The Journal of Headache and Pain

RESEARCH

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Abnormal structural gray matter and structural covariance networks associated with biopsychosocial characteristics in children with multisite pain

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Abstract

Background Overwhelming evidence suggests that adults with chronic pain have altered brain structure and related networks. However, little is currently known regarding changes in structural gray matter and structural covariance networks (SCNs) in children with multisite pain (MP) and their potential relationships with biopsychosocial characteristics.

Methods This study enrolled 444 children with MP and 444 matched controls from the Adolescent Brain Cognitive Development Study. All participants underwent magnetic resonance imaging (MRI) scans following biopsychosocial assessment. Then, SCNs matrices were constructed by the Brain Connectivity Toolbox based on both cortical thickness (CT) and cortical surface area (CSA) among 415 children with MP and 404 controls. Nonparametric permutation tests were employed to examine the group differences in these matrices.

Results Compared with controls, children with MP exhibited both lower CSA and CT in widespread regions involved in the pain matrix, including the anterior cingulate cortex (ACC), middle frontal gyrus (MFG), superior frontal gyrus (SFG), and anterior insula (aIns). While there were no significant group differences in global network measures, children with MP exhibited alterations in nodal network measures in brain regions including the ACC, MFG, and aIns. Besides, children with MP showed significant relationships between abnormal structural gray matter and biopsychosocial characteristics, including general somatic symptoms, conduct disorder symptoms, and sleep quality.

Conclusions Children with MP exhibited abnormal structural gray matter and SCNs in brain regions involved in the pain matrix, which were further associated with biopsychosocial characteristics. These findings could suggest individualized treatments for children with MP, such as transcranial magnetic stimulation therapy, that focus on specific brain nodes within the pain matrix and improve related biopsychosocial characteristics.

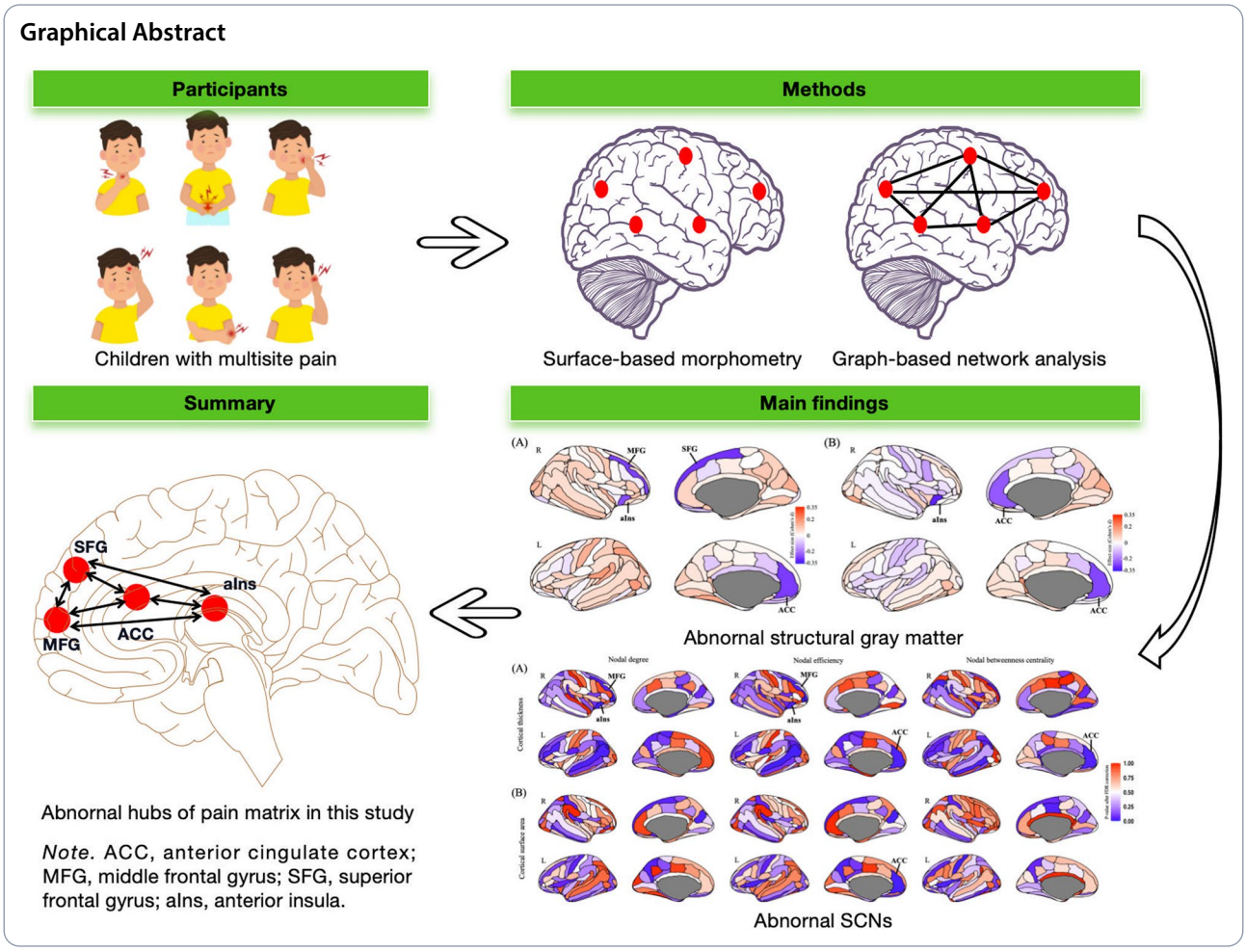
Keywords Multisite pain, Cortical thickness, Cortical surface area, Structural covariance networks, Pain matrix

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Introduction

Multisite pain (MP) in children has emerged as a major public health concern. Approximately one-fifth of children experience various forms of MP, such as headaches, abdominal pain, and musculoskeletal pain [1], and the prevalence of pain tends to rise with age [2]. MP not only affects physical health but is also frequently accompanied by emotional and psychological problems. Anxiety, depression, and sleep disturbances are commonly observed in children with MP [2, 3]. Moreover, persistent pain and the associated psychological distress may further lead to social withdrawal, academic difficulties, and impaired quality of life, while also increasing the risk of chronic pain and psychiatric disorders in adulthood [4, 5]. Therefore, understanding the neural mechanisms underlying pediatric MP and its associations with biopsychosocial characteristics is of great practical significance for early and precise intervention, reducing both physical and psychological burdens, and preventing more severe long-term outcomes in children.

Pain experience has not only been associated with disease, social, and psychological factors, but also with altered brain structure; persistent pain can even induce structural alterations that interfere with normal neurodevelopment [1, 6]. Research in chronic pain patients has shown decreased gray matter density in the insular cortex, primary somatosensory cortex, and motor cortex, as well as reduced gray matter volume in the hippocampus and amygdala [7, 8]. Another longitudinal study further demonstrated that children with MP showed increased functional connectivity between the insula and primary somatosensory cortex, along with decreased functional connectivity between the prefrontal cortex and thalamus, while no abnormalities were observed in gray matter volume and cortical thickness (CT) [9]. In addition, several studies have reported gray matter volume reductions across multiple pain-related networks in children with chronic pain, including the emotion regulation network, default mode network, sensorimotor network, and central executive network [10, 11]. These alterations may reflect differences in pain perception as well as pain-induced neuroplastic changes.

