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Association Between Neural Plasticity and Pain-Related Fear in Chronic Ankle Instability: A Structural Neuroimaging Study

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Context: Pain-related movement fear is a contributing factor to residual pain and functional deficits in chronic ankle instability (CAI), but its underlying neural mechanisms remain unclear.

Objective: We aimed to (1) delineate whether participants with CAI exhibit discernible differences in specific emotion- and pain-related brain regions compared with a healthy control (HC) cohort and (2) explore potential neural mechanisms underlying pain and fear in participants with CAI, with an emphasis on investigating possible associations with pain-related neural plasticity.

Design: Cross-sectional study.

Setting: University research laboratory.

Patients or Other Participants: Twenty-eight participants with CAI (17 men and 11 women; age = 31.28 ± 6.31 years) and 28 HCs (16 men and 12 women; age = 30.18 ± 7.59 years).

Main Outcome Measure(s): We analyzed T1 structural imaging data from participants and assessed their fear of movement and pain intensity using the Tampa Scale of Kinesiophobia (TSK) and the visual analog scale (VAS) for pain, respectively. We compared the mean gray matter (GM) density of pain-related area between the 2 groups and their correlations with the TSK and VAS scores.

Results: In comparison with the HC group, participants with CAI showed a significant decrease in the mean GM density in the prefrontal cortex (PFC) (Cohen d = −0.808) and periaqueductal gray (PAG) (Cohen d = −0.934). In participants with CAI, the mean GM density of the PFC was negatively correlated with TSK scores ($r = -0.531$). During intense exercise, the mean GM density of the PAG was negatively correlated with VAS scores ($r = -0.484$). Additionally, TSK scores were positively correlated with VAS scores ($r = 0.455$).

Conclusions: Our exploratory findings suggest that, in participants with CAI, the atrophy of the PFC and PAG may be associated with pain-related fear. In future clinical diagnosis and treatment for CAI, practitioners should consider the impact of psychological barriers on functional recovery.

Key Words: ankle injuries, magnetic resonance imaging (MRI), neuronal plasticity, kinesiophobia, prefrontal cortex, periaqueductal gray

Key Points

- Participants with chronic ankle instability had atrophy of emotion- and pain-related brain regions (the prefrontal cortex and periaqueductal gray) when compared with healthy controls.
- Ankle pain during sport activities was positively correlated with kinesiophobia of ankle injury, and both were associated with neural atrophy.
- Considering the existence of neuroplasticity caused by chronic pain, psychological management guidance might be meaningful for participants with chronic ankle instability.

Lateral ankle sprain is one of the most frequent sport injuries among physically active individuals. It also has the highest recurrence rate of all lower extremity musculoskeletal injuries.[1] Lateral ankle sprains are often erroneously considered to be an innocuous musculoskeletal disorder that rapidly resolves with minimal treatment and has no long-lasting consequences.[2,3] However, after the initial acute injury of the ankle ligament, 40% to 70% of injured individuals will develop chronic ankle instability (CAI) and experience recurrent ankle sprains, residual pain,

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and feelings of instability.[4,5] Chronic ankle instability may also be accompanied by ongoing symptoms, such as weakness or reduced ankle range of motion, diminished self-reported function, and even early-onset posttraumatic osteoarthritis.[6] Given the current lack of an effective CAI treatment, investigating its clinical pathogenesis is of great importance for its diagnosis and treatment.

Participants with CAI have a high incidence of residual pain, which is associated with ankle-joint functional deficiency.[7] Previous authors reported that 60% of participants with CAI suffered from pain during different levels of activity.[7] It is well documented that, in the musculoskeletal system, chronic pain, including chronic back pain and pain from knee arthritis and ankle sprain, is intimately connected with both emotional and cognitive functions.[8] As a complex emotion, sport-related fear has been found in individuals who develop CAI, and has been related to patients' functional deficits.[2] This fear of exercise, reinjury, and pain is termed *kinesiophobia*. Previous authors showed that, in comparison with healthy controls (HCs), individuals suffering from CAI demonstrated increased kinesiophobia.[9] One of the most commonly used patient-reported outcomes for assessing injury-related fear is the Tampa Scale for Kinesiophobia (TSK).[8] Originally intended for assessing pain phobia in patients with low back pain, this scale is currently also used to assess kinesiophobia in patients with a variety of musculoskeletal injuries, including CAI.[8,10] The TSK scale considers elements of injury-related fear, which include movements regarded by the individual as likely to result in pain and (re)injury.[9,10]

