

Research report

Altered cortical thickness and structural covariance networks in chronic low back pain

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ABSTRACT

Background: Despite regional brain structural changes having been reported in patients with chronic low back pain (CLBP), the topological properties of structural covariance networks (SCNs), which refer to the organization of the SCNs, remain unclear. This study applied graph theoretical analysis to explore the alterations of the topological properties of SCNs, aiming to comprehend the integration and separation of SCNs in patients with CLBP.

Methods: A total of 38 patients with CLBP and 38 healthy controls (HCs), balanced for age and sex, were scanned using three-dimensional T1-weighted magnetic resonance imaging. The cortical thickness was extracted from 68 brain regions, according to the Desikan–Killiany atlas, and used to reconstruct the SCNs. Subsequently, graph theoretical analysis was employed to evaluate the alterations of the topological properties in the SCNs of patients with CLBP.

Results: In comparison to HCs, patients with CLBP had less cortical thickness in the left superior frontal cortex. Additionally, the cortical thickness of the left superior frontal cortex was negatively correlated with the Visual Analogue Scale scores of patients with CLBP. Furthermore, patients with CLBP, relative to HCs, exhibited lower global efficiency and small-worldness, as well as a longer characteristic path length. This indicates a decline in the brain's capacity to transmit and process information, potentially impacting the processing of pain signals in patients with CLBP and contributing to the development of CLBP. In contrast, there were no significant differences in the clustering coefficient, local efficiency, nodal efficiency, nodal betweenness centrality, or nodal degree between the two groups.

Conclusions: From the regional cortical thickness to the complex brain network level, our study demonstrated changes in the cortical thickness and topological properties of the SCNs in patients with CLBP, thus aiding in a better understanding of the pathophysiological mechanisms of CLBP.

Abbreviations: CLBP, chronic low back pain; DLPFC, dorsolateral prefrontal cortex; Σ , small-worldness; E_{glob} , global efficiency; E_{loc} , local efficiency; C_p , clustering coefficient; SCNs, structural covariance networks; HCs, healthy controls; L_p , characteristic path length; VAS, Visual Analogue Scale; ODI, Oswestry Disability Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; 3D-T1, Three-dimensional T1-weighted imaging; TR, Repetition time; TE, Echo time; FOV, Field of View; CAT12, Computational Anatomy Toolbox; SPM 12, Statistical Parametric Mapping; PBT, projection-based thickness; ROIs, regions of interest; BCT, Brain Connectivity Toolbox; SPSS 27, Social Sciences version 27; FWEc, cluster-level family-wise error; AUC, area under the curve; 95 %CI, 95 % confidence interval; FDR, false discovery rate.

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1. Introduction

The mean life-time prevalence of low back pain is estimated to be 38.9 % (Hoy et al., 2012). When it lasts longer than 12 weeks, it is called chronic low back pain (CLBP) (Koes et al., 2010), which is one of the most common and costly musculoskeletal problems in the current society (Andersson, 1999). CLBP is also the leading cause of disability globally (Hartvigsen et al., 2018). Elucidating the mechanisms of CLBP is an important goal to alleviate the economic and social burden.

Despite the underlying pathological mechanism of CLBP not being fully understood, neuroimaging studies have identified brain structural alterations in patients with CLBP (Apkarian et al., 2004; Dolman et al., 2014; Ivo et al., 2013; Kong et al., 2013; Kregel et al., 2015; Luchtmann et al., 2014; Mao et al., 2013; Seminowicz et al., 2011; Ung et al., 2014; Yuan et al., 2017). For example, Apkarian et al. (2004) observed reductions in gray matter volume in the bilateral dorsolateral prefrontal cortex (DLPFC) and right thalamus; Meanwhile, Ivo et al. (2013) noticed a lower gray matter density in the middle cingulate gyrus, thalamus, and DLPFC; Moreover, Seminowicz et al. (2011) reported less cortical thickness in several brain regions, such as the left DLPFC, bilateral anterior insula/frontal operculum, and left primary somatosensory cortex. These findings indicate that alterations in brain structure may be involved in the development of CLBP.

