Altered Brain Functional Network Dynamics in Classic Trigeminal Neuralgia: A Resting-state Functional Magnetic Resonance Imaging Study

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Abstract

Background: Accumulating studies have indicated a wide range of brain alterations in structure and function of Classic trigeminal neuralgia (CTN). Given the dynamic nature of pain experience, the exploration of temporal fluctuations in interregional activity covariance may enhance the understanding of pain process in brain. The present study aimed to characterize the temporal features of functional connectivity (FC) states as well as topological alteration in CTN.

Methods: Resting-state fMRI (rs-fMRI) and three-dimensional T1-weighted images were obtained from 41 CTN patients and 43 matched healthy controls (HC). After group independent component analysis, sliding window based dynamic functional network connectivity (dFNC) analysis was applied to investigate specific FC states and related temporal properties. Then the dynamics in whole brain topological organization were estimated by calculating coefficient of variation of graph-theoretical properties. The further correlation analysis were performed between all those measurements and clinical data.

Results: Two distinct states were identified, of which the state 2, characterized by complicate coupling between default mode network (DMN) and cognitive control network (CC) and tight connections within DMN, expressed more in CTN patients, presented as increased fractional windows and dwell time. Also, patients switched less frequently between states than HC. Regarding to dynamic topological analysis, disruptions in global graph-theoretical properties (including network efficiency and small-worldness) were observed in patients, coupled with decreased variability in nodal efficiency of anterior cingulate cortex (ACC) in salience network (SN) and thalamus, caudate in subcortical network (SC). The variation of topological properties showed negative correlation with disease duration and attack frequency.

Conclusions: The present study indicated disrupted flexibility of brain topological organization under persistent noxious stimulation and further highlighted the important role of “dynamic pain connectome” regions (including DMN/CC/SN) in pathophysiology of CTN from temporal fluctuation aspect. Additionally, the findings provided supplementary evidence for current knowledge about the aberrant cortical-subcortical interaction in pain development.

Background

Classic trigeminal neuralgia (CTN) is a chronic pain disorder, characterized by unilateral paroxysmal electric shock-like or stabbing painful affliction of the face, which limited to the trigeminal territory[1]. With disease progression, episodes of pain occurs more frequently and sustainedly, which seriously effects physical and psychological health[2]. CTN has been generally attributed to compression at the nerve root entry zone by intracranial vascular[3]. However, accumulating evidence suggests that the involvement of centrally mediated facilitation of pain processing or reduced descending inhibitory mechanisms play an important part in the CTN pathogenesis[4, 5]. Therefore, the central nervous system mechanism of CTN has gradually become a research focus.

In order to noninvasively map brain activity, resting state magnetic resonance imaging (rs-fMRI) has been widely used and further revealed several critical brain regions of CTN, including the default-, the salience-, the subcortical- and the sensorimotor network[6–11]. All those regions are closely related to pain perception, modulation, the cognitive-affective interaction, and motor control[12]. Aberrant information transfer within and across brain networks and maladaptive brain plasticity in CTN patients may underpin disease pathogenesis[7]. To be noted, those rs-fMRI studies assumed that the brain connectivity pattern is stationary during scan sessions. However, the real brain activity is highly dynamic and condition-dependent[13]. Correspondingly, recent findings suggested that rsFC can fluctuate spontaneously on multiple time scales[14, 15].

As an intrinsically dynamic experience encoded by “pain connectome”[16], pain fluctuates spontaneously over times and is influenced by many dynamic factors[17–19]. It is the uncovering of dynamics in functional connectivity (FC) across time scales and its interaction with external factors that helps improve the understanding of the central pain processes[20]. Recently, one dynamic ReHo (dReHo) study detected temporal alteration about spontaneous neural activity in TN patients[21], but didn’t focus on changes in dynamic FC. Whereas dynamic functional network connectivity (dFNC) analysis can not only provide time-varying information of FC between resting-state connectivity networks (RSNs)[13], but also capture reproducible connectivity states and calculate temporal properties. By applied in chronic pain studies, such as migraine[22, 23], low back pain[24] and primary dysmenorrhea[25], dFNC has been indicated useful as potential biomarkers of pain and effective to provide insightful viewpoints of pathogenesis[26]. However, the exploration of changes of whole-brain dFNC pattern in CTN is limited.

Previously, some rs-fMRI studies using graph theory has attempted to characterize the global brain modularity as well as key nodal features in CTN to elucidate reorganization process of brain networks[8, 27]. Given that FC between brain regions is constrained by the brain topological organization[28], aberrant dFNC pattern may be additionally accompanied by altered dynamic topological properties.

In the present study, we applied sliding window approach based on rs-fMRI to investigate the time-varying characteristics of CTN patients. Specifically, CTN specific dFNC state was identified and diverse temporal properties were calculated to assess brain dynamics. Moreover, dynamic graph theoretic analysis was used to investigate the temporal changes of global and nodal topological organization. We hypothesized that CTN patients would show altered temporal properties coupled with aberrant network topological dynamics, which would be correlated with clinical characteristics.

