 mm reduction in thickness	r = -0.48 (BPI score)	p = 0.01
	Functional Connectivity			
Insula-ACC Connectivity	Increased connectivity between insula and ACC	18.5% increased functional connectivity	r = 0.58 (BPI score)	p < 0.01
PFC-Brainstem Connectivity	Decreased connectivity in descending pain modulation pathway	13.2% decrease in functional connectivity	r = -0.45 (VAS score)	p = 0.02
	Cognitive and Emotional Impac ts			
Cognitive Impairments (MoCA Score)	Higher gray matter atrophy in PFC and hippocampus	Lower MoCA score in chronic pain patients (24 vs. 28)	r = -0.55 (PFC atrophy and cognitive decline)	p < 0.001
Emotional Disturbances (HADS Score)	Higher connectivity between insula and ACC	Higher HADS score in chronic pain patients (14 vs. 7)	r = 0.58 (insula-ACC connectivity)	p < 0.01

Gray Matter Changes

- **Prefrontal Cortex (PFC)**: Patients with chronic pain exhibited significant gray matter atrophy in the PFC, with a 12.5% reduction in volume compared to controls ($p < 0.001$). The degree of atrophy was strongly correlated with pain severity ($r = -0.62$).
- **Anterior Cingulate Cortex (ACC)**: Gray matter volume in the ACC was reduced by 9.8% ($p = 0.005$), and this reduction was moderately correlated with pain severity ($r = -0.48$).
- **Thalamus and Hippocampus**: Moderate atrophy was observed in these regions, with reductions of 7.4% and 8.1%, respectively. Hippocampal atrophy correlated significantly with cognitive impairment ($r = -0.55$, $p = 0.003$).
- **Cortical Thinning**
- **Prefrontal Cortex**: Patients showed a reduction in cortical thickness by 0.75 mm ($p <$
- 0.001), correlating with higher pain intensity scores ($r = -0.62$).
- **Somatosensory Cortex**: Cortical thinning was observed in the somatosensory cortex, with a reduction of 0.52 mm ($p = 0.01$), correlating with the BPI score ($r = -0.48$).

Functional Connectivity Changes

- **Increased Insula-ACC Connectivity**: Functional connectivity between the insula and ACC was significantly higher in chronic pain patients, with an 18.5% increase compared to controls ($p < 0.01$). This increase was positively correlated with pain severity ($r = 0.58$).
- **Decreased PFC-Brainstem Connectivity**: A 13.2% reduction in connectivity between the PFC and brainstem was observed, reflecting impaired descending pain modulation ($p = 0.02$).

Cognitive and Emotional Impairments

Chronic pain patients exhibited lower cognitive performance, as measured by the MoCA, with a mean score of 24 (vs. 28 in controls), correlating with PFC and hippocampal atrophy. Emotional disturbances, including anxiety and depression, were more pronounced in patients, with a higher HADS score (mean of 14) correlating with increased insula-ACC connectivity.

Discussion

The findings from this study provide strong evidence of significant neuroplastic changes in both the structure and function of pain-related brain regions in chronic pain patients. Gray matter atrophy in the PFC and ACC, combined with altered functional connectivity between the insula and ACC, suggests that chronic pain is associated with both sensory and emotional dysfunction. The increased insula-ACC connectivity likely reflects enhanced emotional processing of pain, while the decreased PFC-brainstem connectivity may underlie the impaired ability of patients to modulate pain [10-15].

Our results are consistent with previous research demonstrating gray matter loss in the PFC, ACC, and thalamus in chronic pain conditions, such as fibromyalgia and neuropathic pain. However, this study adds to the literature by demonstrating a direct correlation between the severity of pain and the degree of neuroplastic change. Moreover, we observed significant cortical thinning in both the prefrontal and somatosensory cortices, suggesting that structural changes extend beyond gray matter volume loss [15-20].

The functional connectivity findings underscore the importance of brain networks in pain perception. Increased insula-ACC connectivity supports the role of the insula in integrating sensory and emotional pain information, while the reduced PFC-brainstem connectivity highlights a dysfunctional pain modulation pathway, which may contribute to the chronicity of pain [21-25].

Conclusion

This study highlights the significant impact of chronic pain on both brain structure and function. The correlation between pain severity and neuroplastic changes underscores the need for targeted interventions aimed at modulating brain circuits involved in pain perception and processing. Future research should explore therapeutic strategies that can reverse or mitigate these neuroplastic changes, potentially improving the quality of life for patients suffering from chronic pain.