Importantly, the kinesiophobia mechanism in participants with CAI remains unclear. Many researchers have recognized that the fear of pain in musculoskeletal diseases may be due to neuroplastic changes.[11] These can result from long-term, persistent pain; psychological disorders; and sensory-motor deficits. This may also be related to persistent symptoms and failed recovery after sport injuries.[11] When pain becomes chronic and alters the brain circuitry involved in its control, pain management becomes increasingly difficult.[12] A number of studies have shown that, when an individual is anticipating the onset of pain, the brain regions involved in pain sensation and modulation become activated. These brain regions are, most importantly, the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the amygdala (AMYG), and the periaqueductal gray (PAG).[12–14] To evaluate these neural alternations, gray matter (GM) volume evaluation, which is facilitated by neuroimaging, has been widely used. Numerous neuroimaging studies involving different types of musculoskeletal pain have revealed extensive GM changes in chronic pain patients in comparison with pain-free HCs.[15–17] These alterations may be related to the emotional, cognitive, and behavioral characteristics of chronic pain patients.[12,14] Nevertheless, there is still little research on pain and kinesiophobia in participants with CAI.

In this study, we aimed to use neuroimaging methodologies to explore the potential neural mechanisms that might underlie the complex interplay between pain and fear in participants with CAI. The main objective was to uncover any GM volume differences in emotion- and pain-related brain regions between participants with CAI and HCs without previous ankle injury. The selection of the regions of interest (ROIs), which were the PFC, the ACC, the AMYG, and the PAG, was based on the aforementioned reviews on pain and kinesiophobia (Figure 1). The secondary objective was to determine the correlations between structural changes in relevant brain regions and the TSK and the visual analog scale (VAS) scores for pain. We hypothesized that, between participants with CAI and HCs, there are differences in emotion- and pain-related brain regions. Moreover, these differences could be associated with the TSK and VAS scores. The TSK and VAS scores could also be mutually correlated.

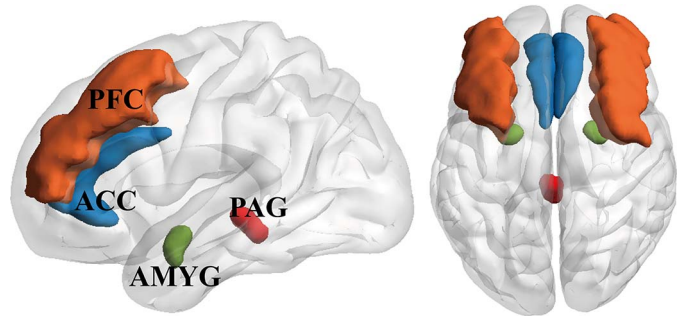

Figure 1. Schematic diagram of the pain- and kinesiophobia-related brain areas. Abbreviations: ACC, anterior cingulate cortex; AMYG, amygdala; PAG, periaqueductal gray; PFC, prefrontal cortex.

METHODS

Study Design

This study used a cross-sectional design. This research has been approved by the Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China (ID 2016-314) for human investigation. All participants provided written informed consent. The study design and data analysis complied with the Strengthening the Reporting of Observational Studies in Epidemiology consensus guidelines.[18]

The prior sample size calculation was performed by comparison with HCs, revealing that participants with CAI showed significantly lower fractional anisotropy values.[4,5] G*power version 3.1 (http://stats.idre.ucla.edu/other/gpower/) was used for the sample size calculation, and the formally used sample size of 28 participants per group was calculated with an effect size of −0.896, power of 0.90, and α of .05, using a 2-tailed test.

Fifty-six participants were recruited from August 2022 to February 2023, comprising 28 participants with CAI and 28 HCs without a history of ankle injury. All participants provided written informed consent before inclusion. Participants were screened, and data were collected by a single investigator, who also assessed demographic and ankle injury information according to predefined criteria. Magnetic resonance imaging measurements and data processing were performed by another researcher, who was blinded to demographic and group assignment information, ensuring unbiased data analysis.[20]

Chronic ankle instability–specific criteria complied with the guidelines of the International Ankle Consortium.[19] The inclusion criteria for the CAI group were the following[21]: (1) Participants had experienced at least 1 significant ankle sprain resulting in pain, swelling, and at least 1 day's interruption of desired physical activity. (2) Participants experienced at least 2 episodes of their ankle "giving way" in the past 6 months or at least 2 occurrences of sprains to the same ankle.[22] (3) Participants' Cumberland Ankle Instability Tool (CAIT) score was lower than 24. (4) Participants predominantly used their