Despite existing studies, several limitations persist in the current literature on pain and its effects on the brain.

First, most studies have primarily focused on adults, leaving the mechanisms underlying structural brain alterations in children with pain largely unclear. Second, many studies have explored single pain conditions, such as back pain or headache, while neglecting the clinical complexity of MP. Existing evidence suggests that brain structural alterations vary significantly across pain syndromes [12]. Compared to single-site pain, MP may better reflect abnormal central nervous system processes in pain perception and modulation, which could indicate long-term vulnerability [9]. Furthermore, current pediatric chronic pain research has focused only on gray matter volume, whereas cortical indices such as CT and cortical surface area (CSA) are genetically independent and may reflect distinct neurodevelopmental processes [13]. Therefore, investigating multiple cortical structural indices and related structural networks is necessary for a more comprehensive understanding of brain structural alterations in children with MP.

The graph theory approach has emerged as a powerful tool for exploring brain network organization. It can characterize functional and structural connectivity across widespread brain regions, thereby revealing the topological organization of brain networks [14]. Previous research has found that multiple large-scale brain networks work in concert to support pain perception, emotional reactivity, and cognitive regulation [7, 10, 15]. Compared with traditional region-based analyses, the graph theory approach can better capture the complex interactions between brain regions and the neuroplastic alterations induced by chronic pain. However, to date, there have been no research investigating alterations in structural covariance networks (SCNs) in children with MP.

Taken together, this study investigated brain structural alterations in children with MP, focusing on changes in SCNS using a graph theory approach. Specifically, this study had three primary goals: (1) to examine whether children with MP exhibited altered CT and CSA related to controls; (2) to explore whether altered SCNs could be observed in children with MP; and (3) to assess whether these brain structural alterations were associated with biopsychosocial characteristics in children with MP. We hypothesized that children with MP exhibit (1) abnormal CT and CSA within brain regions involved in the pain matrix related to controls; (2) altered nodal network measures within pain matrix related nodes; (3) a significant association between brain structural alterations and biopsychosocial characteristics.

Table 1 Demographic characteristics of children with multisite pain and matched controls

Characteristics	Children with multisite pain (*N* = 444)	Matched controls (*N* = 444)	t/χ2	*P*-value
Age (years)	9.51(0.51)	9.50(0.51)	0.32	0.75
Sex, n (%)			0.005	0.95
Female	263(59.23)	265(59.68)		
Male	181(40.77)	179(40.32)		
Body mass index	19.71(4.66)	19.40(4.70)	0.97	0.33
Waist circumference	27.34(4.60)	27.02(4.61)	1.01	0.31
Pubertal status, n (%)			3.09	0.69
Prepuberty	87(19.60)	78(17.57)		
Early puberty	121(27.25)	130(29.28)		
Mid puberty	116(26.13)	115(25.90)		
Late puberty	14(3.15)	12(2.70)		
Post puberty	2(0.45)	0(0.00)		
Not reported/missing	104(23.42)	109(24.55)		
Ethnicity, n (%)			4.91	0.09
Hispanic, Latino, Latina, or Latinx	232(52.25)	200(45.05)		
Non-Hispanic	156(35.14)	174(39.19)		
Not reported/missing	56(12.61)	70(15.77)		
Handedness, n (%)			1.52	0.47
Right-handed	354(79.73)	360(81.08)		
Left-handed	25(5.63)	30(6.76)		
Mixed handed	65(14.64)	54(12.16)		
Combined annual family income	6.52(2.49)	6.71(2.58)	−1.04	0.30
Highest parental education	16.98(2.38)	17.16(2.74)	−0.90	0.37

Continuous variables are reported as mean (standard deviation)

Methods

Study design

For this study, we selected children aged 9–11 years at baseline from the Adolescent Brain Cognitive Development® (ABCD) study. The ABCD study is an ongoing longitudinal, multimodal MRI with questionnaire study designed to recruit more than 10,000 children and track them over a 10-year period at 21 multisites [16]. Institutional review board approval was secured from all participating sites, and informed consent was obtained from parents and participants. The study data are accessible to researchers upon registration with the National Institute of Health's Data Archive (https://nda.nih.gov/abcd).

Participants

The demographic characteristics of children enrolled in this study are presented in Table 1. While some data quality indices were developed by the ABCD Data Analysis, Informatics & Resource Center (DAIRC), all standardized inclusions and exclusions were performed for this study, starting from the total participants enrolled at baseline in the ABCD study.

In this study, the presence of pain was assessed using the Child Behavior Checklist (CBCL), which was completed by the parent(s) regarding their child at baseline. The CBCL pain-related items have been previously

used for the classification of chronic pain using ABCD data [17]. Parents were asked to report if their child had experienced the following physical problems without a known medical cause, either currently or within the past six months: (1) aches or pains (not stomach or headaches), (2) headaches, and (3) stomach aches. Response options to each question included "not true (as far as you know)", "somewhat or sometimes true" and "very true or often true". Based on previous research [4, 9], we operationalized multisite pain as a parental endorsement of at least two of the three pain items at baseline, resulting in a cohort of 444 children with this condition, and details of pain items (locations) was provided in Table S1. Besides, an additional 444 matched controls were selected, defined as children who did not experience pain at any time point. Furthermore, matched controls were strictly matched to children with multisite pain based on sex, ethnicity, body mass index (BMI), waist circumference, pubertal status, handedness, combined annual family income, and highest parental education. The matching procedure was conducted using the "MatchIt" package for the R programming language in RStudio. Finally, the study cohort comprised 444 children with multisite pain and 444 matched controls at baseline (Table 1, Figure S1). All procedures were conducted in accordance with the Helsinki Declaration and approved by the local institutional review board.

Measures of biopsychosocial characteristics

Sex and ethnicity

The child's sex assigned at birth and race/ethnicity were collected at baseline. Given the relatively small number of children with multisite pain who were non-Hispanic Black, Asian, or another race/ethnicity, we categorized race into three categories: (1) Hispanic, Latino, Latina, or Latinx; (2) Non-Hispanic; (3) Not reported/missing.

BMI and waist circumference

In-person measurements of height and weight were used to determine body mass index (BMI). Specifically, BMI was calculated as weight in pounds divided by height in inches squared and multiplied by 703. Waist circumference was measured in inches in person.

Pubertal status

Pubertal status was assessed using the youth-reported Puberty Development Scale. Previous research has assessed a relationship between pubertal development and multiple pain characteristics in ABCD. Puberty category scores ranging between "prepuberty", "early puberty", "mid puberty", "late puberty", and "post puberty" for males and females were categorized as previously published.

Handedness

Handedness was assessed using nine items from the Edinburgh Handedness Inventory based on individuals' self-reported preferences for their dominant hand. Thus, handedness was categorized into three categories: right-handed, left-handed, mixed mixed-handed.