References

1. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Progress in Neurobiology. 2009; 87(2): 81-97. https://doi.org/10.1016/j.pneurobio.2008.09.018
2. Baliki MN, Apkarian AV. Nociception, pain, negative moods, and behavior selection. Neuron. 2015; 87(3): 474-491. https://doi.org/10.1016/j.neuron.2015.06.005
3. Borsook D, Linnman C, Faria V, Strassman AM, Becerra L, & Elman I. Reward deficiency and anti-reward in pain chronification. Neuroscience & Biobehavioral Reviews. 2016; 68: 282-297. https://doi.org/10.1016/j.neubiorev.2016.05.033
4. Buckalew N, Coffman J. Changes in brain structure in chronic pain: the significance of gray matter atrophy. Journal of Neuroimaging. 2013; 23(1): 22-27. https://doi.org/10.1111/j.1552-6569.2011.00641.x
5. Cauda F, Sacco K, Duca S, Cocito D, D'Agata, F, Geminiani GC, & Canavero S. Altered resting state in diabetic neuropathic pain. PLoS ONE. 2009; 4(2): e4542. https://doi.org/10.1371/journal.pone.0004542
6. De Ridder D, Vanneste S, Freeman W. The Bayesian brain: Phantom percepts resolve sensory uncertainty. Neuroscience & Biobehavioral Reviews. 2014; 44: 415. https://doi.org/10.1016/j.neubiorev.2012.04.001
7. Garcia-Larrea L, & Peyron R. Pain matrices and neuropathic pain matrices: A review. Pain. 2013; 154(S1): S29-S43. https://doi.org/10.1016/j.pain.2013.09.001
8. Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, & Apkarian AV. The brain in chronic CRPS pain: Abnormal gray-white matter interactions in emotional and autonomic regions. Neuron. 2008; 60(4): 570-581. https://doi.org/10.1016/j.neuron.2008.08.022
9. Hashm JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, & Apkarian AV. Shape shifting pain: Chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain. 2013; 136(9): 2751-2768. https://doi.org/10.1093/brain/awt211
10. Ichesco E, Quintero A, Clauw DJ, & Peltier SJ. Altered functional connectivity in fibromyalgia: A resting-state fMRI study. Journal of Pain. 2016; 17(2): 286-295. https://doi.org/10.1016/j.jpain.2015.11.004

11. Kucyi A, & Davis KD. The dynamic pain connectome. Trends in Neurosciences. 2015; 38(2): 86-95. https://doi.org/10.1016/j.tins.2014.11.006

12. May A. Chronic pain may change the structure of the brain. Pain. 2008; 137(1): 7. https://doi.org/10.1016/j.pain.2008.02.034

13. Melzack R, & Kat J. Pain. Wiley Interdisciplinary Reviews: Cognitive Science. 2013; 4(1): 1-15. https://doi.org/10.1002/wcs.1201

14. Moulton EA, Pendse G, Becerra LR, Borsook D, & Becerra LR. BOLD responses in somatosensory cortices better reflect heat perception than pain perception. Journal of Neuroscience. 2012; 32(16): 6024-6031. https://doi.org/10.1523/JNEUROSCI.5378-11.2012

15. Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, & Ploner M. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. NeuroImage. 2017; 148: 141-147. https://doi.org/10.1016/j.neuroimage.2017.01.011

16. Pfannmöller J, & Lotze M. Review on altered somatosensory perception in chronic pain. Frontiers in Human Neuroscience. 2019; 13: 13. https://doi.org/10.3389/fnhum.2019.00013

17. Schmidt-Wilcke T. Variations in brain morphology associated with fibromyalgia. Current Rheumatology Reports. 2008; 10(6): 401-407. https://doi.org/10.1007/s11926-008-0067-7

18. Schweinhardt P, & Bushnell MC. Pain imaging in health and disease--how far have we come? Journal of Clinical Investigation. 2010; 120(11): 3788-3797. https://doi.org/10.1172/JCI43498

19. Seminowicz DA, & Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. Journal of Pain. 2017; 18(9): 1027-1035. https://doi.org/10.1016/j.jpain.2017.03.008

20. Tracey I, & Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007; 55(3): 377-391. https://doi.org/10.1016/j.neuron.2007.07.012

21. Vachon-Presseau E, Roy M, Martel MO, Albouy G, Chen J, Lutz A, & Rainville P. The multivariate complexity of chronic pain patients' emotional experience. PLoS ONE. 2013; 8(5): e70785. https://doi.org/10.1371/journal.pone.0070785

22. Wager TD, Atlas LY, Lindquist MA, Roy M, Wo CW, & Kros E. An fMRI-based neurologic signature of physical pain. New England Journal of Medicine. 2013; 368(15): 1388-1397. https://doi.org/10.1056/NEJMoa1204471

23. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011; 152(S3): S2-S15. https://doi.org/10.1016/j.pain.2010.09.030

24. Youssef AM, Macefield VG, & Henderson LA. Pain processing and the relationship between pain intensity and neural activity: A combined EEG and fMRI study. Journal of Neuroscience. 2016; 36(50): 14118-14128. https://doi.org/10.1523/JNEUROSCI.1830-16.2016

25. Zhang S, Chang C, & Guo X. Neuroplastic changes in patients with chronic pain: A meta-analysis of structural brain alterations. Neuroscience Bulletin. 2019; 35(5): 908920. https://doi.org/10.1007/s12264-019-00380-2