The human brain is considered to be a complex network with topological properties (Bullmore and Sporns, 2009). These properties are usually identified and characterized using the graph theory method (Bassett and Bullmore, 2009; He and Evans, 2010). Graph theory is a branch of mathematics that uses nodes and edges to represent networks as elements and their pairwise interconnections (Sporns, 2018), providing information about how segregated or integrated the network is (Rubinov and Sporns, 2010). This offers a novel insight into investigating the alteration of the whole brain. Graphical metrics are composed of global and local metrics, including small-worldness (Σ), global efficiency (E_{glob}), local efficiency (E_{loc}), and clustering coefficient (C_p), etc. (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

A structural covariance network (SCN) of the brain can be constructed by utilizing the cortical thickness or gray matter volume of the subjects (Alexander-Bloch et al., 2013; Zielinski et al., 2010). By employing the graph theory method on the SCN, we can delve into the topological organization of the whole brain (He et al., 2007; Lv et al., 2010). This method can provide a wide range of network-level information, thus enhancing and supplementing traditional brain structure MRI results (Kuang et al., 2020). So far, the graph theory method has been used to analyze the topological properties of SCNs in several pain disorders, such as the alterations in the topological properties (E_{glob} , E_{loc} , and C_p , etc.) in patients with upper limb amputees, chronic migraine, cervical spondylotic myelopathy, and cluster headache, etc. (Bao et al., 2023; DeSouza et al., 2020; Kuang et al., 2020; Lee et al., 2022; Li et al., 2023; Y.L. Li et al., 2021). These findings demonstrated abnormal segregation and integration of brain networks in patients suffering from pain. However, to the best of our knowledge, no research has been conducted that applies the graph theory method to analyze the alterations of the topological properties of SCNs in patients with CLBP.

Therefore, in our current research, we first compared the cortical thickness between patients with CLBP and healthy controls (HCs). Then, brain cortical thickness covariance networks were constructed for patients with CLBP and HCs. The graph theory method was further used to compare the differences in the network topological properties (E_{glob} , E_{loc} , Σ , C_p , characteristic path length (L_p), nodal efficiency, nodal betweenness centrality, and nodal degree) between the two groups.

2. Methods

2.1. Participants

During the period from January 2021 to August 2022, a total of 38

patients with CLBP and 38 age- and sex-balanced HCs were recruited from the Affiliated Hospital 6 of Nantong University (Yancheng Third People's Hospital). The Ethics Committee of Yancheng Third People's Hospital gave its approval for this study (2020–79), and all participants were required to sign informed consent prior to the research.

To be included in this study, patients with CLBP should fulfill the following criteria: (1) pain that has continued or fluctuated over a period of three months or more (Last and Hulbert, 2009); (2) diagnosis of lumbar disc herniation confirmed through clinical manifestations, physical signs, and lumbar CT/MRI imaging; (3) no history of surgical treatment for pain; (4) Visual Analogue Scale (VAS) scores of at least 3 points; (5) no prior history of neurological or psychiatric conditions, major systemic illnesses, head trauma, or comas, as well as other chronic pain disorders; (6) right-handedness. Meanwhile, the requirements for HCs to be recruited were: (1) previous good health, with no record of any neurological issues, diabetes, hypertension, hyperlipidemia, mental health conditions, long-term smoking, alcoholism, or hormone drug usage, etc.; (2) right-handedness. Participants would not be included if they: (1) could not finish MRI scans; (2) had organic brain injuries; (3) had contraindications that prevent MR scanning.

2.2. Clinical measures

Prior to the MRI scan, all participants were asked to complete the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) in order to determine their anxiety and depression status (Fairbank et al., 1980; Huskisson, 1974). Both the SAS and SDS consist of 20 items, each scored on a scale of 1–4 points. The total score for each item is multiplied by 1.25 and rounded to determine the standard score. A standard score of 50 or higher suggests that the individual is experiencing anxiety or depression. Moreover, before scanning, patients with CLBP must fill out the VAS and Oswestry Disability Index (ODI) to evaluate their current pain intensity and the extent of functional impairment (Fairbank et al., 1980; Huskisson, 1974). Using the VAS, patients with CLBP were asked to mark a 10 cm line to represent their pain intensity. The further they marked along the line, the greater the intensity of their pain. Meanwhile, the ODI, which includes pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling, was utilized to assess the level of dysfunction in patients. A higher score indicates a more significant level of functional impairment in the patient.