Methods

Participants and clinical characteristics assessment

In total, this study included 43 patients with CTN matched for age, gender, education with 45 healthy controls (HCs). All patients were recruited from Lanzhou University Second Hospital and diagnosed according to the International Classification of Headache Disorders (ICDH-III)[2] by two experienced

neurologists. NVC were demonstrated for all patients on either MRI or during surgery. Inclusion criteria were: (1) the duration of disease was more than 1 years; (2) unilateral pain in the area innervated by one or more branches of the trigeminal nerve; (3) paroxysmal pain, described as electric shock-like, shooting or stabbing experience, was activated by trigger factors or in trigger areas; and (4) without obvious sensory deficits. Exclusion criteria were: (1) CTN with concomitant continuous pain; (2) had a previous surgical history, especially microvascular decompression (MVD) for CTN, or a history of head trauma; (3) suffered any other pain disorders or neuropsychiatric disease, (4) with metal implanted in the body, particularly metallic fixed dentures; and (5) abnormal MR manifestation (including severe white matter lesions with Fazekas grade 3 and evidence of multiple sclerosis or space-occupying lesions that indicate secondary TN)[9]. CTN patients all received medical treatment, of which the most is carbamazepine, the rest are mecobalamin or other medicine. No control measure about patients' treatment were taken. The research was approved by the Ethics Committee of Lanzhou University Second Hospital. According to the Declaration of Helsinki, written Consent was obtained from every participant after introduction about project for details.

The pain intensity of CTN patients was recorded with visual analogue scale (VAS) ranging from 0 (no pain) to 10 (extreme amount of pain). Patients were required to rate their pain intensity for the last 7 days by marking on the 100mm line of questionnaire, and then averaged score for a week. All questionnaires assessment were performed under the supervision of experimenters.

Magnetic resonance imaging data acquisition

Structural MRI and rs-fMRI data were acquired on a 3.0T Siemens Verio MRI system (Siemens Medical System, Erlangen, Germany) with an 8-channel head coil. During scanning, participants were instructed to stay awake and relaxed but to keep their eyes closed, with earplugs and foam padding used to attenuate noise and reduce head motion. High-resolution three-dimensional structural images were acquired using sagittal Magnetization Prepared Rapid Gradient echo sequence (field of view: 256×256 mm; matrix: 256 × 256; time of repetition = 1900 ms; time of echo = 2.93 ms; resolution = 1 × 1 mm; flip angle = 9°). The rs-fMRI images were acquired via an echo-planar imaging (EPI) sequence (180 volumes; 64 contiguous slices/volume; FOV: 192 × 192 mm; matrix: 64 × 64; spatial resolution = 3 × 3 × 3 mm; TR = 2000 ms; TE = 30 ms; flip angle = 90°). An experienced radiologist inspected the previous MR images of these participants to make sure that each patient was free with abnormalities as described in above exclusion criteria (5).

fMRI data preprocessing and head motion analysis

The rs-fMRI data were preprocessed with the toolbox for Data Processing & Analysis of Brain Imaging (DPABI, <http://rfmri.org/dpabi>)[29]. The first ten volumes of the functional images were discarded. The remaining volumes underwent slice-time correction, then were realigned to correct the motion between time points. Wherein, head motion parameters were computed by estimating the translation in each direction and the angular rotation on each axis for each volume. As a result, the participants with mean framewise displacement (FD) (Jenkinson) larger than 0.2 mm or head displacement more than 1.5 mm,

maximum rotation greater than 1.5° were excluded from the analysis. According to this exclusion criterion, two subjects of HC and two subjects of CTN were excluded. No significant intergroup differences were found in FD ($t = 1.09$, $p = 0.28$). The individuals fMRI data were co-registered to their structural images, followed by segmentation of the gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and normalization to the Montreal Neurological Institute (MNI) space. The normalized images were spatially smoothed with a 6 mm full-width at half-maximum Gaussian kernel.

GICA analysis and identification of independent components

After preprocessing, fMRI images with 170 volumes underwent group independent component analysis (GICA) to be decomposed into different RSNs by using the Group ICA of fMRI Toolbox software (version 4.0b; mialab.mrn.org/software/gift/)[30]. Two data reduction steps were performed in the principal component analysis[14]. First, we reduce the individuals data into 120 principal components, which preserved more than 99% of the variance. Next, we concatenated the reduced data of all participants across time and further reduced the data to 100 principal components using an expectation maximization algorithm[31]. The reliability and stability of the infomax ICA algorithm[32] was ensured by iterating 20 times in ICASSO implemented in GIFT[33] and using the most central run to reconstruct subject-specific time courses and spatial maps of each IC using the GICA back reconstruction algorithm[34]. The group ICs of the 20 runs were clustered to estimate their reliability, with values more than 0.8 were selected[35]. Through one sample t test across all subjects and for each IC, the t-map of ICs was obtained with a threshold of $t > \text{mean}(\mu) + 4\text{SD}(\sigma)$ [36]. Details about labels and spatial maps of each IC are presented in Figure S2, and the peak coordinates of ICs are shown in Table S1.