Combined annual family income and highest parental education

Socioeconomic status was assessed by both combined annual family income and parental education level in this study. For combined annual family income, parents selected a category that best represented their income for the past 12 months, ranging from (1) "less than $5000" to (10) "$200,000 and greater". Parents reported on their or their partner's highest level of education by selecting an education category that ranged from (0) "Never Attended" to (21) "Doctoral Degree".

Cognitive ability The NIH Toolbox cognition battery was adopted to measure cognitive ability among children in the ABCD study. In this study, we extracted data from tests assessing language/verbal intellect, cognitive control/attention, working memory, flexible thinking, processing speed, visuospatial sequencing/episodic memory, reading ability, and fluid reasoning. Besides, two composite scores, crystallized intelligence and a total cognition score, were extracted.

Sleep quality

Sleep quality was assessed using the parent-reported Sleep Disturbance Scale, which contains 26 items across 6 subscales: (1) disorders of initiating and maintaining sleep, (2) sleep breathing disorders, (3) disorders of arousal, (4) sleep-wake transition disorders, (5) disorders of excessive somnolence, and (6) sleep hyperhidrosis. The total score is calculated as the sum of the scores from all 6 subscales, which range from 26 to 130, with higher scores denoting more sleep disturbances and worse sleep quality [18].

Clinical symptoms

In the ABCD study, various clinical symptoms were assessed using the parent-reported CBCL, a tool with established high internal consistency and validity [17]. Raw scores from specific DSM-5-oriented subscales of the CBCL were used to quantify the following symptoms: depression, anxiety, Attention hyperactivity disorder (ADHD), oppositional defiance, conduct disorder, and general somatic symptoms. In addition, raw summary scores from the CBCL were used to assess inattention, as well as broader externalizing and internalizing syndromes.

Personality

In the ABCD study, the UPPS-P for Children Short Form was a 20-item self-report measure used to assess impulsivity in children, which measured five dimensions of impulsivity: negative urgency, lack of planning, sensation seeking, positive urgency, and lack of perseverance [19]. Besides, a modified version of the Behavioral Inhibition System (BIS)/Behavioral Activation System (BAS) scale was adopted to assess individual differences in behavioral motivation systems related to sensitivity to punishment (BIS) and reward (BAS) in the ABCD study. The scale consists of 20 items, comprising one BIS scale and three BAS subscales: drive, reward responsiveness, and fun-seeking [20].

MRI data acquisition

The acquisition and preprocessing of structural MRI data were conducted as described in previous research [16]. The imaging protocol was standardized and harmonized for three 3 T scanner platforms (Siemens Prisma, General Electric 750 and Philips) across all 21 ABCD sites (Table S2). Besides, the imaging parameters for the three 3 T scanner platforms are summarized in Table S3. Furthermore, the ABCD Imaging Acquisition Workgroup (https://abcdstudy.org/scientists-workgroups.html) selected, optimized and harmonized measures and procedures across all 21 multisites [21]. All MRI data were collected from 3 T scanners. Participants underwent T1- and T2-weighted MRI scans, diffusion tensor imaging scans, and resting-state functional MRI scans. In this study, only structural MRI data were used to investigate altered structural gray matter in children with multisite pain; therefore, details about quality control and preprocessing for structural MRI are documented below.

Structural MRI data quality control

The quality control criteria for structural MRI data were based on two key assessments. For the clinical referral assessment, participants who scored a 3 (consider clinical referral) or 4 (consider immediate clinical referral) in the MRI clinical report/findings were excluded. For the imaging inclusion assessment, the score for participants' structural MRI data recommended for inclusion was 1, and therefore, the structural MRI data were included in the subsequent structural MRI data analysis. Finally, 415 children with multisite pain and 404 matched controls participated in the following structural MRI analysis (Figure S1).

Structural MRI data preprocessing

In this study, structural MRI data was preprocessed by FreeSurfer, and the pipeline encompassed the following steps: removal of non-brain tissue, automated Talairach transformation of each participant's native brain, intensity normalization, tessellation of the gray/white matter boundary, automated topology correction, surface deformation following intensity gradients, registration of the participant's native brain to a standard spherical atlas, and reconstruction of the cortical surface. To obtain CT and CSA measurements, the cortical morphologies were smoothed. This smoothing process was repeated using the same kernel size to ensure accurate CSA and CT measurements. During preprocessing, all outputs were subject to meticulous accuracy inspection, with manual corrections applied where necessary. Subsequently, the average CSA and CT values within the total of 148 bilateral brain cortical regions of interest were defined using the Destrieux atlas [22].

Construction of SCNs

The statistical similarity between brain regions defined by the Destrieux atlas was measured by computing Pearson's correlation coefficient across subjects, and an interregional correlation matrix (148 × 148) was constructed from each group. Therefore, group-level SCNs for the CT and CSA were constructed separately for each group. To improve the normality of the correlation, the correlation coefficient r was converted to z-values using the Fisher transformation. By binarizing the correlation matrix using a series of sparsity thresholds, which resulted in specific percentages of connections, a series of unweighted and undirected graphs was obtained for subsequent network analysis. Given that the selection of different threshold values could cause changes in small-world network parameters, we limited the correlation matrices over a wide range of sparsity (6%–40%) to avoid the uncertainty resulting from the threshold choice [23]. The chosen range of sparsity enables the proper estimation of small-world network architectures, and the number of spurious edges in each network is minimized, as indicated in previous studies [23, 24].

Graph-based network analysis

Global and nodal network measures of SCNs were computed using the Brain Connectivity Toolbox [25]. We computed the normalized characteristic path length (which is defined as the shortest path length between all pairs of nodes) and global efficiency (which measures how efficiently information is communicated between nodes) as measures of network integration and the normalized clustering coefficient (which evaluates the influence of different paths based on the connection weights of the node's neighbors) and local efficiency (defined as the number of connections in the neighborhood of a certain node divided by the maximum number of possible connections between the neighbors of this node) as measures of network segregation. Small-worldness, which reflects the optimal balance between network integration

and segregation, was also computed. The nodal degree, nodal efficiency, and nodal betweenness centrality were examined to identify group differences in nodal network measures.

Statistical analysis

Statistical analysis was conducted using various packages in the R programming language within RStudio. In terms of demographic characteristics, the chi-square test was used to assess group differences in sex, pubertal status, ethnicity, and handedness. Group differences in other demographic characteristics were evaluated using two independent samples t-tests. For the cognitive and clinical characteristics, two independent samples t-tests were conducted to investigate the group difference, and a threshold of $P < 0.05$ was considered statistically significant after false discovery rate (FDR) corrections.

During SCN analysis, any biopsychosocial characteristics that showed significant group differences and pain locations were included as covariates. A nonparametric permutation test was employed to investigate statistical differences in network metrics between the groups. First, a network measure (clustering, path length, efficiency, nodal efficiency, betweenness, and degree) was computed separately for children with multisite pain and matched controls. Following that, the CT or CSA values of each subject were allocated into two groups, resulting in an identical sample size for each of the original groups. New values were obtained for network metrics after recalculating the SCNs for both groups. Each permutation test was repeated 1000 times, and a P-value < 0.05 was statistically significant with FDR corrections after multiple comparisons. Considering various densities, we compared the area under the curve (AUC) (density range: 0.06-0.01.06.01-0.4) between the two groups. Next, to examine whether altered structural gray matter and SCNs were associated with biopsychosocial characteristics in children with multisite pain, Pearson correlation analysis was conducted.

