scientific reports

Check for updates

OPEN

Resting-state fNIRS reveals changes in prefrontal cortex functional connectivity during TENS in patients with chronic pain

Yijing Luo[1], Jiahao Du[1], Hongliu Yu[1], Fanfu Fang[2] & Ping Shi[1]✉

Transcutaneous electrical nerve stimulation (TENS) has been used to treat chronic pain. However, the potential efficacy and mechanism of the effect of applying TENS for a short time in chronic pain patients remains unclear. To identify the effect of short-term TENS on chronic pain patients and to clarify the mechanism of the effect, we investigated abnormalities of functional connectivity (FC) within the prefrontal cortex (PFC) using resting-state functional near-infrared spectroscopy (rs-fNIRS). Fifteen patients (56.8 ± 17.4 years, nine females) with chronic pain participated in this rs-fNIRS study. The fNIRS scans included two parts: a 5-minute resting-state scan followed by a 5-minute scan during TENS (150 Hz) application. The pain intensity was measured using a Visual Analog Scale (VAS) and Pittsburgh Sleep Quality Index (PSQI). The spontaneous brain activity of the PFC and resting-state functional connectivity (rsFC) in the PFC were examined during TENS and compared to before TENS. The results showed that Pain intensity significantly decreased after TENS ($p < 0.001$). During TENS, fALFF values were significantly lower in BA46 ($p = 0.0025$) and BA45 (**$p = 0.0056$). rsFC strength increased during TENS compared to before, with significant group-level increases in BA10, BA9, BA46, and BA44/45 ($p < 0.05$). Notably, the variation between BA10 and BA44/45 was highly significant (***$p < 0.001$). These findings suggest that FC between BA10 and BA44/45 was associated with analgesia of TENS in patients with chronic pain, indicating the potential role of FC as a novel objective parameter to predict the outcome of clinical use of TENS for pain relief in chronic pain patients.**

Keywords Chronic pain, Functional near-infrared spectroscopy, Resting-state functional connectivity, Amplitude of low-frequency fluctuations, Transcutaneous electrical nerve stimulation

Chronic pain is a very complex and comprehensive feeling involving multiple dimensions, such as physiological, psychological, emotional, and cognitive[1]. In recent years, there have been more than 300 million patients with chronic pain in China[2] who suffer from pain for a long period, which can lead to abnormal changes in the brain's nervous system and have a severe impact on the quality of life and mental status of patients[3]. Transcutaneous electrical nerve stimulation (TENS), a non-pharmacological treatment, has been widely utilized for pain relief in various clinical conditions due to its advantages of non-invasiveness, high safety, and analgesic effect[4]. Specifically, applying electrical pulses to the surface of the skin could activate nerve fibers and then induce the release of the endogenous opioid, the modification of electrical transmission, and the dilation of blood vessels, ultimately leading to the relief of pain[5,6]. Recent meta-analyses have investigated the efficacy of TENS for relief of pain in adults[7]. In conclusion, moderate-certainty evidence (SMD = -0.96 (95% CI -1.14 to -0.78) shows pain intensity is lower during or immediately after TENS compared with placebo and without serious adverse events. This finding supports the use of TENS as an effective intervention for managing chronic pain conditions. In addition, several functional neuroimaging studies have notably shown modulation of neuronal plasticity and the cortical excitability following the application of TENS[4,8]. However, the underlying neural mechanisms of applying TENS for a short time in chronic pain patients remain unclear.

Resting-state functional near-infrared spectroscopy (rs-fNIRS) is an emerging non-invasive imaging technique that could be used to identify brain areas of aberrant functional activities by measuring the spontaneous brain activity by low-frequency fluctuations in the concentration changes of Oxygenated Hemoglobin (HbO)

[1]School of Health Sciences and Engineering, University of Shanghai for Science and Technology, NO. 516, Jungong Road, Yangpu District, Shanghai 200093, China. [2]Department of Rehabilitation Medicine, the First Affiliated Hospital of the Naval Medical University, Shanghai 200433, China. ✉email: rehabishi@163.com

and Deoxygenated Hemoglobin (HbR) hemoglobin in brain tissue following neuronal activity[9,10]. Several fNIRS researches demonstrated the feasibility of studying pain perception in the brain in vivo[11,12]. In addition, fNIRS possesses several benefits that make it a highly suitable tool for pain measurement in clinical settings, including its portability, non-invasiveness, minimal use of ionizing radiation, ease of use, high temporal resolution, and ability to handle motion artifacts effectively. Brain functional connectivity is the correlation of these spontaneous fluctuations in brain regions, and it is believed to be the basis of communication within the brain network. Brain functional connectivity is used in many different clinical applications[13]; it is also used in the pain research, and many studies have been conducted on subjects with chronic pain[14]. Previous conventional fNIRS studies have demonstrated that chronic pain can increase or decrease functional connectivity (FC) in specific brain regions[15,16]. RSFC was utilized to distinguish individuals who developed chronic low back pain from those who did not, among those diagnosed with newly acquired subacute back pain[17].

FC analysis of fNIRS could be a neuroimaging marker for objective response to pain, but it remains extensively studied[18,19]. In this study, to identify the effect of the application of TENS for a short time on patients with chronic pain and clarify the mechanism of the effect, we examined the differences between Pre-TENS (Pre-T) and During-TENS (During-T) using fNIRS. We will analyze whether FC and spontaneous brain activity of the PFC are changed in chronic pain patients between Pre-T and During-T. By elucidating the immediate prefrontal response to TENS during chronic pain, we aimed to find specifical and sensitive rsFC in the PFC during TENS to serve as a biomarker of clinical improvement in patients with chronic pain. In this study, we hypothesized that the FC of the PFC increases in patients with chronic pain during TENS.

Materials and methods

Participants

Fifteen patients (56.8 ± 17.4 years, nine females) participated in this study. Patients were recruited from the rehabilitation department. The criteria for inclusion in this study were as follows: (1) Patients diagnosed with non-neuropathic pain; (2) Pain persisting for at least three months; (3) Patients were right-handedness; (4) Pain rated verbally (Visual Analogue Scale (VAS): 0 = "no pain" and 10 = "the worst pain imaginable") as at least 3/10 at the time of evaluation. Moreover, participants who met contraindications to TENS were excluded, as were those using psychotropic medications such as antidepressants, anxiolytics, and stimulants. All methods of this study were based on the Declaration of Helsinki and other relevant ethical and guiding principles. The study protocol was approved by the ethics committee of Yueyang Hospital of Integrative Medicine of Shanghai University of Traditional Chinese Medicine and Changhai Hospital of Naval Medical University (Ethics approval number: [ChiCTR2200056394]) and all methods were performed in accordance with relevant guidelines and regulations. All participants provided written informed consent prior to participation in the study.

Experimental equipment

This experiment used a portable fNIRS system (Brite24, Artinis, the Netherlands) was used in this experiment. The system, with wavelengths of 752 and 852 nm, recorded cortical activity at a sampling rate of 10 Hz. The equipment is shown in Fig. 1A. The system captures the patient's cerebral blood oxygen levels, which contain HbO and HbR, in real time.

