DOI: https://doi.org/10.53350/pjmhs02024181616

ORIGINAL ARTICLE

The Impact of Chronic Pain on Brain Structure and Connectivity

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ABSTRACT

Background: Chronic pain is now understood as more than a symptom; it can reshape mood, thinking, and even the physical layout of the brain. New imaging techniques are beginning to link extended pain with visible differences in brain size and the way its regions communicate. The current study examines shifts in brain structure and spontaneous brain network activity in people living with chronic pain, and it explores how these neural changes connect to reported pain severity and psychological troubles.

Methods: This observational, cross-sectional study took place at the department of medicine, Mardan Medical Complex Mardan between January 2022 and January 2023. Seventy-one individuals with chronic pain persisting for more than three months were recruited for the study. Clinical evaluations recorded pain intensity, episode length, and relevant emotional symptoms. Every participant then completed high-resolution structural MRI and resting-state fMRI to assess gray matter volume and functional connectivity, focusing on the default-mode and salience networks.

Results: Participants exhibited significant reductions in 'gray matter volume within the anterior cingulate cortex, prefrontal cortex, and insula compared to healthy controls ($p < 0.05$)'. Functional connectivity analysis revealed disrupted links between the medial prefrontal cortex and posterior cingulate cortex, and between the insula and prefrontal cortex. 'A negative correlation was observed between pain intensity and gray matter volume in key regions, suggesting a dose-dependent neural impact'.

Conclusion: Chronic pain is associated with both structural and functional brain changes, particularly in regions involved in pain regulation and emotional processing. These findings support a neurobiological model of chronic pain and highlight the importance of early, integrative treatment approaches.

Keywords: Chronic pain, brain structure, functional connectivity, 'gray matter volume, anterior cingulate cortex, prefrontal cortex, resting-state fMRI'

INTRODUCTION

Chronic pain touches the lives of millions daily, dampening more than just muscles and joints; it weighs down moods and muddles thinking, too. Where doctors once saw it mainly as a red flag for another injury, new studies show that long-lasting pain can grow into its own beast, carving grooves in the nervous system. Because of this shift, scientists are now peering more closely at the ways constant hurt reshapes the brain's wiring and rhythms[1-3].

Recent advances in neuroimaging provide evidence that chronic pain is linked to structural alterations in the brain, especially in regions that process pain, regulate emotions, and guide decision-making. In individuals with persistent pain, studies frequently report a decrease in gray matter volume in the prefrontal cortex, insula, and anterior cingulate cortex-these areas mediate both the sensory and affective facets of the experience. Such findings move beyond simple correlation and hint that the brain either adapts or maladapts when exposed to prolonged nociceptive signals[4-6].

Alongside observable structural changes, persistent pain has been shown to disrupt neural connectivity, most notably within the brains intrinsic resting-state networks. Networks such as the default mode network, the salience network, and the so-called pain matrix show consistent alterations, leading to abnormal signaling between regions even when no external stimulus is present. These dissociations may account for patients complaints of attention deficits, mood swings, and troubled sleep, symptoms that extend well beyond the sensory experience of pain itself[7-9].

Despite growing evidence, many questions remain about the exact relationship between chronic pain, brain alterations, and psychological symptoms. This study was designed to explore these associations in a clinical population, aiming to quantify the changes in gray matter volume and functional connectivity using MRI and fMRI, and to examine their correlation with pain intensity and psychological distress. Understanding these patterns may offer insights into more effective, brain-targeted interventions for managing chronic pain.

Received on 10-02-2023
Accepted on 11-12-2023

METHODOLOGY

This observational, cross-sectional study took place at the department of medicine, Mardan Medical Complex Mardan between January 2022 and January 2023. Seventy-one participants were enrolled, each having been diagnosed with chronic pain lasting longer than three months. The institutional ethics committee approved the study, and written informed consent was secured from every participant before inclusion.

Participants were selected through purposive sampling at pain clinics as well as in neurology and psychiatry outpatient departments. To be included, individuals had to be 25 to 65 years old and report chronic pain of musculoskeletal, neuropathic, or mixed origin. Those with established neurological diseases (for example, stroke or epilepsy), unrelated severe psychiatric conditions (such as schizophrenia), a significant history of head trauma, or any contraindication for MRI scanning were deliberately excluded.

