Effects of The Prolong Life With Nine Turn Method (Yan Nian Jiu Zhuan) Qigong On Brain Functional Changes in Patients With Chronic Fatigue Syndrome in Terms of Fatigue and Quality of Life

Fangfang Xie
Shanghai University of Traditional Chinese Medicine

Ziji Cheng
Shanghai University of Traditional Chinese Medicine

Yuanjia Gu
Shanghai University of Traditional Chinese Medicine

Ziying Chen
Shanghai University of Traditional Chinese Medicine

Chaoqun Xie
Shanghai University of Traditional Chinese Medicine

Fei Yao (doctoryaofei@126.com)
Shanghai University of Traditional Chinese Medicine

Yanli You
ChangHai Hospital, Naval Medical University

Research Article

Keywords: chronic fatigue syndrome, prolong life with nine turn method, fatigue, quality of life, ALFF, FC

Posted Date: October 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-963598/v1

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Abstract

Background: Chronic fatigue syndrome (CFS) is characterized by persistent fatigue, which often leads to physical and psychological damage. The prolong life with nine turn method (PLWNT) Qigong is considered one of the complementary treatments for improving symptoms in patients with CFS. However, the neurophysiological relevance of these effects remains poorly understood. In this study, we used functional magnetic resonance imaging (fMRI) to study the effects of PLWNT intervention on the neural circuits in subjects with CFS.

Methods: Thirty four CFS patients were randomly divided into a PLWNT group (who received Qigong exercises) and a control group (who received cognitive behavioral therapy, CBT). Both groups were taught by a highly qualified professor at the Shanghai University of Traditional Chinese Medicine once a week and were supervised online during the remaining 6 days at home, over 12 consecutive weeks. We calculated the regional rs-fMRI index ALFF for all subjects. To study the changes of the brain network, we used the brain regions with significant differences in ALFF as the regions of interest for whole-brain FC analysis. The MFI-20 and SF-36 were used for clinical symptom assessment to explore the possible correlation between the rs-fMRI indicators and clinical variations.

Results: The ALFF values of the right superior frontal gyrus (SFG), and left median cingulate gyrus (DCG) were increased, whereas those of the left middle occipital gyrus (OG), right middle OG and left middle temporal gyrus (MTG) were decreased in CFS patients. The FC values between the DCG and middle temporal gyrus (MTG), and those between the left OG and the right OG were enhanced. In addition, the SF-36 were positively with the left OG (r=0.542), SFG(r=0.517) and DCG(r=0.533), MFI-20 were negatively with the left OG (r=-0.583), SFG(r=-0.542) and DCG(r=-0.578). These results were all corrected by FWE (voxel level p < 0.001, cluster level p < 0.05).

Conclusion: In conclusion, PLWNT can relieve the fatigue symptoms of CFS patients and improve their quality of life. CFS patients have abnormal regional spontaneous neuronal activity and abnormal functional connections between regions after PLENT intervention. The study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (Ethics Approval Number: 2018-043), and registered in the American Clinical Trial Registry (12/04/2018), Registration Number is NCT03496961.