Electrical stimuli for TENS were generated by a constant piezoelectric stimulator (Shanghai Weichuang Medical Equipment Company) and delivered through two pairs of surface electrodes (40 mm*40 mm; inter-electrode distance: 3 cm) placed pain site. The conventional TENS (150 Hz) consists of a series of symmetrical rectangular wave pulses (pulse width = 2 ms).

Experimental protocol

Patients were asked about the complete experimental procedure before the experiment. Patients were required to rate their pain intensity on VAS and PQSI before and after the rs-fNIRS scan. The experiment was carried out in a dimly lit, quiet environment. The patients sat quietly in a comfortable position with their eyes closed. The patients were advised against falling asleep, thinking about anything in particular, and avoiding large body movements (especially head movements) and communication. Depending on the shape of the patient's head, we chose the proper size of the NIRS cap and debug it. Then, the experimenter applied electrode sheets to patient's painful area. The experimental protocol started with a baseline measurement of 60 s and lasted about 11 min. The rs-fNIRS signal was acquired for 5 min, then the patient had a break for 10–20 s, followed by applying TENS, and the rs-fNIRS signal was acquired for 5 min during TENS (Fig. 1B).

fNIRS acquisition

This study chose to measure blood oxygen levels in the resting state. The most valuable regions in the fNIRS assessment of pain states include the anterior prefrontal cortex (aPFC), dorsolateral prefrontal cortex (DLPFC), premotor cortex (PMC), supplementary motor area (SMA), the primary motor cortex (M1), and primary somatosensory cortex (SI)[20]. In this study, we chose to measure PFC and some temporal lobe regions and chose a template with 18 optodes (eight light sources and ten detectors) (Fig. 1C). The distance between the sources and the detectors was 3.0 cm. These channels mainly cover SMA and PMA (BA6), DLPFC (BA9, BA46), aPFC (subregion of BA10), MTG (BA21) and TPL (BA38). Registration of fNIRS channel locations based on the Anatomical Automatic Labeling (AAL) atlas and Brodmann were shown in Table 1.

fNIRS data preprocessing

The MATLAB package NIRS_KIT[21] was used for data preprocessing. The recording from the first 15 s was excluded due to potential body movements. Data drift was then reduced using detrending, and artificial motions were corrected using the temporal derivative distribution repair method[22]. To minimize physiological noise due

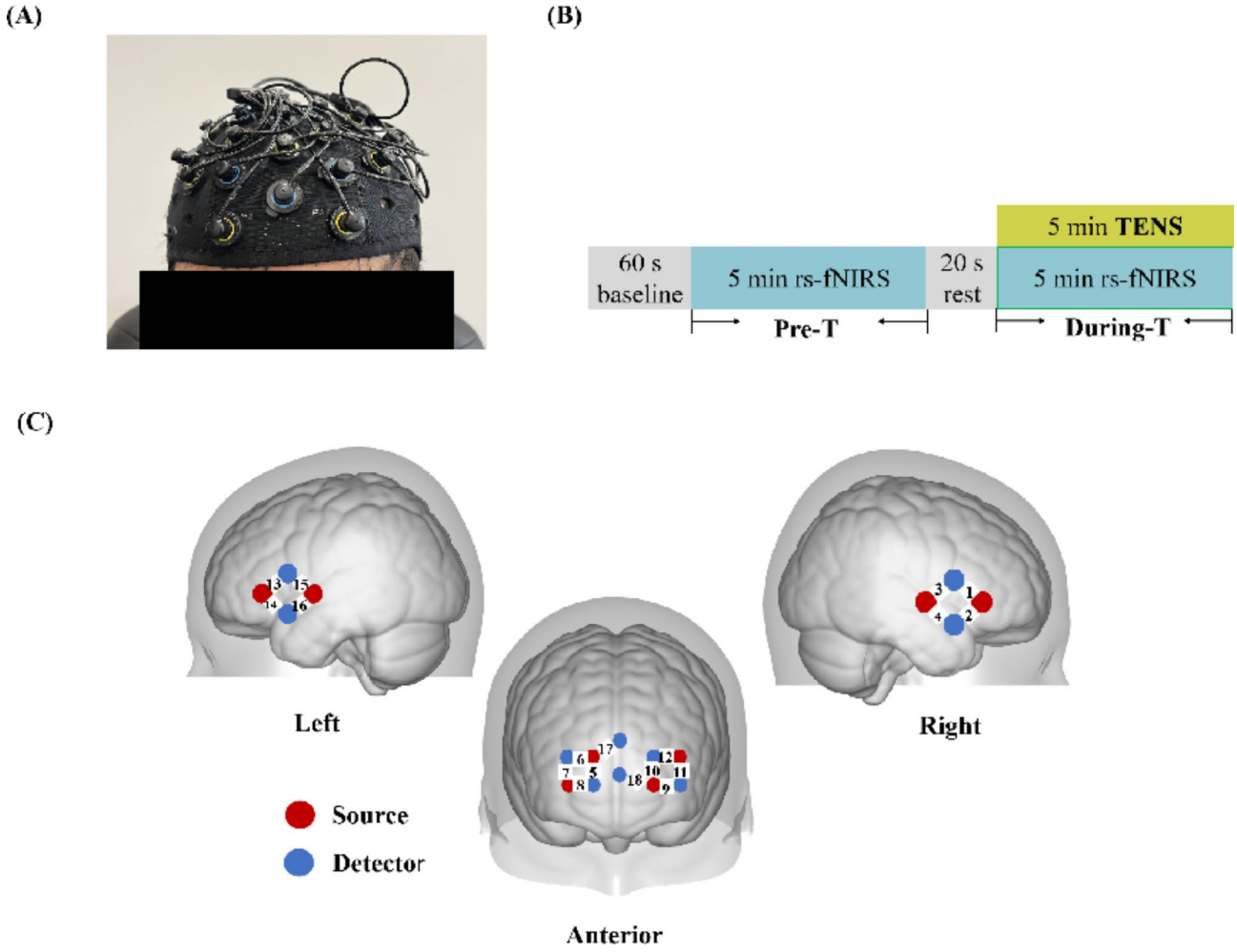

Fig. 1. (**A**) fNIRS system (**B**) Experimental protocol (**C**) Schematic illustration of fNIRS layout (18 channels, eight sources, and ten detectors). The white frames represent channels.

to heart pulsation (1–1.5 Hz), respiration (0.2–0.5 Hz), and blood pressure (Mayer) waves (-0.1 Hz), the data were further filtered with a band-pass of 0.01–0.08 Hz[23]. This study analyzed only HbO signals due to their better signal-to-noise ratio than HbR and their sensitivity to monitoring regional cerebral blood flow[24].