We identified 59 ICs from 100 ICs based on the following evaluation criteria: (1) IC should exhibit peak activations in grey matter; (2) low spatial overlap with known vascular, ventricular, motion, and susceptibility artifacts; (3) should have time courses dominated by low-frequency fluctuations (ratio of powers below 0.1 Hz to 0.15–0.25 Hz in spectrum)[37]. All 59 ICs were then sorted into different nine RSNs according to the spatial correlation values between their spatial maps and atlas used in previous studies[14] (Fig. 1A). Afterwards, additional postprocessing was applied to time courses of 59 ICs as described in Allen et al[14], including detrending, despiking using AFNI's 3dDespike algorithm, filtering using a fifth order Butterworth filter with a 0.15 Hz high frequencies cut-off, and finally regressing out the movement parameters.

dFNC estimation

We computed dFNC between the time courses (170 time points) of ICs using a sliding window approach, which was performed using the DFNC network toolbox in GIFT. A window size with 20-TR (40s) was chosen because previous studies have suggested that FC fluctuations at resting-state would be captured with windows of 30 ~ 60s[38]. We used a tapered window in steps of 1 TR, which was obtained by convolving a rectangle with a Gaussian ($\sigma = 3$) to localize the dataset at each time point. Finally, a total of

150 windows were obtained and 59×59 pairwise FC matrices by regularized precision matrix (inverse covariance matrix)[39] were computed in every window. The L1 norm penalty was imposed in the Graphical LASSO framework with 100 repetitions to promote sparsity in estimations[40]. With Fisher's z-transformation, the correlation values of pairwise functional matrices were converted to z-values to improve normality and comparability and then residualized with nuisance variables, including age and gender[36].

State clustering analysis

To assess the dFNC patterns that reoccur over time, k-means clustering was performed on all FC matrices for all participants. The k-means clustering algorithm was iterated 100 times with L1 distance (Manhattan distance) function to estimate the similarity between matrices[41]. Later, the analysis for cluster number validity was made and determined optimal number of k as 2, based on the silhouette criterion[42], which was computed as a ratio of the similarity between windows in the same cluster compared to similarity with windows in a different cluster. In the next 100 clustering iterations, k = 2 was kept. Eventually, we obtained two reoccurring FC states, of which cluster centroids were determined as the median of all matrices allocated to that state over time. The subject-specific centroids of each state were calculated as median value similarly. Further, the subject-specific centroids belong to each group were averaged to get group-specific centroids for better visualization of group comparison patterns[43].

In order to describe the characteristics of the two cluster states, we mainly focused on the degree of global modularity. Modularity is a valuable measurement from graph theory in interpretation of dFNC states, because it evaluates both functional integration and segregation of networks[44]. Thus, we calculated modularity index Q for each state by using a normal Louvain community detection algorithm in Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net/). Wherein, A larger Q represents a higher tendency of assigning ICs into different modules[45].

We calculated four temporal properties: fractional windows, mean dwell time, number of transitions and transition likelihood. The fractional window is calculated as the proportion of time spent in each state as measured by percentage. The mean dwell time represents average duration of time intervals an individual spent in each state, which was calculated by averaging the number of consecutive windows belonging to one state before switching to another. The number of transitions represents the switching times between states, which estimates the flexibility of brain. And the last one, transition likelihood, represents the percentage of switching probability between states. For between-group comparison of different properties, nonparametric permutation tests (10,000 repetition) were used to assess differences of all those temporal properties mentioned above, treating age and sex as covariates. False discovery rate (FDR) correction were applied for fractional windows and mean dwell time.

For the purpose of evaluating the consistency and validity of the k-means clustering at different window sizes, we repeated the dFNC states analysis with 16-TR (32s) and 24-TR (48s). By calculating Pearson's correlation coefficients between the cluster centroids under different window sizes to represent similarity and find the states consistent with the primary analysis[45].

Dynamic topologic analysis

We applied a graph theory approach to obtain topological metrics across all sliding windows using GRETN software (www.nitrc.org/projects/gretna), so as to observe the variability of topological organization of the functional connectivity network. Based on the framework of graph theory, we defined the 59 ICs as functionally independent nodes with FC between pairs of ICs as edges. At first, FC matrices of all windows were binarized with a series of sparsity thresholds, where edges larger than threshold was designated as 1, and 0 when it was smaller than threshold; only positive FC values were considered. With regard to sparsity, it is defined as the ratio of the number of existing edges divided by the maximum possible number of edges in a network. Referring to previous studies[23, 28], we determined thresholds ranged from 0.10 to 0.35 (with an interval of 0.01) for further analyses.

Next, we calculated both global and regional network properties in a series of adjacent matrix for all participants. The former included: (1) measures of global (E_g) and local network efficiency (E_{loc}); and (2) small-world global metrics of clustering coefficient (C), characteristic path length (L), small-worldness (σ), normalized clustering coefficient (γ), and normalized characteristic path length (λ); and the later was nodal efficiency. As it has been widely used in previous studies, an AUC approach was chosen to avoid the specific selection of a threshold[23]. The detailed interpretation of topological properties is listed in Table S2. For better characterizing the temporal variation of those measurements, we also computed the coefficient of variation (CV) of AUC of network parameters as what was did in Luo et al[28], where CV was calculated as SD/Mean across all sliding windows.