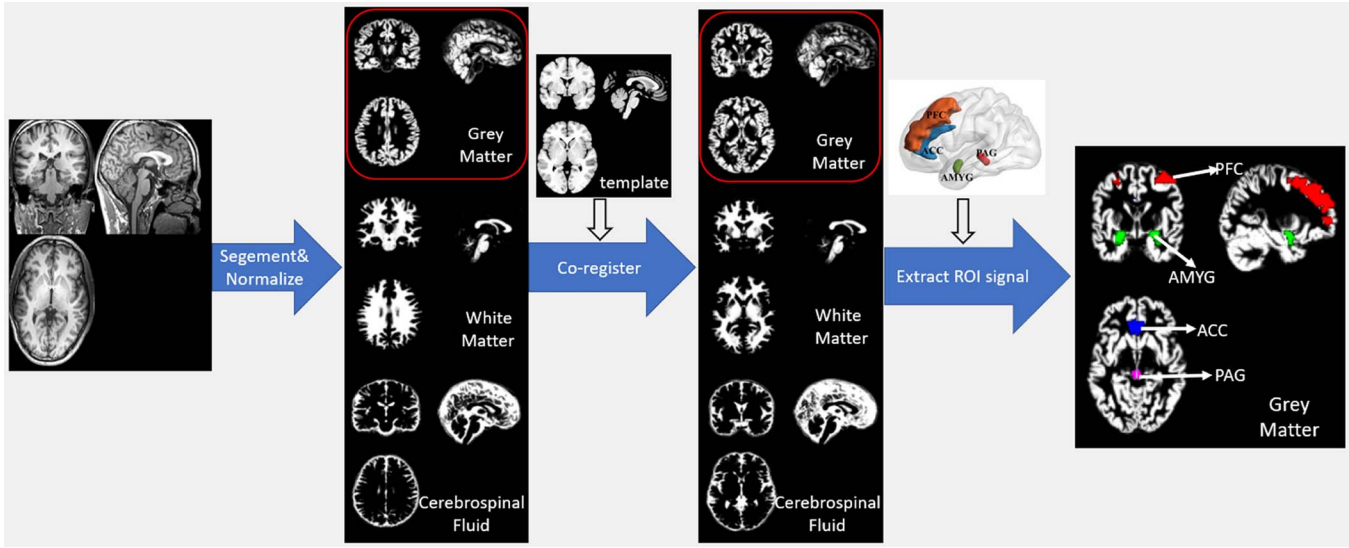

Figure 2. Preprocessing steps for brain imaging data. The figure illustrates key stages: segmentation of brain tissues into gray matter (GM), white matter, and cerebrospinal fluid; normalization to a human brain template space; and coregistration to a standardized brain atlas. The mean GM volume of all voxels within the ACC, AMYG, PFC, and PAG was extracted. Abbreviations: ACC, anterior cingulate cortex; AMYG, amygdala; PAG, periaqueductal gray; PFC, prefrontal cortex.

right foot for kicking. For the HC group, the inclusion criterion was the absence of any ankle sprain history. Exclusion criteria for both the CAI and HC groups were (1) any history of lower extremity surgeries, musculoskeletal ailments, or other injuries (except the lateral ankle sprains in the CAI group); (2) any history of relevant medical conditions, such as autoimmune, cardiovascular, respiratory, neurologic, or other diseases; (3) current use of prescribed drugs; (4) any factor that could prohibit the use of magnetic resonance imaging (MRI), such as metal implants, pacemaker, confined-space phobia, and others; and (5) further protracted, cerebral, or psychiatric illnesses.

Data Collection and MRI Procedures

Before MRI scanning, we collected comprehensive data from participants with CAI, including body mass index (BMI), age, height, weight, and duration of disease. Diagnostics and scores were gathered using paper-based methods in a clinical setting. These included the Tegner Activity Rating Scale for sports level, the CAIT, and the TSK. Additionally, we assessed pain using the VAS for pain at rest (VAS-rest) and the VAS for pain during sports (VAS-sport).[21]

The primary dataset was acquired using a 3.0 Tesla Siemens Prisma scanner. To prevent head movement and decrease noise discomfort during scanning, participants were provided with foam padding and headphones, respectively. Participants were asked to remain motionless, keep their eyes closed without falling asleep, and refrain from having specific thoughts. The study used the T1-weighted 3D anatomic images sequence with the following acquisition parameters: acquisition matrix size = 208 × 300 mm, 0.8 mm^3 isotropic voxels, slice gap = 0 mm, repetition time = 2500 ms, echo time = 2.22 ms, flip angle = 8°.