Analysis of the fractional amplitude of low-frequency fluctuations

The spontaneous low-frequency (typically 0.01–0.08 Hz) oscillations (LFOs) of the human brain are thought to reflect the changes in spontaneous neuronal and physiological activities to a certain extent[25,26]. The fractional amplitude of low-frequency fluctuations (fALFF) can provide a more specific measure of the low-frequency oscillatory phenomena[27]. Because the fALFF approach could selectively suppress artifacts from non-specific brain areas, it could enhance signals from the cortical regions associated with brain activity, making use of the distinct characteristics of their signals in the frequency domain[28]. The fALFF is defined as the total power within the LFOs divided by the total power in the detectable frequency range, which is determined by the sampling rate and duration. Therefore, to characterize spontaneous brain activity, fALFF was calculated as the ratio of the root mean square (RMS) of the power spectrum in the low-frequency range (0,01–0.08 Hz) to the RMS of the power spectrum in the whole frequency range (0.01–0.25 Hz)[29].

Resting-state functional connectivity

In this study, only the HbO signal was used to calculate the rsFC. All rsFC analysis was performed using NIRS-KIT[21]. Pearson's correlation coefficients between the time series of all channels were calculated to determine the FC between each pair of measured channels and to obtain an 18×18 connectivity matrix for each patient. BrainNet Viewer software[30] was used to draw the brain functional network based on the calculated Pearson's correlation coefficient matrix.

Statistical analysis

All statistical analyses were performed using GraphPad 9.0. Clinical characteristics and variables were reported as means and standard deviations. The paired-sample t-tests and false discovery rate (FDR) correction were

ROIs	Brodmann	Channels	MNI coordinates based on AAL		
			X	Y	Z
Anterior prefrontal cortex, aPFC	10	ch5	26.73	77.5	17.87
		ch9	-45.96	69.35	0.73
		ch10	-24.32	80.07	15.6
		ch18	-16.94	82.98	14.76
Dorsolateral prefrontal cortex, DLPFC	9	ch6	32.2	64.13	41.15
		ch12	-31.78	68.86	36.01
		ch17	10.15	72.5	42.76
Dorsolateral prefrontal cortex, DLPFC	46	ch1	68.96	34.94	4.98
		ch7	49.75	56.16	27.41
		ch8	47.39	66.18	4.17
Broca's area	44, 45	ch13	-70.44	33.79	14.03
		ch14	-73.22	28.17	-18
		ch15	-74.71	20.97	16.81
		ch16	-77.27	11.81	-13.9
Middle temporal gyrus, MTG	21	ch4	75.68	9.86	-14.25
		ch11	-51.09	59.41	22.02
Temporopolar area, TPL	38	ch2	71.98	25.55	-13.14
Premotor cortex and Supplementary Motor Cortex, PMA and SMA	6	ch3	32.2	64.13	41.15

Table 1. Locations of regions of interest in functional connectivity (FC) analysis.

Subject No.	Age	BMI	Sex	Diagnosis	Clinical Scores Pre - Post TENS	
					VAS	PSQI
1	68	25.6	M	Knee Pain	4 – 3	6 – 3
2	63	22.9	F	Cervical Pain	3–3	7 – 5
3	25	22.8	M	Myofascitis (buttocks)	5 – 4	12 – 9
4	31	21.7	M	Myofascitis (Lower back)	4 – 3	4 – 3
5	73	18.1	M	Low back pain	5 – 3	12 – 8
6	33	19.9	F	Shoulder and back pain	4 – 3	7 – 5
7	75	19.7	F	Low back pain	6 – 5	17 – 15
8	63	19.9	M	Low back pain	3–3	5 – 4
9	47	19.1	M	Myofascitis (Chest and back)	5 – 4	9 – 5
10	76	28.5	F	fibromyalgia	4 – 3	9–9
11	52	23.7	F	Myofascitis (waist)	3 – 2	5 – 4
12	56	21.6	F	Low back pain	4 – 3	13 – 9
13	60	27.3	F	Myofascitis (Lower back)	5 – 3	10 – 8
14	58	21.8	F	Low back pain	5 – 4	6 – 5
15	41	20.2	F	Low back pain	3 – 2	7 – 6
Mean ± SD (n = 15)	56.8 ± 17.4	21.7 ± 2.2	--	--	4.2 ± 0.9 - 3.2 ± 0.8	8.6 ± 3.6 - 6.5 ± 3.2

Table 2. Demographic and clinical characteristics. Abbreviations: BMI: Body Mass Index; VAS: Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index. Variables are shown with mean ± standard deviation.

employed to compare differences in ALFF values and FC between Pre-T and During-T. Where p values < 0.05 were considered to be different, while p values < 0.01 were considered significantly different.

Results

Demographic and clinical results

Fifteen chronic pain patients (nine females, age 56.8 ± 17.4 years) were finally included in this study. The clinical data of the recruited chronic pain patients are shown in Table 2.

TENS effects on pain intensity

Figure 2 shows the pain scores of patients. The mean VAS scores reduced significantly from 4.2 ± 0.9 before TENS to 3.2 ± 0.8 (t = 7.25, $p < 0.001$). Meanwhile, the mean PSQI scores reduced significantly from 8.6 ± 3.6 before TENS to 6.5 ± 3.2 (t = 6.254, $p < 0.001$).

fALFF results

The findings demonstrate that the brain activation in the PFC of the Pre-T was significantly higher than in the During-T. As demonstrated in Fig. 3, compared to the Pre-T, the During-T exhibited significantly decreased fALFF values in BA10 (ch 9, ch10, ch18), BA46 (ch1), BA9(ch12), BA44/45 (ch13, ch14, ch16). Among them, the changes were very significant in ch1 (**$p = 0.0025$, t = 3.335, FDR corrected) and ch16 (**$p = 0.0056$, t = 3.551, FDR corrected).

Resting-state functional connectivity

Figure 4 presents the group-averaged rsFC metrics of Pre-T and During-T. The brain functional network constructed by Pearson's correlation coefficient is an undirected weighted network. Comparing the sub-graphs in Fig. 4, the rsFC strength of During-T is higher than that of Pre-T.

The mean of the correlation values in all the connection matrices was used as the threshold of all samples. The final brain functional network is produced by applying the threshold T to binarize the Pearson correlation matrices of each sample. Thus, through threshold binarization, the brain functional network can be simplified, and many weak edges are deleted, as shown in Fig. 5. Among them, there are still 36 high connections in During-T, and most of these connections were located in the channels of the BA9, BA10, BA44/45, BA46.

Between-group differences in functional connectivity

To verify the effect of TENS on rsFC, FC strengths before and after TENS were compared using a paired samples t-test and corrected. Group-level connectivity differences between the Pre-T and During-T are shown in Fig. 6; Table 3. Group-level analysis demonstrated that the rsFC strength was significantly higher ($p < 0.05$, FDR corrected) in BA10 (ch5, ch9, ch10, ch18), BA9 (ch6, ch12, ch17), BA46 (ch7, ch8), BA44/45 (ch13, ch14, ch15, ch16) for the During-T. Notably, the variation between BA10 (ch10, ch18) and BA44/45 (ch13, ch14, ch16) was extremely significant (***$p < 0.001$).