1. Introduction

Chronic fatigue syndrome (CFS), also called myalgic encephalomyelitis, is a complex multisystem disease. It is commonly characterized by chronic fatigue lasting more than 6 months that is not alleviated after resting, and accompanied by cognitive dysfunction, sleep problems, autonomic dysfunction, post-exertional malaise, severely impaired activities of daily living, and/or pain in muscles or joints[1, 2]. CFS is associated with poor health-related quality of life, even worse than cancer, multiple sclerosis, and stroke[3]. In fact, approximately 25–29% of CFS patients are house- or bed-bound[4]; over half of the
patients are unemployed\[^{5}\], and only 19% work full time\[^{6}\]. Although the mechanism underlying neurological dysfunction in CFS is not yet clear, CFS may be considered a prototypical disorder of brain connectivity\[^{7, 8}\]. The prevailing neuroimaging studies have suggested that the brain responds differently to a cognitive challenge in patients with CFS, with recruitment of wider regions to compensate for lower or higher information capacity\[^{9}\]. There is increasing neuroimaging evidence of functional and structural abnormalities in the brain of CFS patients, suggesting that the central nervous system is involved in this disorder and that at least some CFS patients may have an underlying neurological basis for their illness\[^{10}\]. Various drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDS), antidepressants, and COX-2 inhibitors, have been used to help relieve and manage the symptoms\[^{11, 12}\]. However, the use of antidepressants is controversial and has significant side effects. Complementary and alternative medicine (CAM) is very popular among patients with diseases/illnesses of unknown etiology\[^{13, 14}\]. Cognitive behavioral therapy (CBT) seems to be a promising CAM for CFS\[^{15–17}\] however, persistent or sustained significant outcomes have been shown in few CFS patients\[^{18}\]. Many other CAM modalities, such as traditional Japanese herbal medicine (Kampo)\[^{19}\], acupuncture\[^{20, 21}\], and Qigong\[^{22, 23}\], have demonstrated to be effective treatment and prevention methods in relieving fatigue, depression, and insomnia.

Qigong (pronounced “chee gung”) is a therapeutic Chinese practice that has been used for thousands of years to optimize and restore energy (Qi) to the body, mind, and spirit\[^{24}\]; based on Taoist philosophy and Chinese medicine theory\[^{25}\], it promotes health and vitality through gentle exercises for the breath, body and mind\[^{26}\]. Prolong life with nine turn method (PLWNT) is a type of Qigong that includes eight kinds of massage manipulations on the abdomen and a kind of upper body shaking. The exercise process focuses on practicing muscles, bones and skin externally, and training the spirit, breath and energy internally, so that the essence is sufficient, and the internal and external coordination is unique. It is a unique method of prolonging life\[^{27}\]. Other forms of Qigong have been found to be equally temporarily effective\[^{28, 29}\]. The findings of PLWNT Qigong interventions may open a new page for the study of the effects of Qigong on humans, which can provide overall coordination to help the body achieve a state of relative equilibrium of yin and yang, dredging meridians, and restoring physiological function. Some studies have reported on the effects of massage techniques on fatigue and quality of life\[^{30–32}\]. Other studies have shown that abdominal massage manipulation therapy of PLWNT can relieve muscle tension and regulate mood through electromyographic signals, neuromuscular synthesis, and nerve rhythm, thereby significantly relieving sleep disorders, fatigue, and depression symptoms of CFS patients and improving their quality of life\[^{33}\]. Our recently published protocol for this project predicts that PLWNT Qigong exercise can improve fatigue, sleep and depression in CFS patients, and improve the quality of life\[^{34}\]. However, the exact mechanism behind this phenomenon is still unknown.

Functional magnetic resonance imaging (fMRI) helps in noninvasive examination, localization, as well as lateralization of brain functions such as language and memory\[^{35}\]. It is a powerful imaging technique, which has received substantial attention in brain disorder research\[^{36–38}\]. Recently, there has been an
apparent shift in the focus of neuroscience research to studies dealing with the brain at ‘resting state’, which involve measurement of ongoing spontaneous brain activity amplitude of low-frequency fluctuations (ALFF) and mapping of interregional functional connectivity (FC)\(^{39-41}\). Related studies have shown that the destruction of normal brain function may be the basis of the core symptoms of CFS, including fatigue, pain, anxiety, and depression, all of which affect the quality of life\(^{42,43}\). More than 80% of CFS patients report symptoms of anxiety and depression, especially sleep problems\(^{44}\). Some neuroimaging studies have shown that CFS patients have reduced gray matter volume and white matter changes\(^{45}\) in seed brain areas (regions of interest, ROI) related to CFS symptoms, such as memory (parahippocampal gyrus, PHG), motor skills (globus pallidus), emotional processing (anterior cingulate cortex), and higher-order neurocognitive functions, which have been widely used to assess the internal state of brain function\(^{46}\). Compared with control group, CFS patients show more extensive activation of brain regions, manifested by functional abnormalities in the prefrontal, parietal, and limbic areas\(^{47}\). However, few studies have investigated the effects of PLWNT intervention on CFS patients in terms of fatigue and quality of life.