Voxel-Based Morphometry Analysis

Gray matter volume analysis was performed using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.unijena.de/cat/) implemented in Statistical Parametric Mapping (version 12; SPM12, Department of Cognitive Neurology, University College London) on MATLAB (Version R2022a; MathWorks Inc).

First, the unified segmentation algorithm was used to segment the brain tissues into GM, white matter, and cerebrospinal fluid, which were then normalized into a human brain template space with a voxel size of 1.5 × 1.5 × 1.5 mm^3.[23] Normalization is crucial as it ensures that the brain structures from different individuals are directly comparable, providing a common framework for further analysis.

Second, the segmented images were coregistered to the standardized human brain atlas. Coregistration is essential for ensuring that the anatomical locations across different scans are aligned, allowing for accurate comparisons and overlays of brain images across different participants. This step facilitates the integration and detailed examination of data from multiple sources.[23] The analysis also included an estimation of the total intracranial volume (TIV) and image quality. Participants whose MRI quality was below the CAT12-estimated C++ level were excluded from the study.

Subsequently, to determine if, between participants with CAI and HCs, variations in the regional GM volume were associated with the central nervous system, ROI-based analysis was carried out. The mean GM volume of all included voxels in the ROI of the ACC, AMYG, PFC, and PAG was extracted.[12–14] Figure 2 visualizes the aforementioned preprocessing steps.

A decrease in GM volume can be indicative of neurologic decline, which may manifest as cognitive and functional impairments. These changes are often considered to be potential biomarkers of underlying neuropathologic processes affecting brain structure and function, which could have significant implications for motor control, sensory perception, and pain processing.[24]

Finally, for further analysis, the regional GM volume of clusters was extracted and standardized using TIV. For standardization, the individual volume within the cluster was divided by the individual TIV and multiplied by the mean TIV of all participants.[25]

Table 1. Participants' Demographics and Patient-Reported Outcome Data

	CAI (n = 28)	HC (n = 28)	*P* Value
Sex, No. female/No. male	11/17	12/16	.791
Age, mean ± SD, y	31.28 ± 6.31	30.18 ± 7.59	.559
BMI, mean ± SD	24.11 ± 3.14	23.52 ± 3.27	.494
Height, mean ± SD, cm	172.14 ± 9.90	169.29 ± 8.72	.257
Weight, mean ± SD, kg	71.71 ± 13.27	67.94 ± 13.88	.303
Tegner, median (IQR)	4.00 (4.00–5.00)	4.00 (3.00–5.75)	.554
TSK, median (IQR)	42.00 (40.00–44.00)	38.00 (32.00–42.75)	.004
CAIT, median (IQR)	19.50 (14.25–22.00)	30.00 (27.25–30.00)	<.001
VAS-rest, median (IQR)	0.00 (0.00–0.38)	0.00 (0.00–0.00)	.014
VAS-sport, median (IQR)	3.00 (1.25–5.00)	0.00 (0.00–0.00)	.001

Abbreviations: BMI, body mass index; CAI, chronic ankle instability; CAIT, Cumberland Ankle Instability Tool; HC, healthy control; TSK, Tampa Scale of Kinesiophobia; VAS, visual analog scale.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software (Version 9.0; GraphPad Software). Descriptive statistics are presented as mean ± SD for normally distributed variables (age, height, weight, BMI) and median with interquartile range for nonnormally distributed variables (Tegner, CAIT, VAS, and TSK scores). Normality was assessed using the Kolmogorov-Smirnov Z test. Appropriate parametric (2-sample *t* test) and nonparametric tests were applied based on these assessments.

Cohen d effect sizes along with 95% CIs were calculated to quantify the magnitude of between-groups differences in GM density, enhancing understanding of their clinical significance.[26] *P* values from the comparisons of GM density within the ROI data of the ACC, AMYG, PFC, and PAG were adjusted for multiple comparisons using the Bonferroni correction.[27] Only ROIs that remained significant after this adjustment were targeted for further study. Age and gender were included as covariates in a general linear model to improve the robustness and accuracy of group comparisons. Spearman correlation coefficients were calculated to explore the relationships between the mean GM density in the 4 brain areas associated with pain and the emotion-related indicator TSK in participants with CAI, both in unadjusted form and adjusted for age and sex.

RESULTS

Demographic and Clinical Features

The study included 28 participants with CAI and 28 HCs, all of whom met the inclusion criteria. No statistically significant differences were observed between the CAI and HC groups in terms of sex, age, height, weight, BMI, or Tegner score ($P > .05$; Table 1). In contrast, the CAI group had statistically significantly higher TSK, VAS-rest, and VAS-sport scores ($P < .05$), whereas their CAIT scores were significantly lower ($P < .001$).