Discussion

The present study showed that functional brain connectivity during TENS intervention significantly differs from those subjected to pre-TENS. Here, we investigate the changes in Spontaneous brain activity and brain functional connectivity associated with TENS intervention. The results showed that the resting-state brain activity decreased, and the rsFC strength increased During-T, especially in the connection between BA10 and BA44/45.

Previous studies demonstrated that spontaneous neural activities during rest were correlated with low-frequency blood-oxygen-level-dependent (BOLD) signals, which the amplitude of ALFF can represent[31]. The current study investigated the resting-state brain activity in the During-T compared to the Pre-T using fALFF. The results showed decreased fALFF values in During-T, consistent with previous studies that reported altered prefrontal activity in chronic pain conditions[32]. The comparison between chronic low back pain (cLBP) subjects and HCs showed increased ALFF in the left dorsal anterior cingulate cortex (ACC) in cLBP subjects[29]. In 2022, Lin et al. investigated the neural correlates of pain in patients diagnosed with knee osteoarthritis (KOA)[33]. The

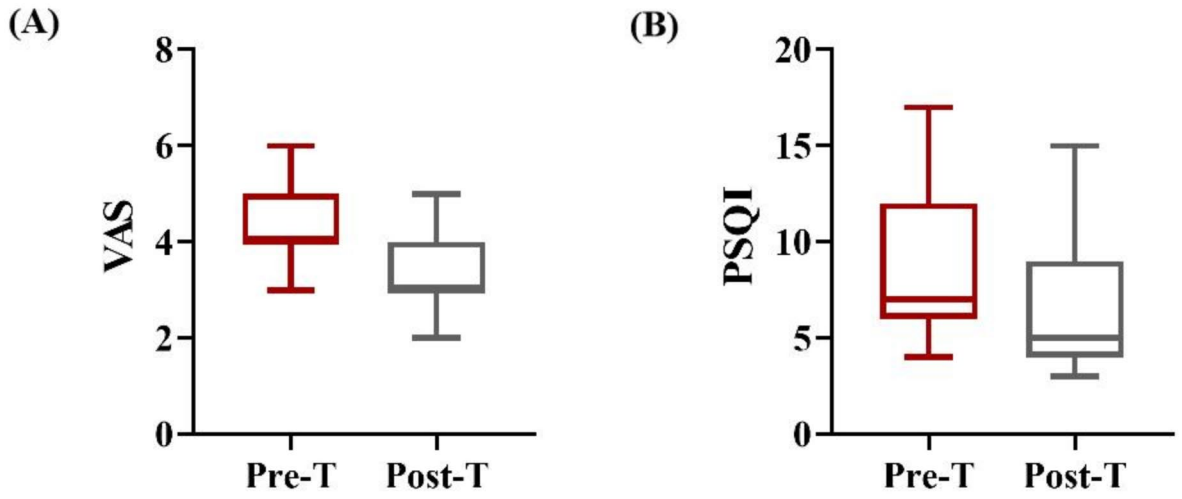

Fig. 2. Pain evaluation. The pain intensity scores were measured by VAS (**A**) and PSQI (**B**) scores for patients in the treatment of TENS.

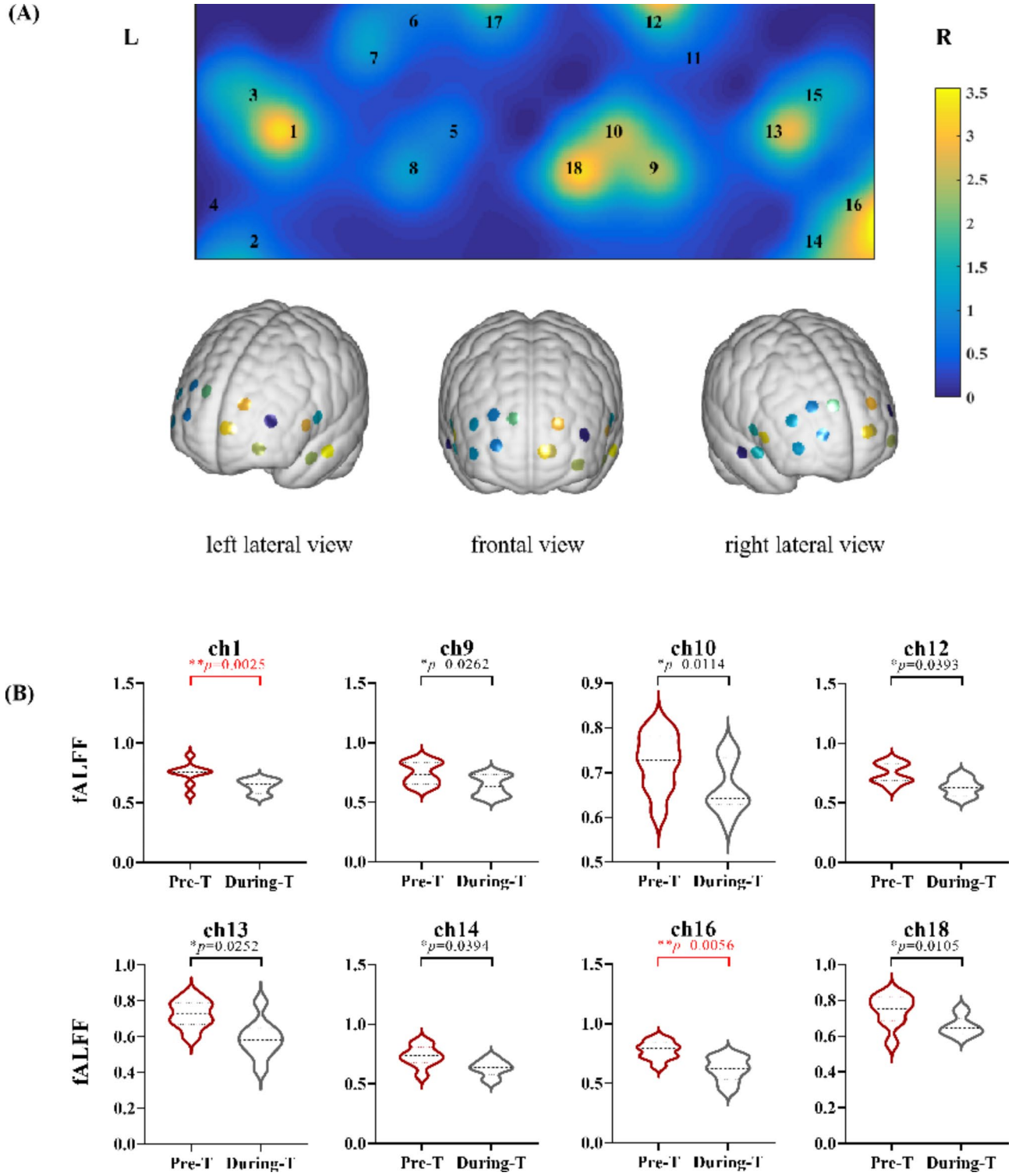

Fig. 3. fALFF analysis. (**A**) 2D and 3D plots of statistical results at the resting state fALFF cluster level, with color values indicating statistical values from paired-sample t-tests. (**B**) eight channels with significant differences. The asterisk indicates a significant difference (**p <0.01).