2.3. MRI scanning and imaging acquisition

Three-dimensional T1-weighted (3D-T1) structural imaging, using the following acquisition parameters: Repetition time (TR) = 7.5 ms, Echo time (TE) = 2.8 ms, Field of View (FOV) = 24 cm×24 cm, Slice thickness = 1.0 mm, Number of slices = 152, Flip Angle = 15°, Voxel size = 0.5×0.5×1 mm, was conducted on all participants in our hospital using a 3.0 Tesla scanner (Discovery 750w, GE, USA).

2.4. Data preprocessing

Initially, the researcher visually examined the original image to ensure there were no issues with motion artifacts, contrast, or incomplete scans. Subsequently, the dcm2nii software (<http://www.mricro.com>) was utilized to transform all the original DICOM images into NIfTI format. Then, preprocessing of all the T1-weighted images was done using the Computational Anatomy Toolbox (CAT12, <http://www.neuro.uni-jena.de/cat/>), within the Statistical Parametric Mapping (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/>), based on MATLAB (R2020b, www.mathworks.com/). The image preprocessing process using CAT12 includes: (1) bias-field correction, (2) skull stripping, (3) alignment with the Montreal Neurological Institute standard template, (4) segmentation into gray matter, white matter, and cerebrospinal fluid, and, (5) smoothing with a 15 mm full-width at half-maximum

isotropic Gaussian kernel for cortical thickness. The cortical thickness, defined as the distance between the gray matter and white matter surfaces, was computed through a fully automated process utilizing the projection-based thickness (PBT) measurement method (Dahnke et al., 2013).

2.5. SCNs construction

Utilizing the Desikan-Killiany Atlas, the cerebral cortex was divided into 68 regions of interest (ROIs) (Desikan et al., 2006). Subsequently, the CAT12 was employed to extract cortical thickness values for each ROI. The Brain Connectivity Toolbox (BCT) in the MATLAB environment was then used to construct SCNs (Rubinov and Sporns, 2010). Regression analysis was employed to eliminate the effects of age and sex on the association with cortical thickness values. Additionally, the anxiety and depression statuses of the subjects were also taken into account and regressed out from the relation to cortical thickness values in order to eliminate their influence. After that, a 68×68 specificity matrix of the correlation coefficients of cortical thickness between all pairs of cortical regions in each group was calculated. Excluding self-connections, negative correlations were set to zero, as they were not mediated by direct fiber pathways (Gong et al., 2012). For the predetermined sparsity level ($S = 0.06: 0.01: 0.5$), the correlation coefficients above the threshold were retained and all others were set to zero. Sparsity is the proportion of the actual number of edges in a network to the maximum number of edges that could potentially exist in the network (Achard and Bullmore, 2007).

2.6. Graph theoretical analysis based on the SCNs

Graph theoretical analysis consisted of two components: global network analysis and local network analysis. We conducted an analysis of five global indicators and three local indicators, including:

(1) C_p : The network C_p size is indicative of the level of clustering and connectivity within the network, with larger coefficients suggesting a higher degree of clustering and connectivity (Huangfu et al., 2023).

(2) L_p : The network L_p is defined as the average shortest path length between all pairs of nodes in the network, thus providing a metric for the network's overall integration (Wu et al., 2021).

(3) Σ : Σ is calculated as C_p divided by L_p , which represents the balance between network segregation and integration (Watts and Strogatz, 1998).

(4) E_{glob} : E_{glob} primarily describes the brain network's capacity for global information transmission, with a higher global efficiency indicating quicker information transfer between network nodes (Zhang et al., 2020).

(5) E_{loc} : E_{loc} is a measure of how well a network can recover from faults and disruptions, and it is calculated by averaging the local efficiency of all nodes in the network (Chen et al., 2024).

(6) Nodal efficiency: Nodal efficiency refers to how efficiently a node in the network transfers information in parallel (Rubinov and Sporns, 2010).

(7) Nodal betweenness centrality: Nodal betweenness centrality measures how much a node influences the flow of information between other nodes in the network (X. Li et al., 2021).

(8) Nodal degree: The level of nodal degree in a network indicates the extent to which a node is connected to other nodes, reflecting its ability to communicate information within the network (Lv et al., 2021).