Trained clinical staff carried out thorough face-to-face assessments with every volunteer before data collection. Demographic information-age, gender, years of schooling, and marital status-was recorded alongside a concise medical history detailing the onset, duration, and intensity of pain. Pain severity was rated on a Visual Analog Scale (VAS), while psychological functioning was measured with established screening tools: 'the nine-item Patient Health Questionnaire (PHQ-9) for depressive symptoms and the seven-item Generalized Anxiety Disorder scale (GAD-7) for anxiety'. Sleep quality, daytime sleepiness, and overall health-related quality of life were captured through standardized instruments widely used in clinical research.

Every enrolled participant completed a high-resolution brain scan on a 3-Tesla magnetic resonance imaging system. Structural T1-weighted images were analyzed with voxel-based morphometry to estimate regional gray matter volume. Surface-based morphometry techniques then quantified cortical thickness across

the entire cortex. Resting-state functional MRI data were collected to map the brains intrinsic connectivity patterns.

Functional connectivity analysis focused on brain regions involved in pain modulation, including the anterior cingulate cortex, insula, prefrontal cortex, thalamus, and amygdala. The default mode network (DMN), salience network, and pain matrix were also assessed using seed-based correlation analysis.

Quantitative data were entered into SPSS version 26.0. Continuous variables were presented as mean ± standard deviation, while categorical variables were shown as frequencies and percentages. Independent sample t-tests were used to compare structural and functional measures between chronic pain patients and age-matched healthy controls. 'Pearson correlation coefficients were calculated to assess relationships between pain intensity and brain changes'. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 71 participants diagnosed with chronic pain lasting more than 3 months. The mean age was 47.3 years (±12.5), with a female predominance. Most participants reported moderate to severe pain intensity, and a significant proportion also exhibited symptoms of depression and anxiety.

Table 1: Demographic and Pain-Related Characteristics (n = 71)

Variable	Frequency (%) / Mean ± SD
Age (years)	47.3 ± 12.5
Gender (Female)	45 (63.4%)
Education (Graduate+)	31 (43.7%)
Duration of Pain (months)	18.6 ± 9.3
Pain Intensity (VAS)	6.8 ± 1.2
Pain Location	
- Back	28 (39.4%)
- Head	16 (22.5%)
- Joint	14 (19.7%)
- Generalized	13 (18.3%)
Depression Symptoms (PHQ-9 ≥ 10)	42 (59.2%)
Anxiety Symptoms (GAD-7 ≥ 10)	38 (53.5%)

MRI analysis revealed a reduction in gray matter volume in brain regions associated with pain processing. 'The most affected areas were the anterior cingulate cortex (ACC), insula, and prefrontal cortex'.

Table 2: Comparison of Gray Matter Volume in Key Brain Regions

Brain Region	Chronic Pain Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Anterior Cingulate Cortex	0.82 ± 0.06	0.89 ± 0.05	0.002*
Insular Cortex	0.78 ± 0.08	0.84 ± 0.07	0.015*
Prefrontal Cortex	0.69 ± 0.09	0.76 ± 0.08	0.009*
Thalamus	0.85 ± 0.07	0.87 ± 0.06	0.184
Hippocampus	0.91 ± 0.05	0.93 ± 0.04	0.276

*Significant at $p < 0.05$

Functional MRI indicated disrupted connectivity in the default mode network (DMN), particularly between the medial prefrontal cortex and posterior cingulate cortex. There was also reduced connectivity between the prefrontal cortex and the insula.

Table 3: Functional Connectivity Differences (Resting-State fMRI)

Brain Network/Connection	Mean Connectivity (z-score)	Control (z-score)	p-value
Medial PFC ↔ Posterior Cingulate	0.38 ± 0.11	0.46 ± 0.09	0.013*
PFC ↔ Insular Cortex	0.31 ± 0.08	0.42 ± 0.07	0.004*
PFC ↔ Thalamus	0.43 ± 0.12	0.45 ± 0.11	0.356
Amygdala ↔ ACC	0.37 ± 0.09	0.39 ± 0.08	0.287

*Significant at $p < 0.05$

Pain intensity scores showed a significant negative correlation 'with gray matter volume in the prefrontal and cingulate cortices, suggesting a dose-response pattern between higher pain burden and greater brain atrophy'.