The nonparametric permutation approach (10,000 iterations) was used again to test for dynamic topological property differences in the AUC of each metric with age and sex as covariates. When group differences in the larger number of nodal properties, a false discovery rate (FDR) correction was used to control the false-positive rate to one per analysis.

Correlational analyses

Given the fact that the dynamic measures obtained in our study were non-normal distribution, we performed Spearman's partial correlation analyses to investigate possible relationships between abnormal properties and clinical data (including illness duration, VAS and attack frequency).

Demographics (age, sex, education) and head motion (FD Jenkinson) were regressed out and $p < 0.05$ was set as statistical significance threshold.

Results

Demographic and clinical characteristics

A total of 84 participants (41 CTN and 43 HCs) met inclusion criteria and were included for analysis. Table 1 summarizes the detail demographic and clinical data of the participants. There was no significant difference between CTN and HC in sex ($p = 0.979$), age ($p = 0.186$) and education ($p = 0.412$).

Table 1
Demographic and clinical characteristics study participants.

	Patients with CTN	Healthy controls	χ^2/t value	<i>P</i> -value
Sex (female/male)	23/18	24/19	0.001	0.979
Age, y	56.34 ± 10.50	53.40 ± 9.73	-1.344	0.186
Education, y	11.66 ± 2.33	12.07 ± 2.24	0.825	0.412
Duration of disease, y	5.79 ± 4.68	NA	NA	NA
Attack frequency (times per day)	7.41 ± 3.91	NA	NA	NA
Score of VAS	6.41 ± 0.91	NA	NA	NA
Medication	Carbamazepine (33)	NA	NA	NA
Values were displayed as mean ± SD (range). <i>p</i> value of gender was calculated by chi-square test and <i>p</i> values of age, education and VAS was obtained by independent-samples <i>t</i> test. CTN, classic trigeminal neuralgia; HC, healthy controls; VAS, visual analogue scale.				

Intrinsic connectivity networks

Based on the GICA framework, 59 independent components (ICs) were defined and selected, and the spatial maps of them are shown in Fig. 1. Specifically, all ICs were assigned into the following nine networks: sensorimotor network (SMN), visual network (VIS), auditory network (AUD), DMN, salience network (SN), cognitive control network (CC), dorsal attention network (DAN), subcortical network (SC) and cerebellum network (CBN). Figure 1B shows the static functional network connectivity (sFNC) matrix, computed with the entire BOLD time course and averaged over subjects. The detailed component labels and spatial information of ICs are presented in Supplementary Table S1 and Supplementary Figure S2.

Clustering analysis and functional connectivity strength in dynamic states

Through the evaluation of dynamic interactions between functional networks by sliding window and k-means clustering method, two recurred functional states of the whole cohort were identified as follows (Fig. 2A): a less frequent but strongly connected State 1 (26%); a more frequent and sparsely connected State 2 (74%). For a more accurate description of connectivity patterns in each state, the 3% strongest functional connections were shown in Fig. 2B and 2C (with absolute strength of correlation coefficients as index). In details, state 1 was characterized by positive connections within and between SMN-VIS-DAN and widely negative connections between SC and other networks (though the absolute FC strength did not reach top 3% except for IC088). While state 2 was distinguished by partly strongly connected components within the DMN and complex coupling between DMN-CC (including both positive and negative correlations between ICs). Additionally, SN participated much more in state 2 and highly connected with DMN.

The modularity analysis (Fig. 3) revealed quite distinct integration and segregation modes of the two states. With a relatively lower Q (0.1876), State 1 presented two functional modules, one of which largely involved SMN, VIS and DAN, while another consisted of the rest networks. By contrast, state 2 got a higher Q (0.3042), with ICs primarily aggregated into three modules. Among them, module 2 mainly included DMN and some part of CC and SN, that predominated in state 2 FC pattern described above.

Group differences in temporal properties

The group-specific centroids of k-means clusters are shown in Fig. 4A and 4B. Although CTN and HC had similar dFNC profiles and connection patterns, we still found some significant group differences in the key temporal properties as is shown in Fig. 5. In HC, the total occurrence of state 1 and state 2 was $33.5 \pm 31.2\%$ and $66.5 \pm 31.2\%$ respectively. However, for CTN patients, a lower occurrence frequency was observed in state 1 ($17.4 \pm 25.5\%$), and a higher occurrence rate in State 2 ($82.6 \pm 25.5\%$), which differed significantly from HC ($p = 0.008$, nonparametric permutation tests, FDR correction) (Fig. 5A). Accordingly, the findings above indirectly reflect that CTN patients had a decline of occurrence in state 1 by 16.1%, but a proportional rise in state 2 (16.1%). Likewise, notably group discrepancy was identified for mean dwell time ($p = 0.019$, nonparametric permutation tests, FDR correction) (Fig. 5B). When compared to HC (mean $\pm$ SD for state 1: 24.6 ± 24.4 ; for state 2: 65.0 ± 51.1), CTN patients were inclined to spend much shorter time in state 1 (14.1 ± 19.3), whereas lingered much longer in state 2 (92.8 ± 53.1), suggesting an abnormal time distribution of patients for each state. Moreover, the transitions between two states of CTN (2.7 ± 2.1) was significantly reduced in comparison to HC (1.8 ± 2.0) ($p = 0.04$, nonparametric permutation tests) (Fig. 5C).