Comparison of Mean GM Volume Between Participants With CAI and HCs

Table 2 indicates that, among the 4 selected brain regions, only the PFC (Cohen d = −0.808; 95% CI = −1.365, −0.251; $P = .005$) and the PAG (Cohen d = −0.934; 95% CI = −1.497, −0.369; $P = .004$) showed statistically significant differences after the Bonferroni correction. This analysis indicated a significantly lower mean GM density in participants with CAI in comparison with HCs (Figure 3). Furthermore, a general linear model incorporating age and gender as covariates revealed significant results. Specifically, the PFC showed a significant difference (β = −.020; 95% CI = −.032, −.008; $P = .001$), indicating lower GM density in participants with CAI compared with HCs. Similarly, the PAG also exhibited a significant difference (β = −.028; 95% CI = −.044 to −.012; $P = .001$), indicating lower GM density in participants with CAI compared with HCs. Detailed effect sizes and 95% CIs are provided in Supplemental Table 1 to precisely quantify the magnitude of differences observed between the groups.

Relationships Between Mean GM Densities in Specific Brain Regions and Clinical Features

In our analysis of the relationships between mean GM density in brain regions associated with pain processing and the clinical scores for pain and fear of movement, significant findings are visually represented and discussed in Supplemental Table 2 and Supplemental Figure 1. Notably,

Table 2. Intergroup Comparison of Mean GM Density in Pain- and Kinesiophobia-Related Brain Areas

Region of Interest	GM Density, Arbitrary Units		Cohen d Effect Size (95% CI)	*P* Value (Uncorrected)	*P* Value (Bonferroni)
	CAI (n = 28)	HC (n = 28)			
PFC	0.400 ± 0.021	0.420 ± 0.028	−0.808 (−1.365 to −0.251)	.001	.005[a]
ACC	0.470 ± 0.040	0.486 ± 0.047	−0.367 (−0.907 to 0.174)	.187	.948
AMYG	0.619 ± 0.045	0.628 ± 0.036	−0.221 (−0.758 to 0.317)	.414	1.000
PAG	0.127 ± 0.033	0.156 ± 0.029	−0.934 (−1.497 to −0.369)	.001	.004[a]

Abbreviations: ACC, anterior cingulate cortex; AMYG, amygdala; CAI, chronic ankle instability; GM, gray matter; HC, healthy control; PAG, periaqueductal gray; PFC, prefrontal cortex.
[a] $P < .01$.

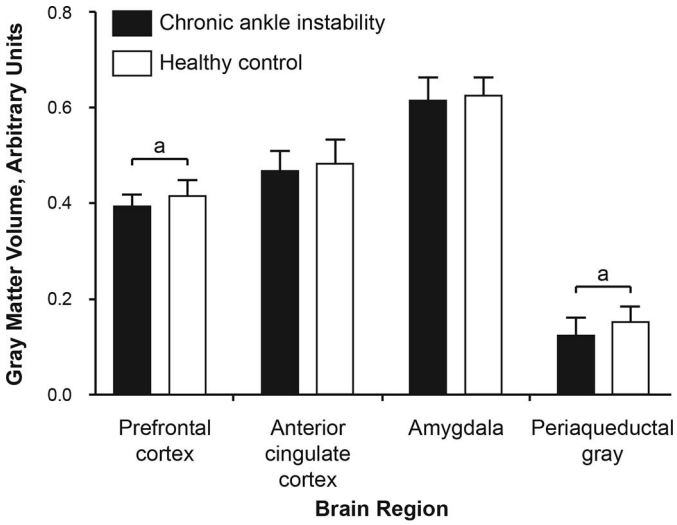

Figure 3. Comparison of the mean gray matter volume in the pain- and kinesiophobia-related brain area between participants with chronic ankle instability and healthy controls. [a] *P* < .01.

we observed that the mean GM density in the PFC of participants with CAI was negatively correlated with TSK scores ($r = -0.531$, $P = .005$; see Figure 4A). However, the correlation between mean GM density in the PAG of participants with CAI and VAS-rest scores showed a trend toward a negative association but did not reach statistical significance ($r = -0.262$, $P = .196$; see Figure 4B). Similarly, GM density in the PAG was negatively correlated with VAS-sport scores ($r = -0.484$, $P = .012$; see Figure 4C), and TSK scores were positively correlated with VAS-sport scores ($r = 0.455$, $P = .020$; see Figure 4D).