Here, we used fMRI to examine the effect of PLWNT intervention on fatigue and quality of life of CFS patients. The neuronal activity and the distribution of high-level node connections play a vital role in the transmission of information throughout the brain\(^{48}\). Based on functional correlation and physiological basis, the entire neurological system of patients with CFS is usually affected\(^{49,50}\). A number of studies have shown that FC and ALFF indicators, which can detect central connections through voxel-based graphical analysis methods, are closely related to physiological indicators such as regional cerebral blood flow, oxygen, and glucose metabolism\(^{51,52}\). Therefore, we used the fMRI fast Fourier transform (FFT) algorithm to identify the changes in the central brain activity in the power spectrum observation area and to evaluate the synergy and antagonism of the BOLD signal at the voxel level to explore the effect of PLWNT on CFS. The purpose of this study was to investigate the neurological abnormalities in CFS patients at resting state and the regulatory effect of PLWNT on the functional network of CFS neuronal activity and functional connections.

2. Materials And Methods

2.1 Subjects

Thirty-four people were recruited for this study, 4 of them (2 in PLWNT group and 2 in control group) were excluded because their head motion was more than 2.5 mm translation (FD standard) during the scanning process. Thus, 30 subjects (15 in the PLWNT group and 15 in the control group) were finally included. The recruitment of the subjects was conducted from December 2018 to September 2019 at the Shanghai University of Traditional Chinese Medicine and Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. We included hospitalized patients with a preliminary diagnosis of CFS, according to the latest Revise Guidelines for Treatment of Chronic Fatigue Syndrome in 2021\(^{53}\). The inclusion criteria were as follows: (1) age between 20 and 60 years; no gender requirement; (2) severe
chronic fatigue that is unexplained after clinical evaluation and has a history of no less than 6 months; fatigue was not caused by the work performed during the trial, and the fatigue was not alleviated after rest; and (3) at least four of these eight symptoms (memory or concentration decline, failure to regain energy after sleep, sore throat, headache, lymph node tenderness, muscle pain, multiple joint pain, and myalgia after exertion for more than 24 hours). The exclusion criteria were as follows: severe cardiovascular and cerebrovascular diseases, endocrine system diseases, motor system diseases, autoimmune diseases, infectious diseases, use of medications that may affect the judgment of the results. The detailed fundamental information of CFS subjects is available in our previously published protocol[27].

2.2 Design

This study was designed as a randomized, parallel-controlled trial. The participants were randomly assigned to the PLWNT group and the control group. Qigong or cognitive behavior education and learning were conducted at Shanghai University of Traditional Chinese Medicine, each taught by a senior exercise teacher and a psychology teacher. Exercise was practiced at home no less than six times a week. The total duration of the study was 12 weeks. We distributed exercises/learning notebooks every week for recording their exercises/learning until the end of the experiment. Detailed information is available in the previously published protocol[27]. The study was conducted in accordance with the Declaration of Helsinki and the International Code of Ethics for Biomedical Research Involving Human Subjects. It was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (Ethics Approval Number: 2018-043), and registered in the American Clinical Trial Registry (12/04/2018), Registration Number is NCT03496961.