2.7. Statistical analysis

The Shapiro-Wilk test was used to determine if the ages and clinical scale scores for all subjects followed a normal distribution. If the data satisfied a normal distribution, the Student's t -test was used to evaluate the differences between the two groups. Otherwise, the Mann-Whitney U test was used. Additionally, a Chi-square test was used to evaluate

the sex differences between the two groups. The analyses were carried out on Statistical Package for the Social Sciences version 27 (SPSS 27).

The two-sample t -test in SPM12 was used to compare the cortical thickness between two groups, with age, sex, SAS scores, and SDS scores as covariates. For the multiple comparisons, cluster-level family-wise error (FWE) correction was employed with a threshold of $p < 0.05$. Furthermore, Pearson or Spearman correlation analyses were utilized to measure the correlations between the average cortical thickness values of the positive brain regions and the clinical scales and pain duration.

The permutation test was employed in graph theoretical analysis to assess differences between topological properties in SCNs of two groups. To start, we calculated the topological properties of the real-world SCNs for two groups with different sparsity. Subsequently, all subjects were randomly reassigned to a new permutation group, and the topological properties within the group were determined. The random permutations were repeated 2000 times to obtain 2000 random SCNs and their related topological properties. Meanwhile, we compared the area under the curve (AUC) of topological properties with different sparsity, and then compared the AUC differences in topological properties between the two groups in the real-world SCNs with 2000 random SCNs. A difference greater than 95 % confidence interval (95 %CI) between the two groups was considered a significant difference. Moreover, false discovery rate (FDR) correction was utilized to make multiple comparisons between nodes ($p < 0.05$).

3. Results

3.1. Demographic and clinical characteristics

A total of 76 subjects were included in this study (38 patients with CLBP and 38 HCs). A summary of the demographic and clinical characteristics of the participants was available in Table 1. There were no considerable differences in age or sex between the two groups. However, patients with CLBP had significantly higher SAS and SDS scores than the HCs.

3.2. Group differences in cortical thickness between patients with CLBP and HCs

Our research demonstrated that, relative to HCs, patients with CLBP experienced a significant thinning of the cortical thickness in the left superior frontal cortex ($p < 0.05$; FWE corrected; Fig. 1 and Table 2).

3.3. Correlations between cortical thickness and clinical scale scores

Results of the correlation analysis indicated a negative relationship between the cortical thickness values of the left superior frontal cortex

Table 1
Demographic information and clinical data.

| | CLBP | HCS | <i>p</i> values |
|-----------------------|------------------|----------------|---------------------|
| N | 38 | 38 | - |
| Age (years) | 60 (54.8–66.0) | 58.5 (52.5–68) | 0.67 ^a |
| Sex (male/female) | 19/19 | 22/16 | 0.49 ^b |
| Pain duration (years) | 4.5 (1, 10) | - | - |
| VAS | 8.2 (7.6–8.6) | - | - |
| ODI | 64 (57.0–68.0) | - | - |
| SAS | 56.3±7.5 | 39.8±3.6 | <0.001 ^c |
| SDS | 58.0 (47.8–62.0) | 38.7±3.9 | <0.001 ^a |

Data are represented as mean ± SD or median (quartiles).

Abbreviations: CLBP: Chronic low back pain; HCs: Healthy controls; VAS: Visual Analogue Scale; ODI: Oswestry Disability Index; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

^a The Mann-Whitney U test was used to obtain the *p* values.

^b The Chi-square test was used to obtain the *p* values.

^c The Student's t -test was used to obtain the *p* values.