results showed that patients with KOA significantly increased in brain activity within the DLPFC compared to healthy subjects. This increased activity in the DLPFC was associated with the suppression of chronic pain. During TENS, the pain gradually subsided. In a study by Eken et al., fNIRS was employed to investigate the hemodynamic response to TENS in patients diagnosed with FM as well as in healthy subjects, which revealed a decrease in hemodynamic activity in patients with FM during TENS stimulation[34]. In addition, their study showed that the condition scores of the "pain + placebo TENS" group were higher than those of the "pain + TENS"

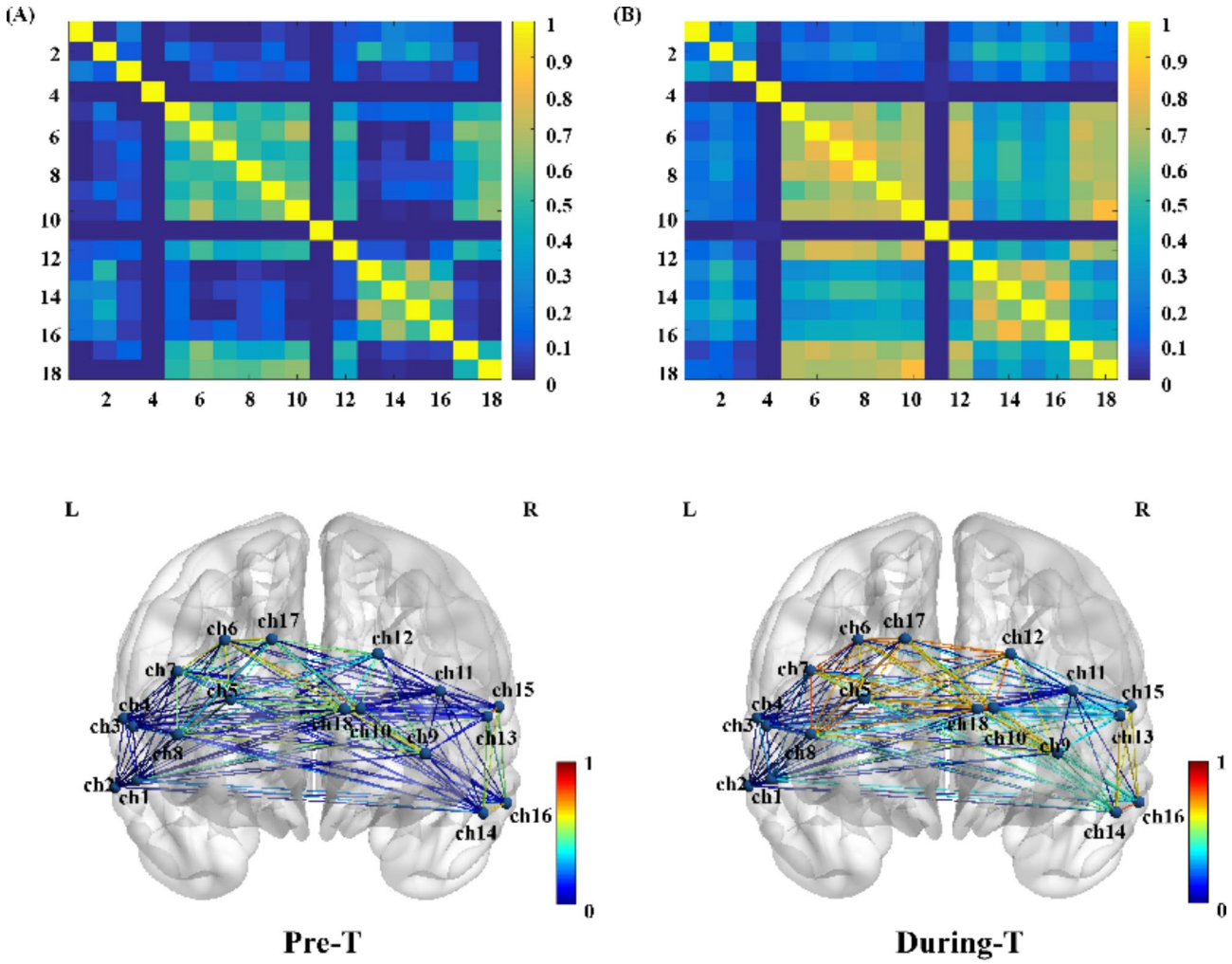

Fig. 4. Pattern of resting-state functional connectivity strength of Pre-T (**A**) and During-T (**B**). Each pixel in the correlation matrix represents the connection strength of each pair of channels.

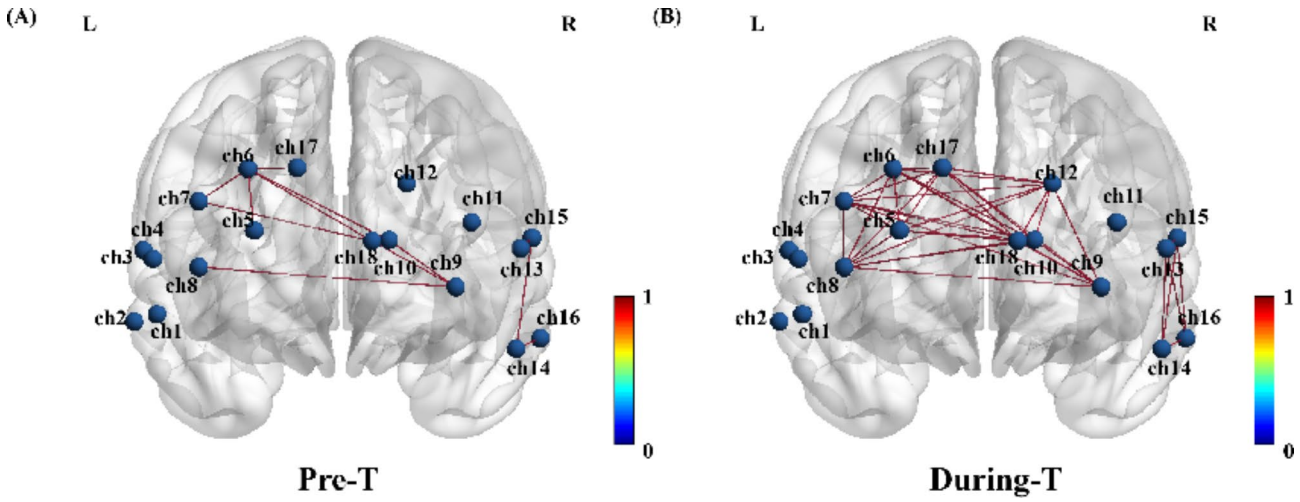

Fig. 5. Brain network diagram Pre-T (**A**) and During-T (**B**) binary matrix.