In addition to the partial Spearman correlation analysis with age and sex as covariates reported in the main results section, we conducted a simple Spearman correlation analysis without these covariates. The results of this additional analysis, which broadly aligned with our main findings, have been included in Supplemental Figure 2 for further reference. These findings underscore significant associations between GM density in specific brain regions and clinical scores for TSK and VAS among participants with CAI, providing deeper insights into the neurobiological correlates of pain and emotional processing in this population.

DISCUSSION

The most important finding of this study is that, in comparison with HCs, participants with CAI had a reduced GM volume in the PFC and PAG. Furthermore, the GM volume of the PFC was negatively correlated with the TSK scores. In addition, the GM volume of the PAG was negatively correlated with VAS-sport scores, which in turn were positively correlated with TSK scores. To the best of our knowledge, this is the first study to investigate the correlations among brain GM volume, TSK scores, and pain in participants with CAI.

Fear Driven by Residual Pain in CAI

Chronic ankle instability is associated not only with an increased incidence of physical disabilities and impairments but also with potential psychological changes related to the disease, such as fear related to injury after ankle sprains.[8] In

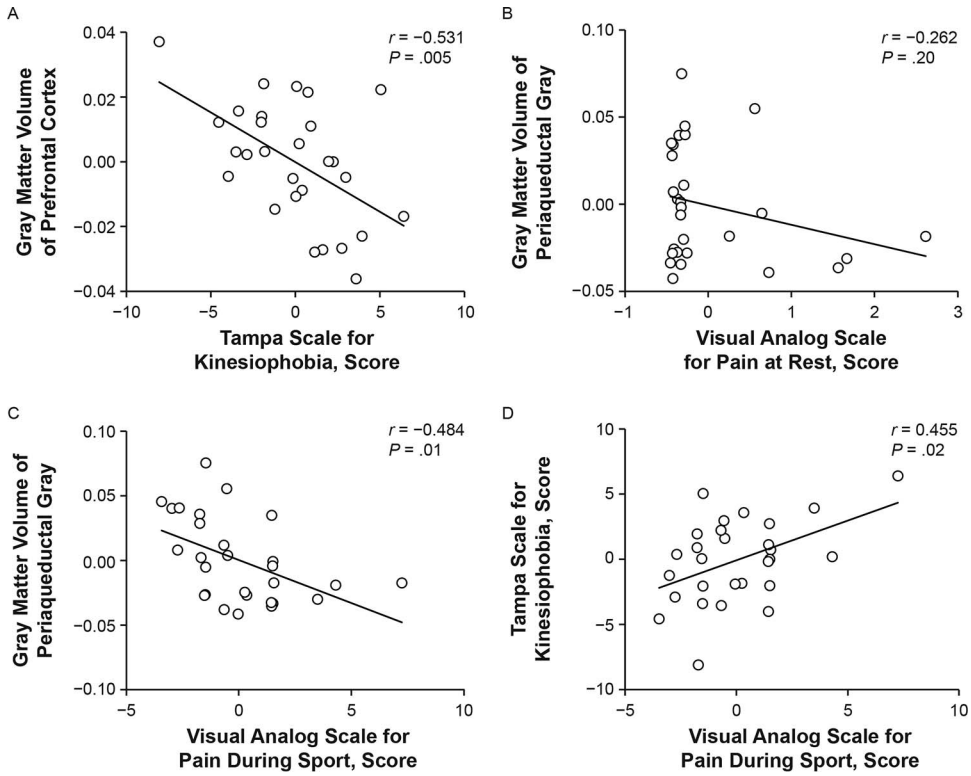

Figure 4. Scatter plots illustrating the correlations between A, Tampa Scale of Kinesiophobia scores and mean gray matter volume of the prefrontal cortex, B, visual analog scale for pain at rest scores and mean gray matter volume of the periaqueductal gray, C, visual analog scale for pain during sports scores and mean gray matter volume of the periaqueductal gray, and D, Tampa Scale of Kinesiophobia scores and visual analog scale for pain during sports scores in participants with chronic ankle instability.

participants with CAI, previous researchers have reported that kinesiophobia was related to the feeling of joint position, postural control, self-reported ankle function, and instability perception.[2,10,28] In this study, participants with CAI had higher TSK scores than HCs. Available evidence emphasizes the importance of injury-related fear in individuals who develop chronicity after ankle sprain injury.[8] Moreover, there was a positive correlation between VAS-sport and TSK scores. Elevated TSK scores suggest increased kinesiophobia, wherein participants with CAI fear movement due to pain or risk of reinjury, leading to reduced activity and worsened instability.[8] This interplay between psychological fear and physical impairment not only affects the quality of life but also serves as a precursor to the varied expressions of pain.[8]