Results

Participants and characteristics

In terms of demographic characteristics, there were no significant differences between children with multisite pain and matched controls (all $P > 0.05$, Table 1). Besides, children with multisite pain and matched controls exhibited comparable cognitive abilities and personalities (all $P > 0.05$, Table 2). However, in terms of sleep quality (Table 2), compared with matched controls, children with multisite pain exhibited higher score of disorders of initiating and maintaining sleep ($t = 14.52$, $P < 0.001$), sleep breathing disorders ($t = 5.51$, $P < 0.001$), disorder of arousal ($t = 8.86$, $P < 0.001$), sleep-wake transition disorders ($t = 11.64$, $P < 0.001$), disorders of excessive somnolence ($t = 12.74$, $P < 0.001$), sleep hyperhidrosis ($t = 7.63$, $P < 0.001$), sleep quality ($t = 15.83$, $P < 0.001$). In terms of clinical symptoms (Table 2), compared with matched controls, children with multisite pain showed more depressive symptoms ($t = 16.47$, $P < 0.001$), anxiety symptoms ($t = 18.69$, $P < 0.001$), ADHD symptoms ($t = 13.82$, $P < 0.001$), oppositional defiance symptoms ($t = 14.64$, $P < 0.001$), conduct disorder symptoms ($t = 10.39$, $P < 0.001$), inattention symptoms ($t = 13.20$, $P < 0.001$), externalizing syndrome ($t = 26.35$, $P < 0.001$), internalizing syndrome ($t = 14.23$, $P < 0.001$), and general somatic symptoms ($t = 47.56$, $P < 0.001$).

Group difference in structural Gray matter

In terms of CT (Table 3, Table S4, Fig. 1A), compared with matched controls, children with multisite pain showed lower CT in the left anterior cingulate cortex (ACC, $t = -4.00$, Cohen's $d = -0.28$, $P = 0.004$ after FDR), right middle frontal gyrus (MFG, $t = -3.91$, Cohen's $d = -0.27$, $P = 0.005$ after FDR), right superior frontal gyrus (SFG, $t = -4.16$, Cohen's $d = -0.29$, $P = 0.005$ after FDR), and right anterior insula (aIns, $t = 3.68$, Cohen's $d = -0.26$, $P = 0.009$ after FDR). In terms of CSA (Table 3, Table S5, Fig. 1B), compared with matched controls, children with multisite pain exhibited lower CSA in the left ACC ($t = -3.80$, Cohen's $d = -0.27$, $P = 0.012$ after FDR), right ACC ($t = -3.47$, Cohen's $d = -0.24$, $P = 0.027$ after FDR), and right aIns ($t = -4.52$, Cohen's $d = -0.32$, $P = 0.001$ after FDR).

Group differences in global network measures

In terms of CT, there were no significant group differences in global network measures, including normalized path length (Fig. 2A), global efficiency (Fig. 2B), small-worldness measures (Fig. 2C), normalized clustering coefficients (Fig. 2D), and local efficiency (Fig. 2E). Regarding CSA, there were no significant group differences in global network measures, including normalized path length (Fig. 3A), global efficiency (Fig. 3B), small-worldness measures (Fig. 3C), normalized clustering coefficients (Fig. 3D), and local efficiency (Fig. 3E).

Group differences in nodal network measures

Compared to matched controls, children with multisite pain exhibited altered nodal degree of right MFG, right aIns, left inferior frontal gyrus, and left Inferior frontal sulcus; abnormal nodal efficiency of left ACC, right MFG, right aIns, right inferior frontal sulcus; and altered nodal betweenness centrality of left ACC, left ventral posterior cingulate cortex, right insular gyri, and right middle frontal sulcus (Fig. 4A).

For CSA, compared with matched controls, children with multisite pain exhibited an altered nodal degree of right SFG and right inferior temporal sulcus. Abnormal

Table 2 Cognitive and clinical characteristics of children with multisite pain and matched controls

Characteristics	Children with multisite pain (*N* = 444)	Matched controls (*N* = 444)	t	*P* after FDR
Cognitive ability				
Language/verbal intellect	106.14(16.83)	104.51(16.96)	1.43	0.29
Cognitive control	94.89(13.32)	93.87(12.99)	1.15	0.45
Working memory	98.84(14.26)	98.91(14.67)	−0.07	0.99
Flexible thinking	95.97(15.19)	95.95(14.85)	0.02	0.99
Processing speed	93.51(21.20)	92.89(21.86)	0.43	0.80
Episodic memory	100.66(16.43)	101.55(16.48)	−0.80	0.69
Reading ability	99.69(17.48)	100.50(19.01)	−0.66	0.76
Fluid reasoning	94.38(17.00)	93.95(17.34)	0.37	0.83
Crystallized intelligence	103.44(17.39)	102.85(18.30)	0.49	0.78
Total general intelligence	98.48(17.29)	97.83(18.09)	0.53	0.77
Sleep quality				
Disorders of initiating and maintaining sleep	14.73(4.70)	10.81(3.20)	14.52	0.00
Sleep breathing disorders	4.31(1.82)	3.71(1.41)	5.51	0.00
Disorder of arousal	4.02(1.55)	3.26(0.96)	8.86	0.00
Sleep-wake transition disorders	9.98(3.51)	7.54(2.68)	11.64	0.00
Disorders of excessive somnolence	8.87(3.51)	6.35(2.24)	12.74	0.00
Sleep hyperhidrosis	3.10(2.00)	2.28(1.05)	7.63	0.00
Total score of sleep quality	45.02(11.93)	33.96(8.56)	15.83	0.00
Clinical symptoms				
Depression symptoms	3.53(3.48)	0.64(1.22)	16.47	0.00
Anxiety symptoms	4.69(3.38)	1.30(1.77)	18.69	0.00
ADHD symptoms	4.74(3.59)	1.80(2.68)	13.82	0.00
Oppositional defiance symptoms	3.24(2.49)	1.15(1.68)	14.64	0.00
Conduct disorder symptoms	2.88(3.83)	0.81(1.70)	10.39	0.00
Inattention symptoms	5.38(4.31)	2.05(3.08)	13.20	0.00
Externalizing syndrome	13.67(8.27)	2.51(3.34)	26.35	0.00
Internalizing syndrome	9.56(8.79)	2.87(4.57)	14.23	0.00
General somatic symptoms	4.13(1.72)	0.13(0.42)	47.56	0.00
Personality				
Negative urgency	8.45(2.76)	8.27(2.76)	0.95	0.59
Lack of planning	7.65(2.44)	7.75(2.49)	−0.59	0.76
Sensation seeking	9.68(2.81)	9.63(2.78)	0.25	0.87
Positive urgency	7.94(3.05)	8.06(3.00)	−0.59	0.76
Lack of perseverance	7.10(2.39)	6.98(2.45)	0.70	0.76
BIS	9.76(3.70)	9.30(3.70)	1.85	0.13
BAS reward responsiveness	10.93(3.06)	10.92(2.77)	0.04	0.99
BAS drive	4.05(2.98)	4.00(2.97)	0.26	0.87
BAS fun seeking	5.64(2.77)	5.54(2.56)	0.57	0.76

Continuous variables are reported as mean (standard deviation). *FDR* False discovery rate, *ADHD* Attention deficit hyperactivity disorder, *BIS* Behavioral inhibition system, *BAS* Behavioral activation system

nodal efficiency was observed in the left ACC and the superior part of the insula. Finally, abnormal nodal betweenness centrality of the left posterior middle cingulate cortex and the right superior part of the insula (Fig. 4B).