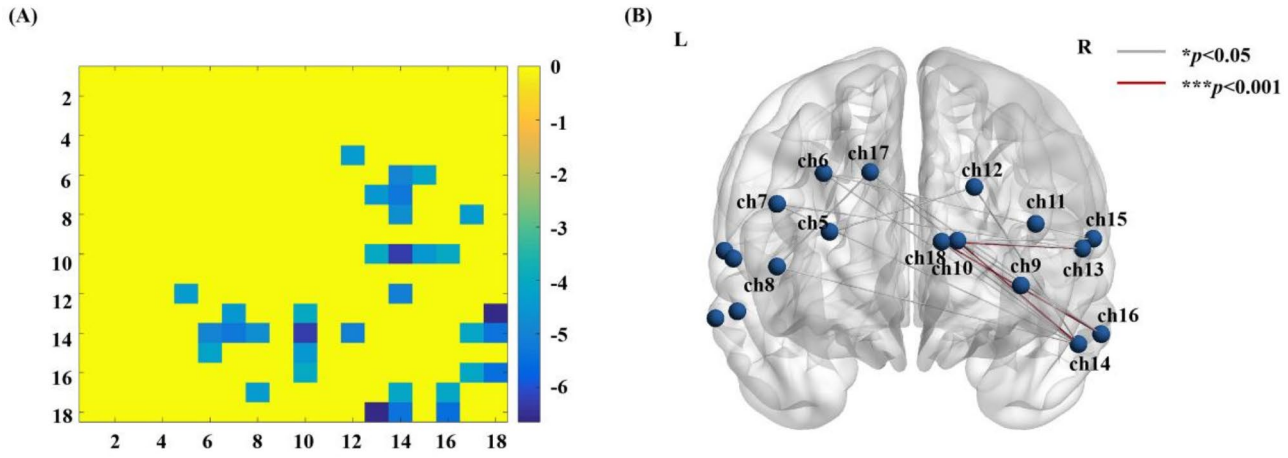

Fig. 6. Comparison of Pre-T and During-T (**A**) The color bar presents the t values. Cold colors indicate a significant increase in FC for During-T compared to Pre-T. (**B**) Channel-based connections with inter-group differences ($^{*}p < 0.05$). Among them. Red lines represent connections with highly significant differences ($^{***}p < 0.001$).

channel	t-value	*p*-value (FDR correction)
ch5-ch12	-4.3877	0.0032
ch6-ch14	-4.9529	0.0017
ch6-ch15	-4.1956	0.0041
ch7-ch13	-4.5022	0.0028
ch7-ch14	-5.2388	0.0012
ch8-ch14	-4.6994	0.0022
ch8-ch17	-4.4510	0.003
ch10-ch13	-4.0115	0.0051
ch10-ch14	-6.3001	0.0004***
ch10-ch15	-4.5160	0.0027
ch10-ch16	-4.0115	0.0051
ch12-ch14	-5.0208	0.0015
ch13-ch18	-6.6486	0.00029***
ch16-ch17	-4.0820	0.0047
ch16-ch18	-5.5048	0.0009***

Table 3. Comparison of Pre-T and During-T.

group. This indicates that TENS had a significant analgesic effect on the left hand of both FM patients. This is consistent with our findings that TENS reduces PFC activation in patients with chronic pain, indicating TENS has the potential to reduce pain.

In the analysis of fALFF, the fALFF values were significantly reduced in BA45 (ch16) and BA46 (ch1) of the prefrontal cortex during TENS. This finding is consistent with the active involvement of the prefrontal cortex in the perception and discrimination of pain. When pain is relieved, neural activity in these regions tends to decrease. BA45 and BA46 are involved in the processing and modulation of pain signaling. BA46 corresponds to the DLPFC, which is recognized as a cognitive-emotional regulatory area that exerts control over pain perception through top-down modulation. Lorenz et al. showed that activity in the DLPFC caused an imbalance between the cortex and the subcortical area and between the cortices producing top-down modulation and controlling pain perception[35]. Seminowicz et al. revealed that in cases of moderate pain stimulation, with a trend towards increasing catastrophization, the top-down modulation of pain in the DLPFC was attenuated, making pain suppression unlikely, resulting in chronic pain[36]. The prefrontal regions, specifically BA45 and BA46, play a role in perceiving and discriminating painful stimuli. These regions are located in the frontal lobe and are responsible for processing pain signals from the somatosensory cortex and spinal cord, thus generating our awareness of painful stimuli. During the TENS intervention, the intensity and frequency of pain signaling afferents may have been modulated and attenuated, thereby reducing pain perception. This reduction in pain signaling may have led to a decrease in BA45 and BA46 neural activity. This may be attributed to the possible alteration of neuromodulatory mechanisms within the brain, including neuronal activity and synaptic

transmission in the prefrontal cortex, during the TENS intervention. This modulation may involve the release of certain neurotransmitters and interactions between neurons to regulate and control pain signals. These modulatory effects may be mediated by influencing the excitatory and inhibitory activities of neurons, resulting in decreased neural activity in regions BA45 and BA46 of the prefrontal cortex. Therefore, the decrease in brain activity in the BA45 and BA46 regions is indicative of reduced pain perception, as supported by our research findings. It indicates that the brain regions involved in processing and interpreting pain signals are less engaged when pain is alleviated. In summary, the BA45 and BA46 regions in the prefrontal cortex are actively involved in the perception and discrimination of pain. When pain is relieved, neural activity tends to decrease in these regions, which is consistent with our research findings.

The study aimed to assess the changes in rsFC of the prefrontal cortex of the brain during TENS. Functional connectivity is defined as a strong temporal dependence between patterns of neural activation in different brain regions, which shows correlations between areas of cortical activity[37]. In FM patients, decreased FC was found across several cortical areas (medial prefrontal cortex, anterior and posterior cingulate areas, somatosensory cortex SII), as well as between the caudate and posterior cingulate areas and the insula[38]. Our study enhanced functional connectivity in the prefrontal lobes during TENS, which is consistent with previous studies. Disrupted functional connectivity within the PFC has been associated with increased pain catastrophizing. This increased connectivity may play a role in the regulatory function of the PFC in pain processing, ultimately leading to a reduction in pain perception and pain-related cognitive processes. Ultra-high-field imaging has shown that cognitive strategies to alleviate pain increase whole-brain connectivity[39]. We found that a higher performance of pain attenuation was predominantly associated with higher functional connectivity. We suggest that this increased connectivity is required to actively suppress activity in regions that contribute to pain processing, as previously reported. In particular, strengthened functional connectivity occurred mainly in the aPFC (subregion of BA10) and DLPFC (BA9 and BA46). The aPFC and DLPFC are essential components of the prefrontal cortex. BA10 is the largest area of the prefrontal cortex and plays a crucial role in self-referential processes, attention regulation, working memory, decision-making, and detecting important stimuli. This indicates that BA10 likely has a significant cognitive function in processing pain, such as appropriate attentional redirection, pain awareness, and pain response[40]. Research has indicated that the prefrontal cortex, specifically the BA10 area, is linked to the intensity of pain experienced. Miskowiak et al. conducted a study to investigate the impact of negative emotions on pain perception and brain activity. The findings revealed a significant association between the PFC, specifically BA10, and pain intensity in individuals with chronic pain. In other words, higher pain levels were accompanied by increased activity in the PFC[41]. Baliki et al. investigated the correlation of the functional connectivity between the PFC with other brain regions and the progression of pain processing. The results indicated a significant relationship between the functional connectivity of the PFC, particularly the basal ganglia, and the onset and transition of chronic pain. These findings suggest that the PFC, including BA 10, may be crucial in developing pain[17].