When evaluating the transition likelihoods between two distinct states, substantially group differences regarding the probability of staying in a state and switching to another were found. Figure 5D shows that CTN patients preferred to stay in the sparsely connected state 2 ($98.5 \pm 2.8\%$, $p = 0.026$, nonparametric permutation tests), and were less likely to switch to the strongly connected state 1 ($1.5 \pm 2.8\%$, $p = 0.026$, nonparametric permutation tests), which is entirely opposite in HC (mean $\pm$ SD for staying in state 2: $96.9 \pm 4.5\%$; for transition to state 1: $3.1 \pm 4.5\%$). While there was no group difference with respect to the preference of staying in state 1 (mean $\pm$ SD for CTN: $3.3 \pm 4.1\%$; for HC: $96.7 \pm 4.1\%$, $p = 0.374$, nonparametric permutation tests) or transferring to state 2 (mean $\pm$ SD for CTN: $3.0 \pm 3.6\%$; for HC: $97.0 \pm 3.6\%$, $p = 0.378$, nonparametric permutation tests). The results are consistent with and further support the findings about fractional window and dwell time. In summary, all those results indicated an affection to the stability of strong connections in state 1 in CTN patients, with increased expression of sparse connections in state 2 in proportion. Correlation analysis did not find any relationships between temporal metrics and clinical characteristics.

In validation analysis, when the window size was set to 16-TR and 24-TR respectively with the rest of parameters unchanged, two cluster states were obtained of each run. State 1 and state 2 under both window sizes (include 16-TR and 24-TR) showed similar FC pattern with the ones under 20-TR window

size (see supplementary Table S4 and S5 for detailed r and p). We also observed consistent between groups differences in temporal metrics under both window sizes (Figure S3 and S4).

Dynamic topological properties

Significant differences between CTN and HC were identified when comparing CV for AUC of network efficiency ($p = 0.007$ for E_g and $p = 0.06$ for E_{loc} , nonparametric permutation tests) (Fig. 6A and 6B) and small-world metrics ($p = 0.029$ for σ , $p = 0.035$ for γ , $p = 0.017$ for L , nonparametric permutation tests). Yet we didn't find abnormal alterations of patients in dynamics of AUC of λ and C ($p = 0.074$ and $p = 0.138$ respectively, nonparametric permutation tests) (Fig. 6C ~ 6G). With regard to the temporal variability of nodal efficiency (AUC), CTN patients showed decreased values in IC 1, IC 42 and IC 77 ($p = 0.001$ for IC 1 and IC 77; $p = 0.002$ for IC 42, FDR corrected). IC 1 (peak MNI coordinate: -0.5, 47.5, -3.5) mainly located in anterior cingulate cortex (ACC) (Fig. 7A). While IC 42 (-2.5, 11.5, 0.5) mainly located in bilateral caudates and IC 77 (-0.5, -24.5, 6.5) located in bilateral thalamus, both of which belong to SC network.

In the further analysis of correlations between dynamic topological properties and clinical data in the CTN group, we found that CV of AUC of σ , γ and L were negatively correlated with disease duration (Spearman's $\rho = -0.421$, -0.433 , -0.388 respectively; and uncorrected $p = 0.009$, 0.018 , 0.007 respectively) (Fig. 8A ~ 8C). Additionally, the CV of Gamma (AUC) was negatively correlated with the pain attack frequency (Spearman's $\rho = -0.338$, uncorrected $p = 0.041$) (Fig. 8D).

Discussion

Investigation about temporal features of FC has been proved valuable to reflect neural mechanisms of pain development[46]. As far as we know, it is the first dFNC study combined with graph theory to investigate the temporal properties of states and variability of whole brain topological organization in CTN patients. Based on the two reoccurring dFNC states with distinct connectivity configuration: an infrequent state 1 with strong connections and a frequent state 2 with sparse connections, there were three major findings associated with CTN: (Ⅹ) Patients showed more fractional windows and longer dwell time in state 2, which is predominantly characterized by tight connections between DMN and CC and locally positive connections within DMN; (Ⅹ) CTN patients demonstrated decreased transition numbers, paralleled by disruptions of variability in both global (including network efficiency and small-worldness) and local (nodal efficiency) topological properties, which suggested an impaired flexibility of information transfer in patients. More importantly, the damages in dynamics of nodal efficiency highlighted the crucial role of ACC, thalamus and caudate in the pathophysiology of CTN; (Ⅹ) The negative correlation between global dynamic properties and disease duration as well as attack frequency further suggested a clinical relevance.