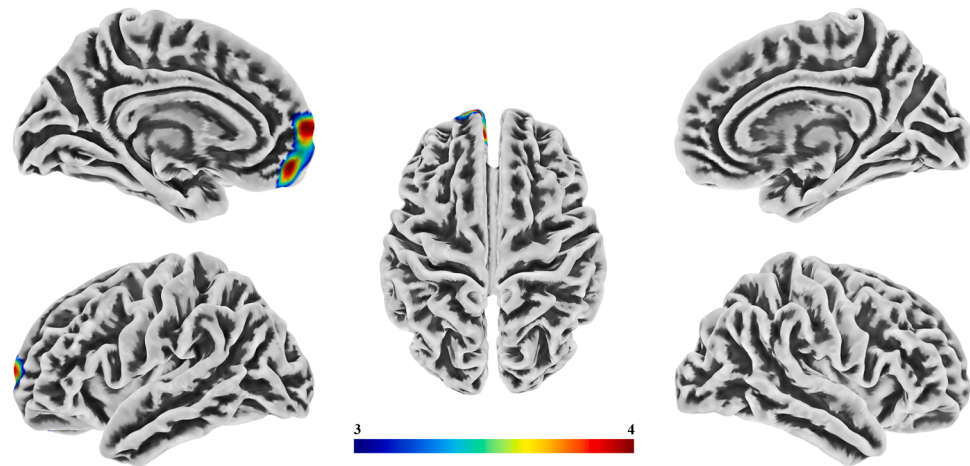


Fig. 1. Group differences in cortical thickness between patients with CLBP and HCs. The left superior frontal cortex of patients with CLBP was significantly thinner than that of the HCs. Abbreviations: CLBP: Chronic low back pain; HCs: Healthy controls.

Table 2
Group differences in cortical thickness between patients with CLBP and HCs.

| Hemisphere | Region | Cluster size | <i>p</i> value (FWEc, <i>p</i> < 0.05) |
|------------|------------------|--------------|--|
| Left | superior frontal | 235 | 0.0001 |

Anatomical labels were based on the Desikan–Killiany atlas.
Abbreviations: CLBP: Chronic low back pain; HCs: Healthy controls; FWEc: Cluster-level family-wise error.

and VAS scores in patients with CLBP (Fig. 2), while there was no significant correlation between the cortical thickness of the left superior frontal cortex and the ODI score or pain duration.

3.4. Group differences in global SCNs analysis between patients with CLBP and HCs

Global network analysis indicated that patients with CLBP had lower E_{glob} , Σ , and longer L_p than those of the HCs ($p < 0.05$, Fig. 3, and Fig. 4), yet no significant differences were seen in C_p or E_{loc} between the two groups.

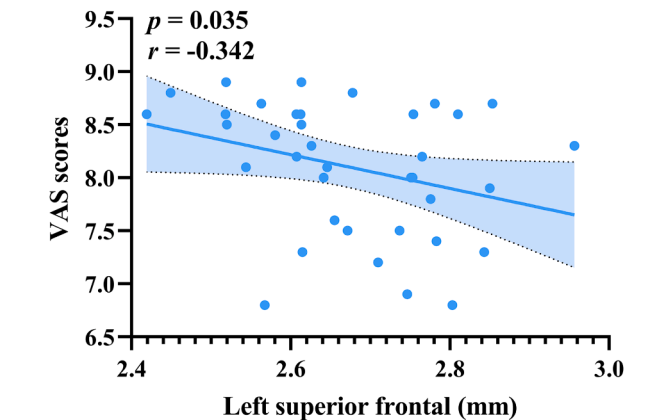


Fig. 2. Correlations between cortical thickness and clinical scale scores. Results of the correlation analysis revealed that the cortical thickness of the left superior frontal cortex had a negative association with VAS scores in patients with CLBP. Abbreviations: VAS: Visual Analogue Scale; CLBP: Chronic low back pain.

3.5. Group differences in regional SCNs analysis between patients with CLBP and HCs

Results from the analysis of the local network suggested that there was no significant difference between the two groups in terms of nodal efficiency, nodal betweenness centrality, or nodal degree (all $p > 0.05$; FDR corrected).

4. Discussion

As far as we know, this was the first study to investigate the alterations of the topological properties of the SCNs using the graph theory analysis in patients with CLBP. The results of our study were as follows: (1) compared to HCs, patients with CLBP exhibited less cortical thickness in the left superior frontal cortex. Moreover, a negative correlation was observed between the VAS scores and the cortical thickness values of the left superior frontal cortex in patients with CLBP. (2) patients with CLBP further showed lower E_{glob} and Σ as well as longer L_p , relative to HCs.