Notably, the variation between BA10 and BA44/45 was highly significant. BA44/45 are associated with language processing and cognitive control of pain. Thus, enhancing the strength of functional connectivity between these two brain regions may help improve patients' experience of and emotional response to pain. In conclusion, the strength of functional connectivity between BA10 and BA44/45 as an indicator of TENS for chronic pain may provide a new direction for personalized pain management and is expected to contribute to improving the quality of life of chronic pain patients.

Limitations

It is important to note several limitations of this study. Primarily, this study lacked the sham-TENS control conditions, which may impact participants' expectations and behavior due to their knowledge of the conditions, with potential implications for brain activity. To further validate our results and control for these potential biases, we plan to include sham-TENS control conditions in future studies to more accurately assess the effects of real TENS and control of psychological expectations. Additionally, we acknowledge the lack of short-distance measures for removing global hemodynamic changes as a limitation. This absence may affect the accuracy of our functional connectivity measurements, as global physiological fluctuations were not adequately accounted for. Future studies will incorporate short-distance channels to better control for these global changes, thereby enhancing the specificity and reliability of our findings. Furthermore, the treatment time of the typical TENS device XY-K-SJD series has six grades: 5 min, 10 min, 15 min, …, and 30 min. We should recruit more subjects that can be subdivided into the time of TENS treatment to explore the change of FC under different treatment times, which may get more comprehensive results. Finally, this study explored the immediate response of TENS to the brain, and dynamic follow-up is needed in the future to observe whether the correlation results of this study can be further verified with the decrease in patients' pain levels.

Conclusions

In conclusion, in this study, objective neuroimaging brain mapping parameters (FC coefficients) and conventional subjective assessment methods (VAS or PQSI) provided evidence regarding recovery for the TENS analgesic effect in chronic pain patients. The results showed that the FC of pain-related regions, including BA9, BA10, BA44/45, and BA46, could be used as a new quantitative method to evaluate the pain reduction effectiveness of TENS in chronic pain patients.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Received: 14 June 2024; Accepted: 12 November 2024
Published online: 25 November 2024