dFNC states

Increased reoccurrence fraction in state 2

Compared with HC, the expression of sparsely connected state 2 in CTN patients increased by 16.1% and the occurrence of strongly connected state 1 dropped in almost the same proportion, paralleled by consistent alterations in the mean dwell time. Patients also showed a higher transition likelihood of switching to or staying in state 2. These findings collectively suggested a preference of CTN patients for state 2, characterized by extensively sparse connections but strong FC within DMN and between DMN and CC. In previous studies, such weak and diffuse dFNC state, like state 2 we observed, was always considered steadier and as the average of a vast number of additional states that varying less[14, 47], which may also explain the similarity between state 2 and sFNC pattern. Some studies further linked that state with self-referential processing and drowsiness[48, 49]. Correspondingly, the characteristic FC within DMN of state 2 has been implicated in self-referential process, and the activation of DMN occurs when attention wandering away from pain[16]. With similar dFNC analysis, Tu et al found that migraine patients had reduced expression of DMN, which was proposed to stem from weaker alpha band oscillation and eventually lead to reduced mind wandering experience[23]. Based on that, our findings are consistent with an electroencephalography study about chronic orofacial neuropathic pain, which demonstrated significantly greater activity over the theta and alpha ranges in patients[50], that reversely supported the increased DMN activation. Therefore, the higher occurrence and longer dwell time of state 2 indicated that CTN patients preferred to stay in a state with more mind wandering and interoceptive awareness.

Tight and complicated FC between DMN and CC also characterized state 2, including extensive positive connections and several negative connections. As a “task-positive” network, CC engages in external stimuli and tasks, and would be activated significantly in attention and executive control to modulate the descending pain system when under pain-related stimuli. Thus, CC generally exhibits negative FC with DMN, wherein the latter is typically recognized as a “task-negative” network[51, 52]. One recent rs-fMRI study of chronic migraine revealed disrupted negative FC between DMN and CC of patients[51]. Another study investigated migraine brain using dynamic amplitude of low-frequency fluctuations (dALFF) also found decreased dynamics in both DMN and CC[53]. In the present study, the higher occurrence of a state with obvious FC between DMN and CC may indicate that state as a neural substrate for the dysregulation of static FC between networks in CTN. The disturbance of DMN-CC decoupling possibly reflects an imbalance of switching between internally and externally directed cognition and further influence cognitive and emotional processing of pain[54].

Additionally, the ICs in State 2 were subdivided into three modules with higher modularity index, interpreted as stronger segregation between neural network groups[55]. As were indicated in previous studies, dysfunction in integration characterizes pain, such as migraine, CTN and other neuropathic pain[56, 57], and may facilitate the processing of pain-related information[58]. Also, the disconnections between modules probably reflect interruptions on inter-system communication[58] and impairments in cognitive performance that are known to be a complication of pain[16, 59]. Therefore, the increased fractional and mean dwell time, and highest modularity in State 2 in patients indicates increased periods of excessive functional segregation in CTN and potentially a reduced ability to flexibly switch to state 1.

Decreased reoccurrence fraction in state 1

State 1 was characterized by widely positive connections, especially within and between SMN-VIS-DAN, all of which are parts of sensory system and participate in the information processing of external stimulus[54]. With regard to the SMN, accumulating studies demonstrated the center role of somatosensory cortex in processing and modulating pain[12]. As to somatic motor cortex, it has been linked with pain processing by providing feedback from various layers to distinct thalamic nucleus anatomically[60]. It has been reported that CTN patients commonly show mild hypoesthesia[2, 61]. Previous morphological research about CTN showed decreased gray matter volume (GMV) in SMN, including secondary somatosensory cortex, primary motor cortex and premotor area[9]. Thus, our findings provided further functional evidence supporting the injury to SMN. In addition, pain experience is always along with several sensory inputs, such as vision, audition, and olfaction, which may interfere with each other. Altered FC within VIS and AUD network has been revealed in previous functional research about chronic migraine[54]. Taken together, the observed decreased expression of sensory network related FC may suggest the failed modulation between and within sensory related networks and probably leading to attenuated perception in CTN patients.

To be noted, there were obvious negative connections between SC and cortical networks in state 1. We speculate the shorter duration of patients in the strongly connected state may partly reflect the dysfunction of cortical-subcortical interaction, which was confirmed by following analysis (see “variability of nodal efficiency analysis” for details). Other dFNC studies of multiple diseases, including low back pain[24], migraine[23], schizophrenia[62], and bipolar disorder[63] also found similar state with aberrant FC between SC and disease related cortical areas, wherein all disease share a common thalamocortical dysrhythmia model. Thus, the present findings may provide supportive evidence of dFNC analysis in declaring neural mechanism by separating temporally contiguous states alone.

Temporal variability of topological metrics

Consistent with the decreased number of transition, CTN patients displayed robustly disrupted temporal variability of global topological properties. Previously, several studies using graph theory have reported altered topological properties in chronic pain disorders[64–67]. As the integration and segregation of large scale brain network fluctuates time serially[14], dynamic topological analysis based on dFNC can provide additional information. In our study, CV represents the discreteness of network windows and further reflect the flexibility of rapid shift between mental states, which has been proved important to maintain responsive ability of brain[68], as well as help optimize behavior during pain for a better task performance[69]. The present results showed lower dynamics of E_g , E_{loc} , σ , γ and L in CTN patients, which suggested a broken temporal variability of the overall functional brain networks. Similarly, Wu et al explored the dynamic topological properties about primary dysmenorrhea and found altered temporal stability of global parameters[25], which suggested brain network reorganization. The findings in our study implied a less efficient information transfer throughout the whole brain and may confirm the vulnerability of the resting state network in CTN. Moreover, CV of topological properties in our study was

found to be correlated with disease duration and attack frequency, which further indicate the potential value of that parameter as a biomarker for illness progression.