We identified less cortical thickness in the left superior frontal cortex in patients with CLBP compared to HCs. The superior frontal cortex is associated with emotional regulation and cognitive control (Frank et al., 2014; Niendam et al., 2012). It is thought to be involved in the regulation of pain perception and the processing of pain emotions and cognition (Chatterjee et al., 2023). Our results, in accordance with the research conducted before, showed that the gray matter volume of the left superior frontal cortex was significantly lower in patients with CLBP (Asada et al., 2022). Meanwhile, other pain disorders also show a cortical thinning of the left superior frontal cortex, such as cervical spondylosis, persistent post-traumatic headache, and new daily persistent headache (Chong et al., 2018; Szabo et al., 2022; Woodworth et al., 2019). Moreover, a previous study identified functional connectivity impairments of the left superior frontal cortex in patients with CLBP (Kong et al., 2013). Other pain disorders have also been seen to show functional changes in the left superior frontal cortex using resting-state fMRI techniques (Huang et al., 2019; Tsai et al., 2018; J. Yang et al., 2023; Zhang et al., 2021). For instance, J. Yang et al. (2023) reported a lower fractional amplitude of low-frequency fluctuation in the left superior frontal cortex in patients with toothache compared to HCs. Tsai et al. (2018) identified a lower functional connectivity between the left superior frontal cortex and left precentral in patients with left trigeminal neuralgia. These abnormal functional changes of the left superior frontal cortex may be linked to the structural alterations of the left superior frontal cortex.

Additionally, results of the correlation analysis indicated that the

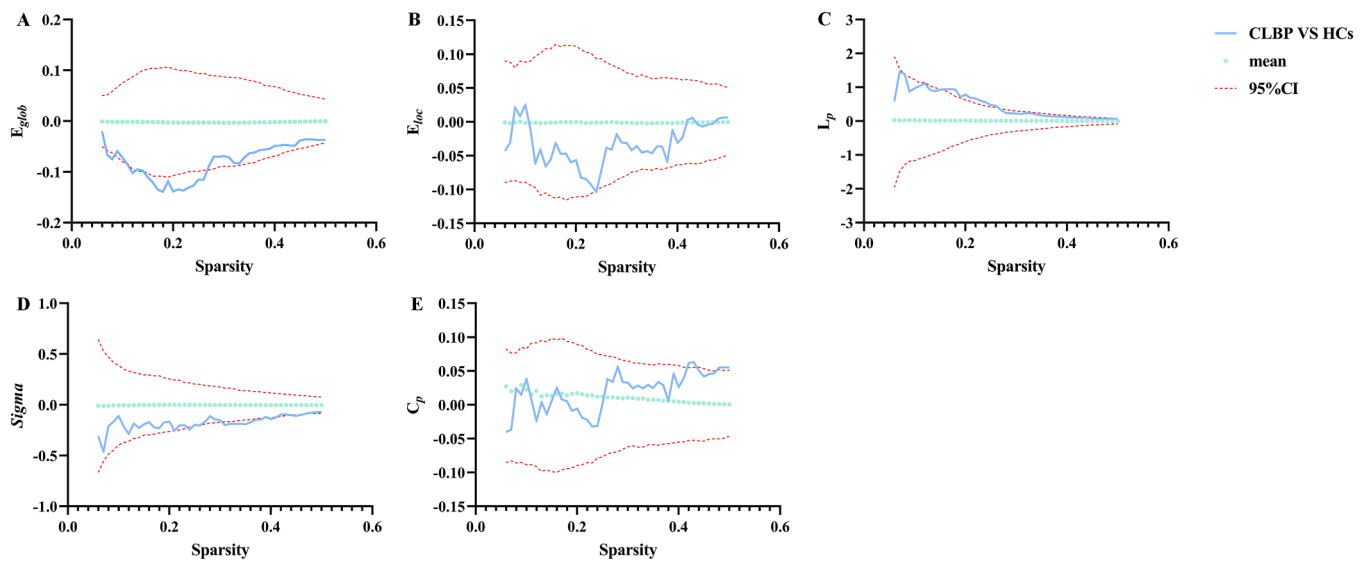


Fig. 3. Differences in global network properties at different sparsity levels between patients with CLBP and HCs. (A) E_{glob} ; (B) E_{loc} ; (C) L_p ; (D) Σ ; (E) C_p . Patients with CLBP had lower E_{glob} , Σ , and a longer L_p than HCs. The green • indicates intergroup variations in the permutation random SCNs, while the red dash lines represent 95 %CIs. The blue solid lines illustrate intergroup discrepancies of real SCNs. Blue solid lines falling outside the 95 % CIs signify that the intergroup difference of real SCNs was significant at $p < 0.05$, thereby demonstrating a significant difference between CLBP and HCs. The positive values indicate CLBP > HCs, and negative values indicate CLBP < HCs. Abbreviations: CLBP: Chronic low back pain; HCs: Healthy controls; SCNs: Structural covariance networks; 95 %CIs: 95 % confidence intervals; E_{glob} : Global efficiency; E_{loc} : Local efficiency; L_p : Characteristic path length; Σ : Small-worldness; C_p : Clustering coefficient.