References

1. Miller, R. M. & Kaiser, R. S. Psychological Characteristics of Chronic Pain: a Review of Current Evidence and Assessment Tools to Enhance Treatment. *Curr Pain Headache R* 22, doi:ARTN 2210.1007/s11916-018-0663-y (2018).
2. Fan, B. F. *Report on the Development of Pain Medicine in China* (China Pain Medicine Development Report, 2020).
3. Li, X. H. et al. Oxytocin in the anterior cingulate cortex attenuates neuropathic pain and emotional anxiety by inhibiting presynaptic long-term potentiation. *Cell Rep* 36, doi:ARTN 10941110.1016/j.celrep.109411 (2021). (2021).
4. Mokhtari, T. et al. Transcutaneous Electrical Nerve Stimulation in Relieving Neuropathic Pain: Basic Mechanisms and Clinical Applications. *Curr Pain Headache R* 24, doi:ARTN 1410.1007/s11916-020-0846-1 (2020).
5. Sluka, K. A. & Walsh, D. Transcutaneous electrical nerve stimulation: Basic science mechanisms and clinical effectiveness. *J. Pain.* **4**, 109–121. https://doi.org/10.1054/jpai.2003.434 (2003).
6. Jin, D. M., Xu, Y., Geng, D. F. & Yan, T. B. Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: a meta-analysis of randomized controlled trials. *Diabetes Res. Clin. Pr.* **89**, 10–15. https://doi.org/10.1016/j.diabres.2010.03.021 (2010).
7. Johnson, M. I., Paley, C. A., Jones, G., Mulvey, M. R. & Wittkopf, P. G. Efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain in adults: a systematic review and meta-analysis of 381 studies (the meta-TENS study). *Bmj Open.* **12**, (2022). doi:ARTN e05107310.1136/bmjopen-2021-051073.
8. Zarei, A. A., Jensen, W., Jadidi, A. F., Lontis, E. R. & Atashzar, S. F. Gamma-band enhancement of functional brain connectivity following transcutaneous electrical nerve stimulation. *J. Neural Eng.* **19** ARTN 02602010.1088/1741-2552/ac59a1 (2022).
9. Pinti, P. et al. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Ann. Ny Acad. Sci.* **1464**, 5–29. https://doi.org/10.1111/nyas.13948 (2020).
10. Xu, S. Y., Cheong, L. I., Zhuang, Y., Couto, T. A. P. & Yuan, Z. Conducting concurrent Electroencephalography and Functional Near-Infrared Spectroscopy recordings with a Flanker Task. *Jove-J Vis. Exp.*, (2020). doi:ARTN e6066910.3791/60669.
11. Peng, K. et al. Morphine Attenuates fNIRS Signal Associated With Painful Stimuli in the Medial Frontopolar Cortex (medial BA 10). *Front Hum Neurosci* 12, doi:ARTN 39410.3389/fnhum.00394 (2018). (2018).
12. Sharini, H., Fooladi, M., Masjoodi, S., Jalalvandi, M. & Pour, M. Y. Identification of the Pain process by Cold Stimulation: using Dynamic Causal modeling of effective connectivity in Functional Near-Infrared Spectroscopy (fNIRS). *Irbm.* **40**, 86–94. https://doi.org/10.1016/j.irbm.2018.11.006 (2019).
13. Fox, M. D. & Greicius, M. Clinical applications of resting state functional connectivity. *Front. Syst. Neurosci.* **4** https://doi.org/10.3389/fnsys.2010.00019 (2010).
14. Petrovic, P. & Ingvar, M. Imaging cognitive modulation of pain processing. *Pain*. **95**, 1–5. https://doi.org/10.1016/S0304-3959(01)00467-5 (2002).
15. Li, Y. et al. Neural correlates of 12-h abstinence-induced craving in young adult smokers: a resting-state study. *Brain Imaging Behav.* **11**, 677–684. https://doi.org/10.1007/s11682-016-9544-3 (2017).
16. Yuan, K. et al. The implication of Frontostriatal Circuits in young smokers: a resting-state study. *Hum. Brain. Mapp.* **37**, 2013–2026. https://doi.org/10.1002/hbm.23153 (2016).
17. Baliki, M. N. et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat. Neurosci.* **15**, 1117–. https://doi.org/10.1038/nn.3153 (2012).
18. Masoumbeigi, M. et al. rTMS Pain Reduction Effectiveness in non-specific chronic low back Pain patients using rs-fMRI functional connectivity. *J. Med. Biol. Eng.* **42**, 647–657. https://doi.org/10.1007/s40846-022-00721-8 (2022).
19. Pang, D. Q. & Liao, L. M. Abnormal functional connectivity within the prefrontal cortex in interstitial cystitis/bladder pain syndrome (IC/BPS): a pilot study using resting state functional near-infrared spectroscopy (rs-fNIRS). *Neurourol. Urodynam.* **40**, 1634–1642. https://doi.org/10.1002/nau.24729 (2021).
20. Gonzalez-Castillo, J. et al. Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 8762–8767. https://doi.org/10.1073/pnas.1501242112 (2015).
21. Hou, X. et al. NIRS-KIT: a MATLAB toolbox for both resting-state and task fNIRS data analysis. *Neurophotonics*. **8** https://doi.org/10.1117/1.NPh.8.1.010802 (2021).
22. Fishburn, F. A., Ludlum, R. S., Vaidya, C. J. & Medvedev, A. V. Temporal derivative distribution repair (TDDR): a motion correction method for fNIRS. *Neuroimage*. **184**, 171–179. https://doi.org/10.1016/j.neuroimage.2018.09.025 (2019).
23. Xu, S. Y. et al. Altered Functional Connectivity in the Motor and Prefrontal Cortex for Children With Down's Syndrome: An fNIRS Study. *Front Hum Neurosci* 14, doi:ARTN 610.3389/fnhum.00006 (2020). (2020).
24. Fu, G. Y. et al. The neural correlates of the face attractiveness aftereffect: a functional near-infrared spectroscopy (fNIRS) study. *Neuroimage*. **85**, 363–371. https://doi.org/10.1016/j.neuroimage.2013.04.092 (2014).
25. Yang, H. et al. Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage.* **36**, 144–152. https://doi.org/10.1016/j.neuroimage.2007.01.054 (2007).
26. Zou, Q. H. et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J. Neurosci. Meth.* **172**, 137–141. https://doi.org/10.1016/j.jneumeth.2008.04.012 (2008).
27. Yu, Y. et al. Altered amplitude of low-frequency fluctuations in inactive patients with nonneuropsychiatric systemic Lupus Erythematosus. *Neural Plast.* Artn 940861210.1155/2019/9408612 (2019). (2019).
28. Wang, B. et al. Decreased Complexity in Alzheimer's Disease: Resting-State fMRI Evidence of Brain Entropy Mapping. *Front. Aging Neurosci.* **9** ARTN 37810.3389/fnagi.2017.00378 (2017).
29. Zhang, B. L. et al. Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. *Brit J. Anaesth.* **123**, E303–E311. https://doi.org/10.1016/j.bja.2019.02.021 (2019).
30. Xia, M. R., Wang, J. H. & He, Y. BrainNet Viewer: A Network visualization Tool for Human Brain Connectomics. *Plos One*. **8** https://doi.org/10.1371/journal.pone.0068910 (2013).
31. Zhou, F. Q. et al. Altered low-frequency oscillation amplitude of resting state-fMRI in patients with discogenic low-back and leg pain. *J. Pain Res.* **11**, 165–176. https://doi.org/10.2147/Jpr.S151562 (2018).
32. Zhang, S. S., Wu, W., Yang, J. M. & Wang, C. H. Abnormal spontaneous brain activity in Acute Low-Back Pain revealed by resting-state functional MRI. *Am. J. Phys. Med. Rehab.* **96**, 253–259. https://doi.org/10.1097/Phm.0000000000000597 (2017).
33. Lin, G. W. et al. Resting-state functional connectivity alteration in elderly patients with knee osteoarthritis and declined cognition: An observational study. *Front Aging Neurosci* 14, doi:ARTN 100264210.3389/fnagi.1002642 (2022). (2022).
34. Eken, A., Kara, M., Baskak, B., Baltaci, A. & Gökçay, D. Differential efficiency of transcutaneous electrical nerve stimulation in dominant versus nondominant hands in fibromyalgia: placebo-controlled functional near-infrared spectroscopy study. *Neurophotonics* 5, doi:ARTN 01100510.1117/1.NPh.5.1.011005 (2018).
35. Lorenz, J., Minoshima, S. & Casey, K. L. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain*. **126**, 1079–1091. https://doi.org/10.1093/brain/awg102 (2003).
36. Seminowicz, D. A. & Davis, K. D. Cortical responses to pain in healthy individuals depends on pain catastrophizing. *Pain.* **120**, 297–306. https://doi.org/10.1016/j.pain.2005.11.008 (2006).

37. Rubinov, M. & Sporns, O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. **52**, 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003 (2010).
38. Cifre, I. et al. Disrupted functional connectivity of the Pain Network in Fibromyalgia. *Psychosom. Med.* **74**, 55–62. https://doi.org/10.1097/PSY.0b013e3182408f04 (2012).
39. Schulz, E. et al. Ultra-high-field imaging reveals increased whole brain connectivity underpins cognitive strategies that attenuate pain. *Elife*. **9** ARTN e5502810.7554/eLife.55028 (2020).
40. Dorociak, K. E. et al. Pain influences Neuropsychological Performance following Electrical Injury: a cross-sectional study. *J. Int. Neuropsych Soc.* **29**, 35–45 (2023). doi:Pii S135561772100147810.1017/S1355617721001478.
41. Miskowiak, K. W. & Petersen, C. S. Neuronal underpinnings of cognitive impairment and - improvement in mood disorders. *CNS Spectr.* **24**, 30–53. https://doi.org/10.1017/S1092852918001062 (2019).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (62371300), Military High-level Scientific and Technological Innovation Talent Project ([2020]NQ06128), and Changhai Hospital Clinical New Technology Incubation Project (2024XA0004).

Author contributions

Y.L, J.D, and P.S did research concept generation; Y.L and J.D did experimental methodology design and experimental collection; P.S performed experimental design validation and verification, research project management, and research funding acquisition; Y.L performed experimental data analysis, data collation and management, first draft of the paper, and visualization of experimental results; J.D and H.Y reviewed the paper; P.S and F.F performed the supervision and guidance of the research project.

Declarations

Ethical approval

This study was approved by the Ethics Committees of Yueyang Hospital of Integrative Medicine of Shanghai University of Traditional Chinese Medicine and Changhai Hospital of Naval Medical University, and by the China Clinical Trial Registry (ChiCTR2200056394).

Informed consent

Verbal informed consent was obtained from patients to publish their anonymized information in this article.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to P.S.