Regarding to nodal efficiency, regions with decreased temporal variability were observed mainly located in ACC of SN as well as thalamus and caudate of SC, indicating reduced efficiency or flexibility of these regions when communicating with each other. As the key nodes of SN, ACC plays a critical role in marking salient events (such as pain) for further processing and giving controls for better cognitive and behavioral response[70]. Accordingly, the function of SN seems to be entirely contrary to DMN, activated when attention was maintained on pain, and suppressed conversely[16]. Previous studies have found increased FC between insular and ACC[9] in CTN patients, also their decreased GMV[71, 72]. Moreover, ACC is involved in the rewarding effects of pain relief and displays tight coupling with brainstem pain-control circuit (such as periaqueductal gray [PAG] and locus ceruleus [LC]) to provide regulation from high neural system[73]. Thus, in the present study, reduced dynamics of ACC efficiency in CTN may induce abnormal modulation and switching between SN and other “dynamic pain connectome” regions, then lead to dysfunction in coping with changing environments and needs.

Thalamus has been demonstrated as a part of ascending pain pathway[6], and a relay and integration center connecting subcortical and cortical regions. Previous investigations using electroencephalography and magnetoencephalography techniques have shown that chronic neuropathic pain is associated with thalamocortical dysrhythmia[74, 75]. Likewise, rs-fMRI study demonstrated increased infra-slow oscillation activity of thalamus[6]. In our dFNC study, we further suggested reduced temporal variability in the functional efficiency of thalamus, especially located in the ventroposterior medial region. In general, ventroposterior medial thalamus is under inhibition of γ -aminobutyric acid (GABA) released from the thalamic reticular nucleus, which process was supposed to play a key role in controlling thalamocortical rhythm[76]. Moreover, aberrant thalamic firing, especially increased burst firing in the somatosensory thalamus without an overall hyperactivity, has been proved associated with neuropathic pain[62]. With respect to our results in temporal fluctuation, it has been indicated that signal variability was associated with the balance of synaptic excitation and inhibition, where the greater variability may represent better neuronal plasticity, for further adaptation to changing environment[77, 78]. Therefore, attenuated flexibility of thalamic efficiency in CTN may be linked with excessive thalamic firing, either as a predisposing factor or consequence, subsequently perhaps contribute to the vulnerability of thalamocortical connectivity, and cause constant perception of pain.

Caudate is another key nuclei of SC network and receive nociceptive information from the trigeminal nuclei through direct projections from lamina I neurons of the trigeminal spinal nucleus, while independently of the thalamus[79]. The caudate nucleus plays a critical role in the evaluation of the agreement between the action and the outcome, as well as planning and performing tasks necessary to achieve complex goals[80]. Several morphological studies have suggested reduced GMV of caudate in chronic pain disorders, such as TN[72], cluster headache[81] and knee osteoarthritis[80]. Consistent with that studies, our findings provided additional functional evidence from the perspective of dynamic

topology. Thus, the lower efficiency of caudate may partly explained by an adaptation to chronic stimulation or an inhibition of facial movement to avoid eliciting pain[3, 9].

Limitation

In the present study, some limitations should be considered. Firstly, the patients enrolled were all taking medications, commonly carbamazepine, thus drug effects cannot be exactly distinguished from the findings. It is required to investigate the relationship between medication and cerebral changes. Secondly, with recent advancement in fMRI, multiband acquisition allows scanning with a shorter TR and elevated temporal resolution[82] and has been recommended to explore the dynamic nature of brain activity[83]. In future investigations, it would be expected to increase the estimation power by using fast fMRI. Finally, it is awaited to use multimodal approaches, including GM and WM morphological analysis as well as GABA related metabolic researches, on more brain regions, such as PAG and rostroventral medulla from aninociceptive system, to identify more fine-grained changes in “dynamic pain connectome”.

Conclusion

To sum up, this is the first study to assess dynamic connectivity properties of CTN. Abnormal temporal pattern, characterized by complex connections between DMN-CC and hyper-connectivity within DMN, was found mainly in patients. Additionally, we observed disrupted flexibility in state transition and global topological organization, furthermore identified key brain regions (ACC in SN and thalamus and caudate in SC) with decreased temporal variability of efficiency. Reduced dynamics of topological properties further correlated with both disease duration and pain frequency. These results collectively suggested an temporal disturbance of whole brain networks due to chronic pain and further highlighted the crucial role of “dynamic pain connectome” regions (including DMN/CC/SN) in pathophysiology of CTN, also provided supplementary evidence for current knowledge about the dysfunction of cortical-subcortical interaction in pain development.

Abbreviations

ACC: anterior cingulate cortex; AUD: auditory network; CBN: cerebellar network; CC: cognitive control network; CTN: classic trigeminal neuralgia; dFNC: dynamic functional connectivity; DAN: dorsal attention network; DMN: default mode network; HC: healthy controls; ICs: independent components; SC: subcortical network; sFC: static functional connectivity; SMN: sensorimotor network; SN: salience network; VAS: visual analogue scale; VIS: visual network.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Lanzhou University Second Hospital approved the research protocol, and the procedures conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from participants.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare no biomedical financial interests or potential conflicts of interest.