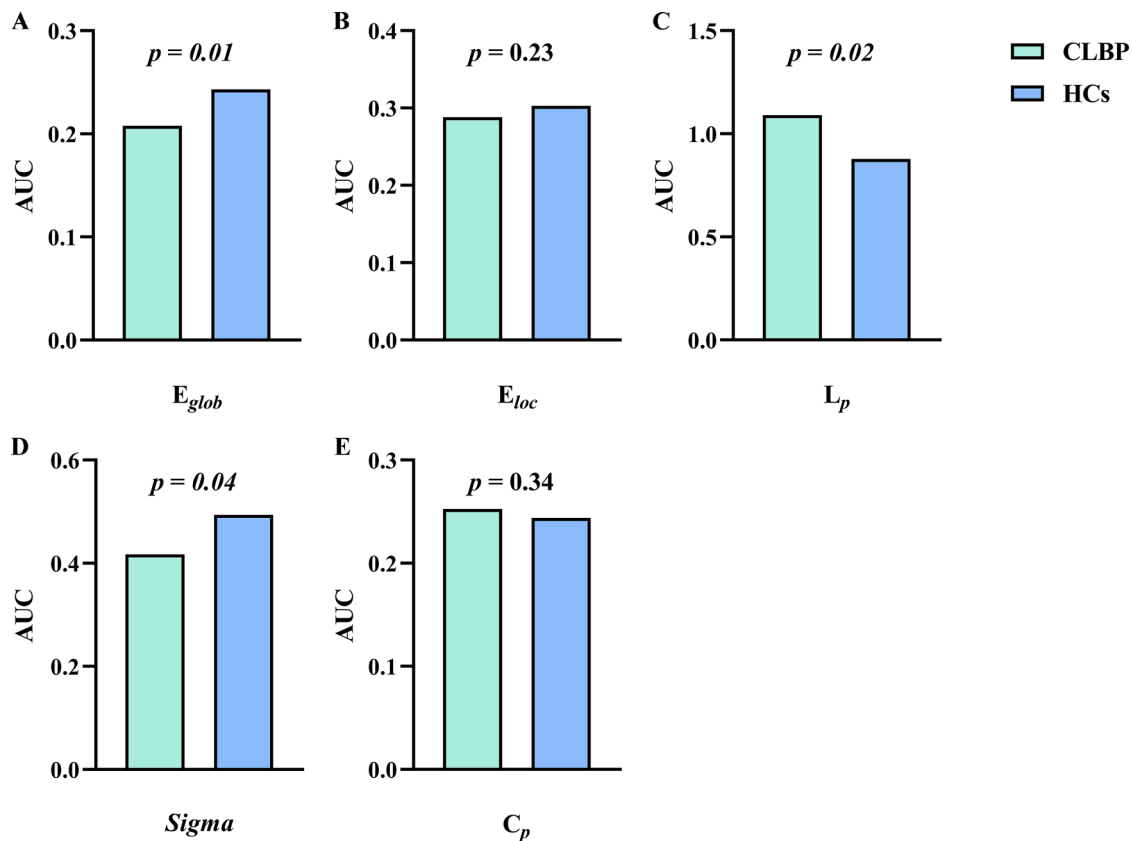


Fig. 4. Differences in global network properties between patients with CLBP and HCs. (A) E_{glob} ; (B) E_{loc} ; (C) L_p ; (D) Σ ; (E) C_p . Abbreviations: CLBP: Chronic low back pain; HCs: Healthy controls; AUC, area under the curve; E_{glob} : Global efficiency; E_{loc} : Local efficiency; L_p : Characteristic path length; Σ : Small-worldness; C_p : Clustering coefficient.

cortical thickness of the left superior frontal cortex had an inverse relationship with the VAS scores, suggesting that thinning of the left superior frontal cortex was associated with higher pain levels in patients

with CLBP. Research has shown that repetitive transcranial magnetic stimulation is an effective treatment for patients with phantom limb pain (Scibilia et al., 2018). Further research using this approach to

stimulate the left superior frontal cortex may relieve CLBP.