Relationships between Gray matter structure and characteristics in children with multisite pain

In terms of clinical symptoms (Fig. 5A), children with multisite pain showed significant relationships between general somatic symptoms and CT of the left ACC ($r = -0.09$, $P = 0.04$), as well as CT of the right MFG ($r = -0.17$, $P < 0.001$). Besides, there was a significant correlation between conduct disorder symptoms and CT of the right aIns ($r = -0.11$, $P = 0.03$). For sleep quality (Fig. 5B), children with multisite pain exhibited a significant association between disorders of excessive somnolence and CT of right aIns ($r = -0.13$, $P = 0.008$). Moreover, sleep hyperhidrosis exhibited a significant correlation with CSA of the left ACC ($r = 0.11$, $P = 0.02$).

Table 3 Group difference of structural gray matter between children with multisite pain and matched controls

Brain region	Children with multisite pain (*N* = 415)	Matched controls (*N* = 404)	t	Effect size	*P* after FDR
Cortical thickness					
Left ACC	2.95(0.13)	2.99(0.13)	−4.00	−0.28	0.004
Right MFG	2.97(0.16)	3.01(0.16)	−3.91	−0.27	0.005
Right SFG	3.21(0.15)	3.25(0.14)	−4.16	−0.29	0.005
Right aIns	3.08(0.19)	3.13(0.19)	−3.68	−0.26	0.009
Cortical surface area					
Left ACC	1637.36(232.47)	1701.03(247.09)	−3.80	−0.27	0.012
Right ACC	2144.54(270.00)	2212.08(286.51)	−3.47	−0.24	0.027
Right aIns	413.26(75.27)	436.76(73.51)	−4.52	−0.32	0.001

Continuous variables are reported as mean (standard deviation). *ACC* Anterior cingulate cortex, *MFG* Middle frontal gyrus, *SFG* Superior frontal gyrus, *aIns* anterior insula, *FDR* False discovery rate

Discussion

To our knowledge, this is the first study to adopt a graph theory approach to investigate brain structural alterations and related SCNs in children with MP, considering both CT and CSA. We found that children with MP exhibited both lower CSA and CT in widespread regions involved in the pain matrix, including the ACC, MFG, SFG, and aIns, compared to controls. There were no significant group differences on global network measures; however, in terms of nodal network measures, children with MP exhibited alterations in brain regions, including the ACC, MFG, and aIns. Besides, children with MP showed significant relationships between brain structural alterations and biopsychosocial characteristics, including general somatic symptoms, conduct disorder symptoms, and sleep quality. These findings shed light on the impact of MP on the brain's structural organization in children and the involvement of hubs within the pain matrix.

In this study, compared with controls, children with MP exhibited significant lower CT in the bilateral ACC, right MFG, right SFG, and right aIns. The ACC has been demonstrated as a critical region mediating pain experience [26]. Structural alterations of the ACC have been linked to pain-related neural mechanisms [26], with cortical thinning in particular being considered a core feature of central sensitization [27, 28]. Our findings suggested that altered CT of the ACC may imply impaired emotional and cognitive processing when facing pain, especially in regulating negative emotions and distress. As part of the prefrontal cortex, the MFG and SFG are both closely related to higher-order cognitive functions and emotional control. It has been suggested that the SFG not only connects with the DMN and motor network, but also, together with the MFG and inferior frontal gyrus, participates in the cognitive execution network [29]. Structural alterations of the SFG have been shown to affect pain perception as well as cognitive control over negative emotions [30, 31]. Thus, CT alterations in the SFG and MFG may contribute to stronger negative impacts on pain perception in children with MP.

The aIns, a hub of the salience network (SN), is responsible for integrating internal body signals with external threat cues and for emotional arousal, and it also plays a key role in pain perception [32, 33]. Lower CT of the right aIns may reflect deviations in expectation and subjective salience of stimuli after persistent multi-site pain input, resulting in stronger emotional responses. Previous studies have also found structural changes in the right insula of chronic pain patients, which may relate to reward system dysfunction and worsening affective symptoms [34]. This suggests that neural plasticity changes induced by MP not only progressively affect pain perception itself but may also exacerbate negative affect

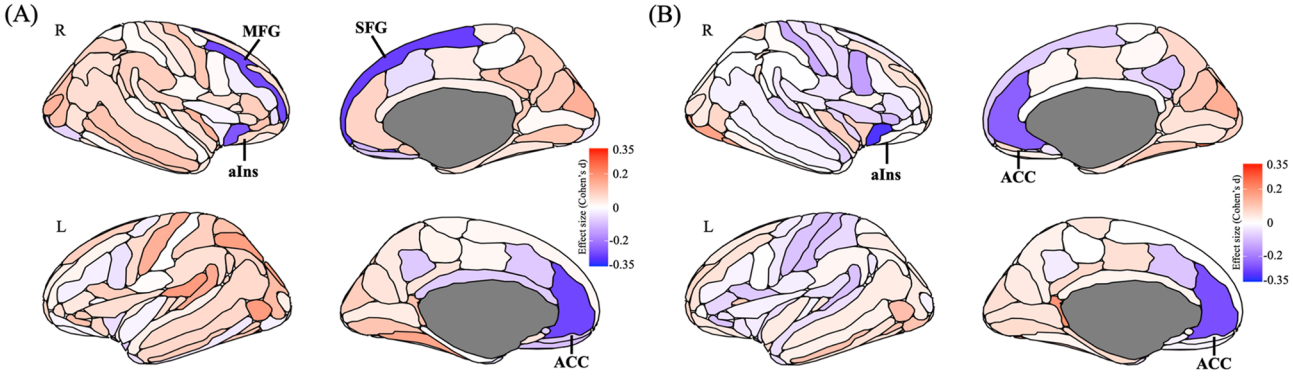


Fig. 1 Group difference of (**A**) cortical thickness and (**B**) cortical surface area between children with multisite pain and matched controls. L, left; R, right; ACC, anterior cingulate cortex; MFG, middle frontal gyrus; SFG, superior frontal gyrus; aIns, anterior insula; FDR. The color bar for brain regions represented Cohen's d value (effect size) between groups