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Authors' contributions

PFZ and YLJ contributed to the conception and design. JZ, GYL, PFZ and YLJ contributed to the methodology. LYM, WJH and JW contributed to software and data curation. PFZ, YLJ contributed to the MR data acquisition. JH contributed to the clinical data acquisition. PFZ contributed to the data analysis and original manuscript writing. YLJ JZ and GYL contributed to the manuscript review and Editing. JZ, GYL are project administration. The author(s) read and approved the final manuscript.

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Figures

Figure 1

The spatial maps of 59 independent components and corresponding static functional network connectivity matrix. (A) 59 ICs were identified and grouped into 9 functional network. (B) sFC between the

whole time courses of selected ICs were calculated and averaged over subjects. Color bar represents correlation values, i.e., Fisher's z-transformed Pearson correlation coefficient. SMN, sensorimotor network; VIS, visual network; AUD, auditory network; DMN, default mode network; SN, salience network; CC, cognitive control network; DAN, dorsal attention network; SC, subcortical network; CBN, cerebellar network; sFC, static functional connectivity.

A Cluster centroids for each state

B Functional connectivity of state with edge bundling

C Functional connectivity of state with edge strength

Figure 2

Clustering analysis results. (A) Cluster centroids for each state: state 1, less frequent but with stronger inter-connection; state 2, more frequent with relatively sparse connection. (B and C) The 3% strongest functional connections in each state are displayed, (absolute value of correlation coefficients was used), where B has edges bundled together for better characterizing connection patterns and C further shows connectivity type. The transition of colors in B means connections between networks. Red lines of C represent positive functional connectivity, while blue lines represent negative connections. SMN, sensorimotor network; VIS, visual network; AUD, auditory network; DMN, default mode network; SN, salience network; CC, cognitive control network; DAN, dorsal attention network; SC, subcortical network; CBN, cerebellar network.

Modular distribution for each state

Figure 3

Modular analysis results. State 1 showed two modules (module 1 in red; module 2 in blue), whereas state 2 showed three modules (module 1 in green; module 2 in red, module 3 in blue). Edges between nodes represents 3% strongest functional connections in each state. In state 2, four nodes of module 2 are labeled with their components numbers because of their widespread connections, including IC21, IC31, IC55, IC83, all of which located in DMN. IC, independent component. DMN, default mode network.

A The state specific cluster centroids for HC

B The state specific cluster centroids for CTN

Figure 4

The two dFNC patterns of the two groups. (A) The state specific centroid matrices for HC. (B) The state specific centroid matrices for CTN. CTN, classic trigeminal neuralgia; HC, healthy controls; SMN, sensorimotor network; VIS, visual network; AUD, auditory network; DMN, default mode network; SN, salience network; CC, cognitive control network; DAN, dorsal attention network; SC, subcortical network; CBN, cerebellar network.

Figure 5

Analysis results of temporal properties. (A) Fractional windows, representing the percentage of all the windows in each state, (B) mean dwell time (i.e. the time duration a subject spent in each state) and (C) number of transitions (used to measure switching times between states) are displayed for CTN and HC. Square dots in B and bars in C reveal the mean values with shadow and error bar representing standard error. (D) Differences between groups in transition likelihood are shown. Asterisks (*) represent significance of $p < 0.05$ and asterisk (**) indicate $p < 0.01$ (FDR correction was used for fractional windows and mean dwell time). Taken together, CTN patients showed extreme preference for state 2, accompanied by decreased transition numbers and probabilities. CTN, classic trigeminal neuralgia; HC, healthy controls.

Figure 6

CV comparing of global topological properties (AUC). Violin plots (A ~ G) represent CV of AUC of global efficiency, local efficiency, clustering coefficient, characteristic path length, sigma, gamma and lambda respectively for CTN (red) and HC (blue). All asterisks indicate a significant group differences (*, $p < 0.05$; **, $p < 0.01$). Horizontal lines in boxes indicate group medians. CV, coefficient of variation; CTN, classic trigeminal neuralgia; HC, healthy controls.

Figure 7

CV comparing of nodal efficiency (AUC). The CV for AUC of nodal efficiency of (A) IC1 (located in ACC), (B) IC42 (located in caudate) and (C) IC77 (located in thalamus) are displayed using violin plots for CTN (red) and HC (blue). All asterisks indicate a significant group difference (**, $p < 0.01$, FDR corrected). Horizontal lines in boxes indicate group medians. CV, coefficient of variation; CTN, classic trigeminal neuralgia; HC, healthy controls; IC, independent component; ACC, anterior cingulate cortex.

Figure 8

Correlation between clinical characteristics and CV of topological properties (AUC) for CTN group. (A ~ C) The disease duration was negatively correlated with CV of AUC of Sigma, Gamma and characteristic path length. (D) The CV of Gamma showed negative correlation with attack frequency. L, characteristic path length; CV, coefficient of variation; CTN, classic trigeminal neuralgia.

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