2.3 Intervention

PLWNT group

Qigong professors at Shanghai University of Traditional Chinese Medicine, who have been engaged in Qigong education for at least 5 years, were in charge for the supervision of the exercise and corrected the exercise posture during the entire intervention period for one hour every Sunday. Professional Qigong teachers spent 10 minutes to perform stretching and relaxation exercises, as well as movement introductions and demonstrations. In addition, they explained precautions during the process and answered the participants’ questions. Subsequently, the teachers gave 30 minutes of action guidance and correction to each of the participants. Finally, all of the participants practiced Qigong for 20 minutes together. For the remaining 6 days of the week, all the participants in the WeChat cluster had to join WeChat video supervision and practice for 30 minutes at 6 o’clock every day. If some of the participants found it inconvenient, the private WeChat video surveillance exercise was conducted. Each participant filled in the “Working Practice Record” after every exercise. The entire practice process lasted for 12 weeks. The content of PLWNT Qigong intervention was the same as in our previous research[27]. The nine specific forms of manipulations are shown in Figure 1.
Step 1. Preparatory position.

First, relax the whole body, concentrate on your thoughts, evenly breathe, put your tongue against the upper jaw, hold your dantian with your mind, and operate step by step.

Step 2. PLWNT’s first eight types of abdominal massage

1. Press the Danzhong acupoint (under the xiphoid process) with three fingers in both hands, make a circle 21 times from the left and complete in 3 minutes.
2. With three fingers in both hands, rub down from Danzhong acupoint and move to the pubic symphysis below the umbilicus, complete 21 times in 3 minutes.
3. With three fingers in both hands, rub up from the pubic symphysis to the two sides, and rub and walk to Danzhong point until the hands were handed over, 21 times are completed in 3 minutes.
4. With two hands and three fingers, push down from Danzhong acupoint and push it straight to the pubic symphysis 21 times, which is completed within 3 minutes.
5. Rub the abdomen with the right hand from the left 21 times and complete within 3 minutes.
6. Rub the abdomen with the left hand and from the right 21 times, within 3 minutes.
7. Place the left hand on the left side of the lower waist and kidney, with the thumb forward, and the four fingers supporting the back, gently pinch it; With three fingers on the right hand, push straight from the bottom of the left breast to the groin, completing 21 times in 3 minutes.
8. Place the right hand on the right side of the lower waist and kidney, with the thumb forward, and the four fingers supporting the back, gently pinch it; With three fingers on the left hand, push straight from under the right breast to the groin, completing 21 times in 3 minutes.

Step 3. Seated rocking method

Sit cross-legged, hold your hands slightly, and press your knees. The toes of both feet are also slightly bent, and the upper body is turned clockwise 21 times before turning from the left and back from the right. Then turn it counterclockwise 21 times.

Control group

CBT therapists with sufficient professional qualifications [e.g., diploma in CBT, or other professionally accredited qualifications involving CBT as a major part of training (e.g., a clinical or counseling psychologist degree)] were invited to conduct CBT by giving lectures or psychological consultations on the prevention and treatment of CFS for one hour, once a week. For the remaining 6 days of the week, all the participants in the WeChat cluster had to join WeChat video surveillance and listen to lectures for 30 minutes every day. If some of the participants found it inconvenient, the private WeChat video surveillance Microsoft PowerPoint learning was conducted. Each participant was asked to fill in the “Working Practice Record” after each video study to ensure that the other conditions were the same as
those of the PLWNT group. The entire practice process lasted for 12 weeks. The detailed information is available in the previously published protocol[27].

2.4 Data acquisition

The fMRI data were obtained from all the participants, using the 3.0-T Trio Siemens System at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China. The 32 head coils were used for scanning. In resting state BOLD signal acquisition single excitation gradient echo-plane imaging (GE-EPI) sequence, 30 participants were scanned as follows: repetition time (TR) = 1,900 ms; effective echo times (TE) = 2.93 ms; sagittal slices = 188; thickness/skip = 1.2/0.6 mm; field of view (FOV) = 256×256 mm²; matrix = 240×256 mm²; voxel size = 1.0×1.0×1.0; phase encoding direction = A > > P; and flip angle (FA) = 90°. The subjects were asked to close their eyes and rest for 10 minutes, and not to think about anything before the scan. They were instructed not to move their head during data collection. We obtained 242 three-dimensional image volume parameters as follows: TR = 2,000 ms; TE = 30 ms; section thickness = 1 mm; sagittal slices = 32; FOV = 256×256 mm²; matrix = 64×64 mm²; and FA = 90°. Both groups of the subjects were tested before and after the experiment.