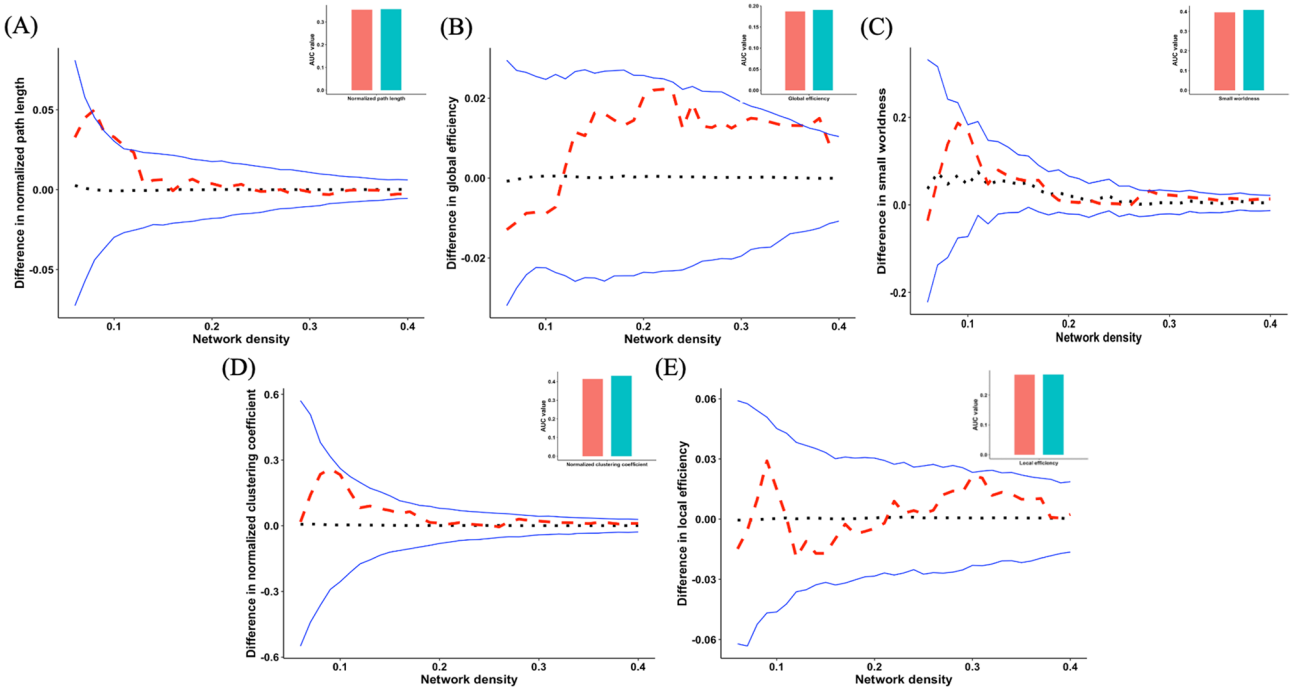


Fig. 2 Group differences of structural covariance networks based on cortical thickness in "integration" metrics including (**A**) normalized path length and (**B**) global efficiency; (**C**) "small-worldness" metric; "segregation" metrics including (**D**) normalized clustering coefficient, and (**E**) local efficiency

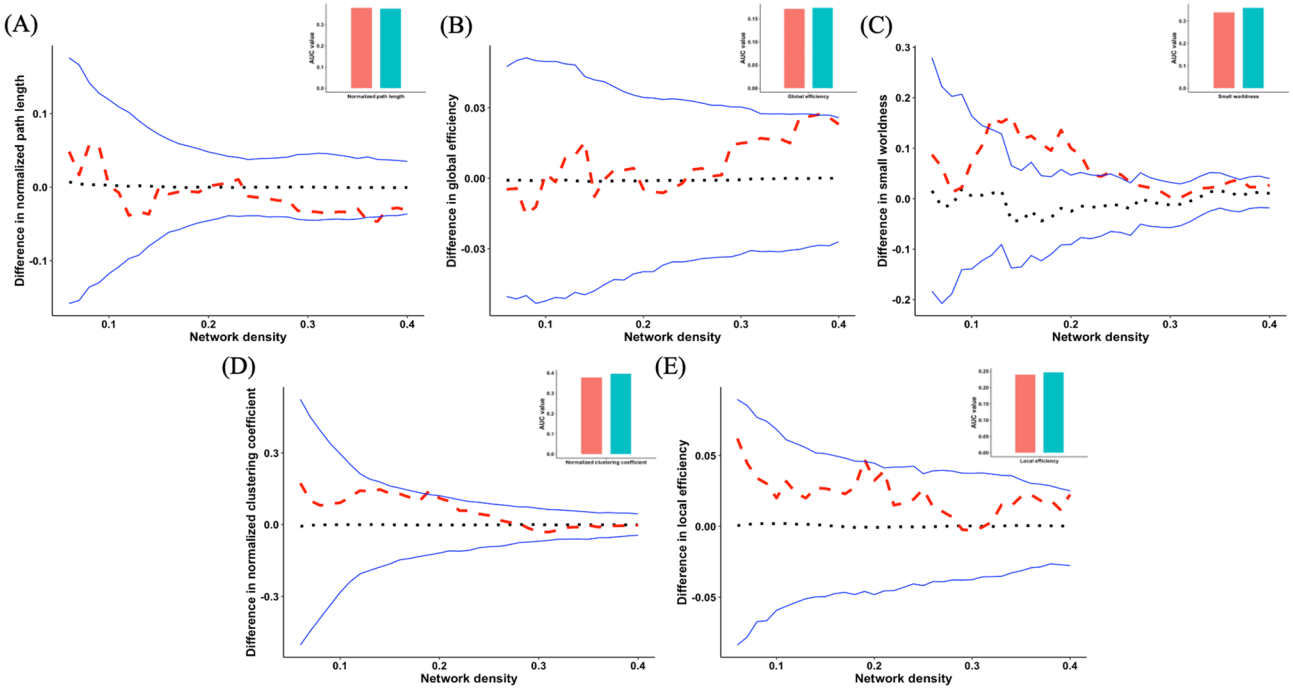


Fig. 3 Group differences of structural covariance networks based on cortical surface area in "integration" metrics including (**A**) normalized path length and (**B**) global efficiency; (**C**) "small-worldness" metric; "segregation" metrics including (**D**) normalized clustering coefficient, and (**E**) local efficiency