Based on multiple studies cited, the percentage of participants with CAI who reported pain ranged from 18% to 79%, with an average reported rate of 58%.[6,20,29,30] Al Adal et al noted that increased ankle-joint instability correlates with a higher likelihood of reporting ankle pain.[7] Hiller and colleagues found that 51.6% of CAI participants reported occasional ankle pain, with 33.9% of cases being mild and 29.0% moderate.[29] Pain-inducing activities included walking (8%), running (22%), and postsport movements (25%).[30] In our study, only 7 of 28 participants with CAI had VAS-rest scores greater than 0, and 10 of 28 had VAS-sport scores of 5 or higher, which is broadly consistent with other literature. Pain is one of the driving factors affecting central nervous system changes in musculoskeletal disorders.[11] Our findings indicate that participants with CAI have significantly higher pain scores at rest and during sports compared with HCs, suggesting significant adverse outcomes. This effect is particularly pronounced during physical activities, when exacerbated residual pain leads to pain hypersensitivity. Therefore, particularly when activity is increased, pain can induce central plasticity changes.

Neural Mechanisms of Pain-Induced Plasticity in CAI

A recent review of neuroimaging studies on chronic musculoskeletal disorders (MSD) revealed a decrease in the GM volume in the ACC and PFC regions in patients with knee osteoarthritis.[15] Similarly, our study observed lower GM volume in the PFC and PAG in participants with CAI, highlighting the pivotal role of the PFC in both the perception and emotion of pain.[12,14] Additionally, the presence of the residual pain in CAI can modify the function of the PFC due to the neuronal projections from the PAG, a key midbrain structure involved in endogenous pain inhibition and sensation.[13] The midbrain limbic and prefrontal structures may induce disease progression from acute to chronic pain. These structures also influence descending modulatory pathways, facilitating the transmission of harmful stimuli and affecting sensory-motor representations and neuronal properties.[11,14] Our findings align with those of Mainero et al, who linked reduced connectivity between the PAG and frontal areas to more frequent migraine attacks, indicating disruptions in the descending pain inhibition system that may lead to chronic pain.[31]

The adaptive plasticity of the central nervous system can reverse the detrimental reorganizations caused by chronic musculoskeletal disorders.[32] Research indicates that both surgical and rehabilitation interventions, which either increase motor cortices' thickness or normalize their representations, can effectively reverse changes in brain structure and function.[33] This implies that the observed decrease in GM might not stem from neurodegeneration, which is typically irreversible, but from other changes in neuronal tissue.[24] Chronic pain may reduce GM through 2 primary mechanisms: (1) It triggers structural and functional changes in glial cells, leading to their activation. These cells then alter neurotransmitter transport by releasing cytokines, affecting the balance between glutamate and γ-aminobutyric acid, which could exacerbate pain signals and reduce GM volume.[34] (2) Chronic pain also causes prolonged activation of the hypothalamic-pituitary-adrenal axis, elevating cortisol levels and causing dendritic shrinkage, thus further decreasing GM volume.[24,35] Understanding these mechanisms in participants with CAI is crucial to comprehend the complex dynamics between neurotransmitter imbalances and neural plasticity, enhancing our grasp of the pathophysiological processes that lead to GM changes in chronic pain. This knowledge is vital for developing targeted therapeutic strategies to address these neuroplastic alterations.

The GM volume of the PFC in participants with CAI negatively correlates with TSK scores, indicating that reductions in GM may be associated with increased kinesiophobia. The PFC processes the emotional and cognitive components of pain perception. The PFC provides top-down regulation of sensory and emotional processes, including the inhibition of sensory and emotional pain signals, through its descending projections to different brain and spinal regions.[36] Its projections serve as the primary cortical inputs to the PAG, a key component of the spinal-level descending inhibitory pain control system.[12,36] In our CAI study, we found that the GM volume in the PAG also showed a negative correlation with VAS-sport. As a result, we hypothesize that the presence of a negative feedback loop between damaged pain regulation circuits and pain modulation after ankle sprains not only increases chronic pain, but also causes pain-comorbid cognitive and emotional deficiencies. Nevertheless, further research is needed to uncover the functional changes and causal relationships in the neural centers related to chronic pain and pain-related fear in participants with CAI.