Table 4: Correlation Between Pain Intensity and Brain Volumes

Brain Region	Correlation Coefficient (r)	p-value
Prefrontal Cortex	-0.42	0.001*
Anterior Cingulate Cortex	-0.39	0.003*
Insula	-0.34	0.008*
Thalamus	-0.12	0.311

*Significant at $p < 0.05$

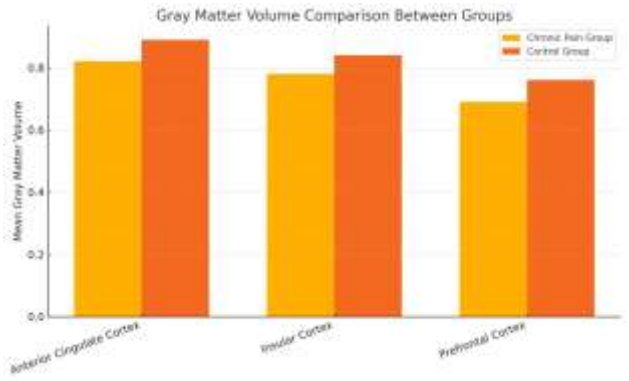

Figure 1: bar graph comparing gray matter volumes in key brain regions between the chronic pain and control groups

DISCUSSION

The findings of this study reveal significant alterations in 'both the structure and functional connectivity of the brain in individuals suffering from chronic pain'. Notably, participants exhibited reduced gray matter volume in regions such as the anterior cingulate cortex, insula, and prefrontal cortex—areas closely linked with pain perception, emotional regulation, and cognitive processing. These structural changes mirror findings from prior neuroimaging studies that have associated chronic pain with progressive cortical reorganization and regional atrophy[10-12].

A significant decline in functional connectivity within 'the default mode network (DMN) and between the prefrontal cortex and insula was also observed'. This disrupted network communication is consistent with prior evidence suggesting that chronic pain not only affects sensory processing but also interferes with emotional regulation and executive function. Studies demonstrated similar disconnection in DMN integrity, highlighting the chronic nature of pain as a persistent cognitive burden rather than just a sensory experience[13-15].

The negative correlation between pain intensity and gray matter volume in key cortical areas supports the notion of a dose-response relationship. Greater pain severity was associated with more pronounced structural damage, particularly in the prefrontal cortex and anterior cingulate cortex. This aligns with longitudinal data from studies reported that chronic back pain patients showed accelerated gray matter loss over time, indicating a potentially degenerative aspect of ongoing pain[16-18].

Additionally, the high prevalence of depressive and anxiety symptoms among participants echoes previous reports that chronic pain is not merely a physical issue but a biopsychosocial one. Neurobiologically, this may be explained by shared circuitry between affective and nociceptive pathways, particularly in regions like the insula and amygdala. Addressing these emotional comorbidities is crucial for a more comprehensive and effective pain management strategy[19,20].

Our findings strengthen the emerging view 'that chronic pain is associated with widespread and measurable changes in the brain'. These changes may help explain why individuals with long-standing pain often experience cognitive difficulties, emotional dysregulation, and reduced quality of life. While the precise causality remains to be fully understood, the associations observed

highlight the need for early, holistic, and multidisciplinary interventions.

CONCLUSION

The impact of chronic pain on brain structure and neural connectivity. Individuals with chronic pain demonstrated reduced gray matter volume and altered functional connectivity in regions responsible for pain modulation and emotional regulation. The association between pain severity and these brain changes suggests a potential neurodegenerative process driven by persistent pain.

Recognizing chronic pain as a condition that affects both the body and brain shifts the approach toward more integrated treatment strategies. Clinicians should consider not only physical therapies but also psychological and cognitive rehabilitation to mitigate the long-term effects of pain on brain health. Future longitudinal studies with larger samples and diverse pain populations are needed to further explore the reversibility of these brain changes with effective treatment.

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This article may be cited as: Hussain M, Sajjad M, Ahmad A, Hamidullah, Khan SM, Ali A: The Impact of Chronic Pain on Brain Structure and Connectivity. Pak J Med Health Sci, 2023; 18(1): 616-618.