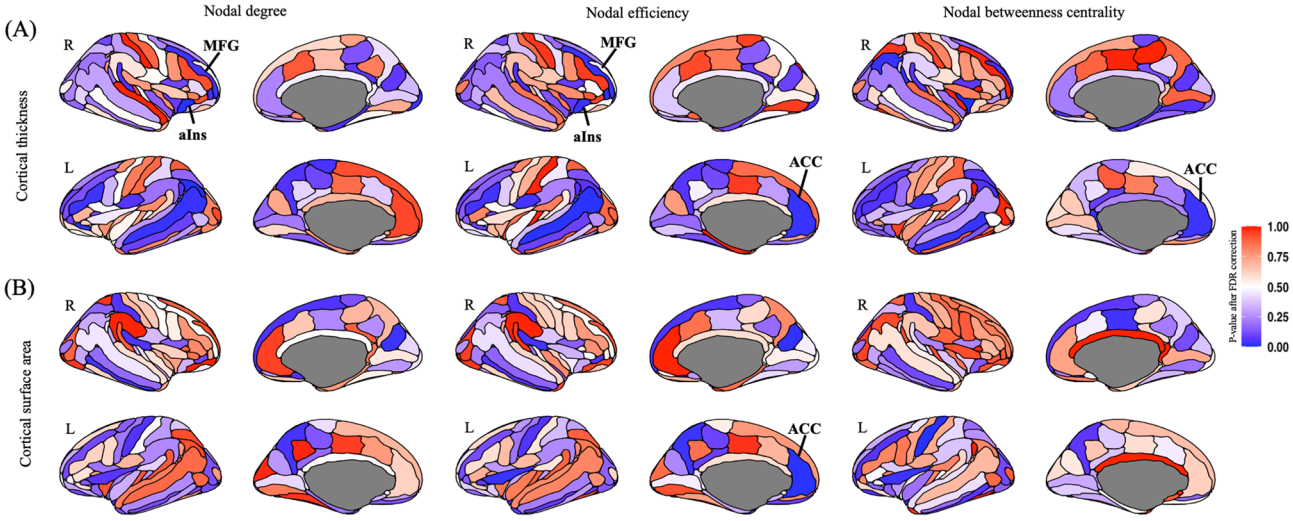


Fig. 4 Group differences in nodal network metrics (nodal degree, nodal efficiency, and nodal betweenness centrality) of structural covariance networks based on (**A**) cortical thickness and (**B**) cortical surface area. The color bar for brain regions represented p value after false discovery rate (FDR) correction. ACC, anterior cingulate cortex; MFG, middle frontal gyrus; aIns, anterior insula

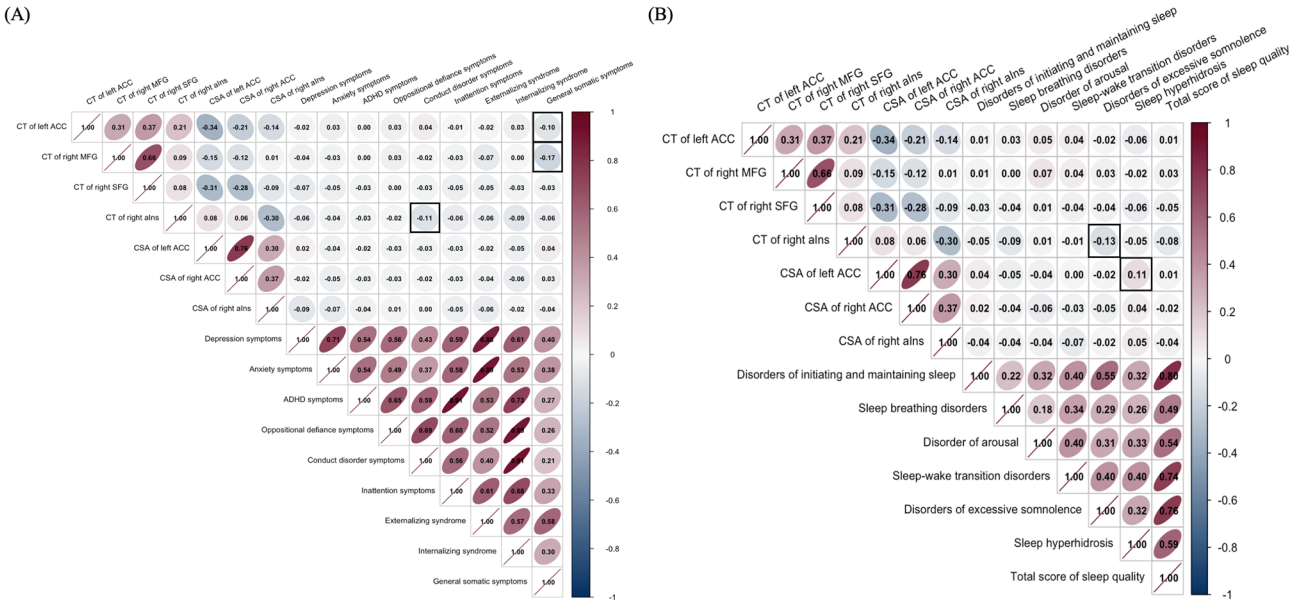


Fig. 5 The relationships between gray matter structure showed significant group differences and (**A**) clinical symptoms, as well as (**B**) sleep quality. The color bar represented the correlation coefficient. The black square represented significant correlation ($P < 0.05$). CT, cortical thickness; CSA, cortical surface area; ACC, anterior cingulate cortex; MFG, middle frontal gyrus; SFG, superior frontal gyrus; aIns, anterior insula; ADHD, attention deficit hyperactivity disorder

and hypervigilance toward pain through interactions between the SN and reward system, thereby forming a vicious cycle.

In addition, our results revealed lower CSA in the bilateral ACC and right aIns in children with MP. As key nodes within the pain-processing circuit, these alterations indicate functional abnormalities in attentional allocation, cognitive control, and nociceptive information integration, which may predispose individuals to pain-related cognitive and emotional biases [35]. Abnormal CSA of these regions suggests that MP may exert long-term effects on the cortical structures of critical nodes during early developmental stages in children. Moreover, abnormal nodal degree of CT was observed in several pain matrix nodes, including the right MFG, inferior frontal gyrus, and right aIns. Nodal degree, an indicator of the number of connections between a region and others, reflects its information integration capacity and involvement within the network. The MFG and inferior frontal gyrus, as components of the CEN, play critical

roles in cognitive control, sustained attention, and pain inhibition [36, 37]. Decreased nodal degree may indicate impaired allocation of attentional resources and cognitive regulation during pain processing, thereby increasing susceptibility to stronger pain experience and negative emotions. The right aIns, responsible for integration and relay of interoceptive and external threat signals [33], exhibited a decreased nodal degree, suggesting impairment in salience processing in children with MP, which may lead to hypervigilance and exaggerated emotional responses to pain-related stimuli.

Moreover, abnormal nodal efficiency was documented in the left ACC and right MFG of children with multisite pain. Nodal efficiency reflects the speed of information transfer between a node and other nodes within the network. The ACC, through projections to the prefrontal cortex and amygdala, is involved in top-down emotional regulation [38]. Reduced efficiency of the ACC may indicate limited structural cooperation with other brain regions, weakening emotional regulation of pain and increasing comorbidity of pain and negative affect, thus further exacerbating the pain burden. Besides, children with MP showed abnormal betweenness centrality in the left ACC, left posterior middle cingulate cortex, right insula, and right middle frontal sulcus. Betweenness centrality reflects the hub role of a node in global information transfer [25]. Reduced betweenness centrality in the ACC may suggest insufficient coordination across networks, impairing the integration of pain perception, emotional experience, and cognitive control. The PCC, generally regarded as a core node of the DMN [39], is closely related to self-referential processing and internal attention. Alterations in left posterior middle cingulate cortex centrality may indicate excessive immersion in self-related negative experiences during pain processing [40]. Abnormalities in insula centrality further emphasize its critical bridging role in whole-brain networks. As a key hub of the SN, the insula not only integrates salient interoceptive and exteroceptive stimuli but also mediates switching between the DMN and CEN [41]. Impairments in switching may hinder the timely processing of relevant stimuli and the coordination of behavioral, emotional, and physiological responses [10, 41]. Abnormal centrality of the right middle frontal sulcus may weaken top-down control of pain-related information by the prefrontal executive system, thereby impairing inhibitory or reappraisal abilities.