Clinical Implications

Previous researchers have shown that, in participants with CAI, pain- and injury-related fear could predict functional decline and increased disability.[2] Based on our further explorations of their neural mechanism, better treatment methods could be designed. As mentioned before, the loss of brain GM (caused by chronic pain) could be restored by various physical rehabilitation programs,[32,33] including calf stretching; joint mobilization; intrinsic foot, ankle, and pelvic girdle complex strengthening; static and dynamic balance; and a combination of functional and gait training.[9,37] In addition to the traditional physical rehabilitation methods, psychological rehabilitation guidance is particularly meaningful for such patients.[38] The actual efficacy of psychological training for ankle sprain individuals still needs further research; however, studies have shown that this approach is beneficial for individuals recovering from trauma.[39]

Limitations

This study has the following limitations. (1) Detecting a causal relationship between brain structural abnormalities

and "chronic pain and related pain-related fear" in ankle instability is challenging due to the cross-sectional design of this study. (2) Our study analyzed only the GM volume and structural similarity, lacking further exploration of additional functional indicators. (3) This study used a simplified brain area definition (using templates); however, CAI-related neural changes may involve only partial brain subregions. (4) The assessment of pain in our study relied primarily on the VAS for pain intensity, which may not fully capture the multidimensional aspects of pain experienced by individuals with CAI. (5) Our study primarily included participants who reported no pain at rest, potentially overlooking those with constant resting pain. This selection bias limits our understanding of the full spectrum of chronic pain in CAI.

Future Directions

We propose that chronic pain and pain-related fear in participants with CAI are linked to maladaptive neural remodeling. To further explore these relationships, future researchers could use task-based blood oxygen level–dependent functional MRI combined with magnetic resonance spectroscopy to investigate neurotransmitter dynamics in the PFC and PAG under different activity states, enhancing understanding of pain processing mechanisms. Longitudinal repeated measurements from the acute to the chronic phase may help researchers to understand the causal relationship between neural changes in the PAG and the PFC and the formation of chronic pain and pain-related fear. Increasing sample sizes and using voxel-wise analysis could improve the precision in localizing brain changes and enhance detection sensitivity. Finally, broadening pain assessments to include thermal, vibrational, and pressure-sensitivity tests alongside traditional measures could provide a deeper, more comprehensive understanding of the pain profiles in CAI. Considering the varied factors influencing neural-plasticity changes in CAI participants, there is a need for a more comprehensive examination and understanding of these factors, as well as considering the individual differences in pain experiences among patients to more accurately understand the mechanisms behind these changes.

CONCLUSIONS

Our exploratory findings suggest a potential association between the atrophy of the PFC and PAG and pain-related fear in participants with CAI, warranting further investigation. Future clinical diagnosis and treatment approaches for CAI should consider the impact of psychological barriers on functional recovery.

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DATA STATEMENT

The original imaging data used to support the findings of this study have not been made available because of patient privacy; the extracted MRI data are available upon reasonable request.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Intergroup comparison of the average gray matter density in the pain and the kinesiophobia-related brain area.

Supplemental Table 2. Spearman correlation analysis of mean GM density, TSK scores, and VAS scores in CAI patients, adjusted for sex and age.

Supplemental Figure 1. This figure illustrates the correlation analysis results between average GM density in the anterior cingulate cortex, amygdala, prefrontal cortex, and periaqueductal gray regions and clinical indicators (Tampa Scale for Kinesiophobia and visual analog scale [VAS] for pain) in patients with chronic ankle instability. Red circles: Highlight statistically significant correlations ($P < .05$), suggesting a positive relationship between increased GM density and higher Tampa Scale for Kinesiophobia and VAS scores. Gray scale and colors: Depict the strength of positive correlation coefficients (R-values). Darker shades indicate stronger correlations, emphasizing the direct relationships pertinent to our study hypotheses. R-values: Displayed to measure the strength and direction of relationships, focusing only on positive correlations, showcasing the extent of correlation from 0 to the strongest observed. Abbreviations: GMV, gray matter volume.

Supplemental Figure 2. The Spearman correlation coefficients between mean gray matter densities in specific brain regions and clinical scores for chronic ankle instability patients, conducted without adjusting for age and gender covariates. These correlations assess the direct relationships, offering additional insights into the intrinsic associations. A, Correlation between Tampa Scale of Kinesiophobia scores and prefrontal cortex grey matter, showing a significant negative association ($r = -0.380$, $P = .046$). B, Correlation between visual analog scale for pain at rest and periaqueductal gray matter, which shows a trend towards a negative association but does not reach statistical significance ($r = -0.282$, $P = .146$). C, Correlation between periaqueductal gray matter and visual analog scale for pain during sports, displaying a significant negative association ($r = -0.526$, $P = .004$). D, Correlation between Kinesiophobia scores and visual analog scale for pain during sports, indicating a significant positive relationship ($r = 0.401$, $P = .034$).

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