Moreover, we identified alterations in the topological properties of their SCNs in patients with CLBP. Patients with CLBP demonstrated lower E_{glob} , lower Σ , and longer L_p than those in HCs. E_{glob} of a network reveals its capability for parallel information transmission, and a higher E_{glob} indicates a faster rate of information transmission (Li et al., 2022). L_p is a widely-utilized metric of integration in the network, representing the average shortest path length between all pairs of nodes in the network (Rubinov and Sporns, 2010; Watts and Strogatz, 1998). Σ evaluates the extent to which a graph displays small-world properties, meaning that most nodes are not directly connected, yet can be accessed from any starting point with a limited number of edges (Páscoa Dos Santos et al., 2023). Abnormalities in these topological properties of patients with CLBP demonstrate a decline in their brains' capacity to transmit and process information, potentially influencing their pain tolerance and pain processing capabilities. Comparable alterations in the topological properties of SCNs have been observed in other pain diseases (Bao et al., 2023; DeSouza et al., 2020; Kuang et al., 2020; Li et al., 2023; Y.L. Li et al., 2021). For instance, in comparison with HCs, patients with menstrually-related migraine and those with chronic migraine exhibited a lower E_{glob} than HCs, and those with menstrually-related migraine were also found to have a longer L_p (DeSouza et al., 2020; Li et al., 2023). Meanwhile, patients with cervical spondylotic myelopathy, carpal tunnel syndrome, and upper limb amputees demonstrated a smaller Σ (Bao et al., 2023; Kuang et al., 2020; Y.L. Li et al., 2021). Moreover, our findings on the topological properties of SCNs in patients with CLBP partially overlapped the results of a study on the topological characteristics of their functional networks (H.J. Yang et al., 2023). Compared to HCs, patients with CLBP showed lower E_{glob} and Σ , and longer L_p (H.J. Yang et al., 2023). Similar abnormal alterations of the topological properties of functional networks have also been observed in patients with lower back pain, which showed that, relative to HCs, patients with lower back pain exhibited a longer L_p as well as a lower E_{glob} (Liu et al., 2018). This suggests that there may be a correlation between the SCNs and functional networks in patients with CLBP. However, it is essential to conduct future simultaneous research on the SCNs and functional networks of patients with CLBP to verify this correlation.

There was no denying that our research was not without limitations. This cross-sectional study cannot establish a cause-and-effect relationship between cortical thickness, SCN changes, and CLBP. Meanwhile, due to the limited sample size in this study, the stability of the results may be compromised. Moreover, we did not take into account the effect of opioids in our study; however, since the utilization of opioid analgesics in China is much lower than the global average, we assume that this will not have a major influence on our findings (Huang et al., 2020). Finally, our research was limited to examining alterations in the structural network of patients with CLBP, without exploring any changes in the functional network. Further investigation is necessary to gain a better understanding of this topic.

5. Conclusions

To summarize, our research established that patients with CLBP had less cortical thickness in the left superior frontal cortex, which was linked to their pain intensity. Most notably, this research has, for the first time, established the topological characteristics of the SCN alterations in patients with CLBP. Our results demonstrated that the integration ability and efficiency of the brain structural network in CLBP patients were impaired. These findings contribute to a better understanding of the pathophysiological mechanisms of CLBP and provide a novel insight into the treatment of CLBP.

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CRediT authorship contribution statement

Wen-Hui Li: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Si-Yu Gu:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Feng-Chao Shi:** Writing – original draft, Project administration, Investigation, Data curation. **Shu Wang:** Writing – original draft, Investigation, Formal analysis, Data curation. **Cheng-Yu Wang:** Formal analysis, Data curation. **Xin-Xin Yao:** Formal analysis, Data curation. **Yi-Fan Sun:** Formal analysis, Data curation. **Chuan-Xu Luo:** Formal analysis, Data curation. **Wan-Ting Liu:** Formal analysis, Data curation. **Jian-Bin Hu:** Formal analysis, Data curation. **Fei Chen:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Ping-Lei Pan:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors reported no conflicts of interest for this work.

Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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