In addition, an abnormal nodal degree of CSA was identified in the right SFG and right inferior temporal sulcus. Consistent with the observed decrease in nodal degree in prefrontal regions for CT, a reduction in the degree of the SFG and inferior temporal sulcus also suggests vulnerability in executive control, which may reflect impairments in goal maintenance and sustained attention [38]. Furthermore, decreased nodal efficiency was observed in the left ACC and right dorsal insula. The reduced efficiency and centrality of these regions suggest impaired coordination within the network, hindering timely attentional shifts and resource allocation when facing pain stimuli [42]. The simultaneous impairment of nodes involved in the SN and DMN suggests that children with MP may not only have a reduced capacity to capture and regulate external stimuli but also be more prone to self-focused negative experiences, thereby aggravating pain perception and emotional burden [4, 42].

Besides, the severity of general somatic symptoms was negatively correlated with lower CT values of the left ACC and right MFG. Considering that ACC thinning often reflects central sensitization and impaired emotional regulation [35], and the MFG, as a core node of the CEN, is crucial for attentional allocation, cognitive inhibition, and pain regulation [38], these structural alterations may imply that children lack effective emotional buffering and cognitive control when facing persistent somatic discomfort, thereby increasing subjective pain experience. Moreover, the severity of conduct disorder symptoms was significantly negatively correlated with a lower CT of the right anterior insula. Previous studies have shown that structural abnormalities of the aIns are closely associated with impulsivity, aggression, and antisocial behavior [43, 44]. In children with MP, long-term negative affect and painful experiences may compromise the structural integrity of the aIns, further impairing its role in emotional regulation and social behavior control, and manifesting as more severe conduct problems [45]. This suggests that pain is not merely a somatic issue but may also increase psychosocial and behavioral risks through neural circuit alterations. This study also found that disorders of excessive somnolence were negatively correlated with CT of the right aIns, while sleep hyperhidrosis was positively correlated with CSA of the left ACC. Existing evidence has demonstrated that the aIns is closely related to arousal, fatigue, and autonomic regulation, and its structural abnormalities may impair the processing of arousal signals, leading to daytime sleepiness and fatigue [46, 47]. On the other hand, emotional sweating is considered to be mainly regulated by the limbic system, with the amygdala, cingulate cortex, and hypothalamus projecting to preganglionic sympathetic neurons in the intermediolateral nucleus of the spinal cord, thereby triggering sweat gland activity [48]. Thus, structural alterations of the ACC may indicate its enhanced or dysregulated involvement in emotional autonomic responses, which can manifest as excessive sweating during sleep.

These findings in this study revealed that children with MP exhibited structural changes in brain nodes involved

in the pain matrix, including the ACC, MFG, SFG, and aIns. These findings highlighted the importance of targeting network-level abnormalities in the treatment of pediatric pain. Previous research has found that neuromodulatory techniques, such as transcranial magnetic stimulation, could be used to modulate activity in these affected regions, potentially restoring balance in the pain processing networks and improving clinical outcomes [49, 50]. Additionally, behavioral interventions like cognitive behavioral therapy and mindfulness-based interventions can specifically target brain networks involved in cognitive control and emotional regulation [51]. These interventions could help improve pain perception and emotional regulation by addressing dysfunctions of these brain regions. We believe that personalized, network-based interventions could offer more targeted and effective treatments for children with MP, providing new insights for the clinical management of chronic pain in this population.

This study has several limitations that should be acknowledged. First, this study primarily focused on structural indices such as CT and CSA, without incorporating functional connectivity, white matter structures, or multimodal imaging data, which may limit the comprehensiveness of understanding pain-related neural mechanisms in children. Second, though CBCL pain-related items have been previously used for the classification of chronic pain, they were not equivalent to clinical pain diagnoses. Future research should validate the classification of chronic pain using standardized diagnostic criteria. Third, pain-related items, such as pain duration, pain frequency and pain severity, were not available for children with MP in this study. Future research should provide details about these pain-related items and make sure all cases have similar level of these items, further examine potential correlations between pain-related items and brain structural indices. Furthermore, the small effect sizes in this study may limit the generalizability of our finding. However, the small effect sizes didn't imply clinical irrelevance, particularly in the context of pediatric chronic pain, where even minor changes in brain structure could lead to significant long-term consequences. Moreover, these changes were significantly associated with biopsychosocial characteristics, such as general somatic symptoms, conduct disorder symptoms, and sleep quality. These findings suggested that these small effects still have important clinical relevance, especially when considering the long-term impact of pain on the brain [5, 52]. We suggest that future research should employ longitudinal designs with large sample sizes to investigate the cumulative effects of these small structural changes and their clinical significance over time, which can provide a more comprehensive understanding of the long-term effects of chronic pain on the developing brain and offer stronger support for early interventions.

Conclusions

In summary, children with MP showed both lower CSA and CT and altered nodal network measures in widespread regions involved in the pain matrix, which was further associated with biopsychosocial characteristics. These findings shed light on the impact of MP on the brain's structural organization in children and the involvement of hubs of the pain matrix. These findings suggest that MP may induce structural alterations and SCNs in brain regions involved in the pain matrix, which is associated with pain processing and affects pain perception and emotional regulation in children. Further personalized treatments targeting these brain regions may help alleviate pain and related symptoms while improving psychosocial functioning in this patient population.

Abbreviations

SCNs	Structural covariance networks
MP	Multisite pain
CT	Cortical thickness
CSA	Cortical surface area
ACC	Anterior cingulate cortex
MFG	Middle frontal gyrus
SFG	Superior frontal gyrus
aIns	Anterior insula
BMI	Body mass index
ABCD	Adolescent Brain Cognitive Development
CBCL	Child Behavior Checklist

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02174-1.

Supplementary Material 1.

Acknowledgements

We thank the Adolescent Brain Cognitive Development (ABCD) Study for sharing this dataset for this study. And we also thank the Home for Researchers editorial team (www.home-for-researchers.com) for the language editing service.

Authors' contributions

Zusheng Cheng: Conceptualization, Methodology, Data curation, Methodology, Writing - reviewing and editing; Cheng Xu: Conceptualization, Methodology, Data curation, Writing - original draft; Cheng Zhu: Conceptualization, Methodology, Data curation, Writing - original draft; Hui Xu: Conceptualization, Methodology, Data curation, Formal analysis, Software, Visualization, Investigation, Supervision, Funding, Writing - original draft, Writing - Review & Editing.

Funding

This study was funded by the Key Research Center of Philosophy and Social Sciences of Zhejiang Province（Institute of Medical Humanities, Wenzhou Medical University).

Data availability

The data that support the findings of this study are available on request from the corresponding authors.

Declarations

Ethics approval and consent to participate

This study was approved and consented by the Ethics Committee of Wenzhou Medical University in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 5 September 2025 / Accepted: 30 September 2025
Published online: 30 October 2025

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