The structural imaging data were processed using MATLAB 2015a (MathWorks, Natick, MA, USA) and SPM12 (Wellcome Department of Cognitive Neurology, UK). MRICON was used to convert DICOM scan format to NIFTI format and eliminate the 10 abnormal time points before the scan. Next, we eliminated the difference in the scanning time of the fMRI signal compartment and the artifacts caused by slight head movement. We excluded the subjects whose head motion was greater than 2.5 mm translation (FD standard). Then, we match the functional image after head movement correction with the cut structure image to achieve the mapping of the individual image to the standard brain template space, and then unified it to the Montreal Neurological Institute (MNI) space, and re-sampled at 3 mm×3 mm×3 mm voxel size. Subsequently, we co-registered the functional image with the T1 image, used 10 mm full-width half-maximum (FWHM) to check the space for smoothing, de-trended the resampled image, and then calculated the ALFF of each participant index. To study the changes of the brain network, we used the brain areas with significant differences as the regions of interest for the whole-brain FC analysis.

2.5 Amplitude of low-frequency fluctuations (ALFF)

The ALFF uses the level of the BOLD signal and the FFT algorithm to convert the smooth signal of each voxel from the time domain to the frequency domain, thereby obtaining changes in brain activity in the power spectrum observation area. ALFF mainly calculates the value distributed in the range of 0.01–0.08 Hz after the square of the power spectrum, reflecting the strength of neuronal activity in each brain area.

2.6 Functional connectivity (FC)

FC is the degree of correlation of BOLD sequences in different brain regions in the time dimension. Each voxel of the brain area contains a time series, which represents the level of the area-dependent signal
changes over time. We used brain regions with significant differences in ALFF as regions of interest to perform whole-brain FC analysis to study the changes in the brain network. The changes in the time series can determine that the brain regions that positively correlate with the BOLD signal are functionally synergistic and negative. The related brain areas are antagonistic. The most common FC is voxel-wise FC, that is, the functional connection based on seed points. The specific process is to select a seed point and calculate the correlation between the seed point and the BOLD signal of all voxels in the whole brain.

2.7 Statistical analysis

The clinical data were analyzed using SPSS 21.0 software package (SPSS version 21.0, SPSS Inc. Chicago, IL, USA). For measurement data, such as age and scale score, the average value ± standard deviation (S) was used. The measurement data complying with the normal distribution and the test of homogeneity of variance were tested by an independent sample t-test. For non-normally distributed measurement data, pairwise comparisons between groups were based on the Mann–Whitney nonparametric test for two independent samples. In addition, to evaluate the abnormal brain activity of CFS patients, after data preprocessing, we used SPM12 to perform a two-sample t-test between the ALFF average image groups, with p < 0.05 and the brain area corrected by FWE (family-wise error) considered statistically significant at p < 0.05. Then, we took the ALFF different brain areas as the points of interest and counted the differences in FC between the ROI and the whole brain. The specific process was to make functional connections between the seed areas (ALFF different brain areas) and all voxels of the whole brain. We used Fisher transform to obtain the correlation value of the normal distribution z scores of the two sets of images with $z = \log_e \frac{1+r}{1-r}$ (r is the correlation coefficient), which obtained the FC average image. A two-sample t-test was performed between the groups. Differences were statistically significant at p < 0.05 and the brain area corrected by FWE. We used XJVIEW to present the results. The Spearman correlation analysis was used to study the possible relationship between the ALFF brain nerve activation area and the clinical features of the MFI-20 and SF-36 scale scores.

3. Results

3.1 Demographic and clinical characteristics

Thirty-four people were recruited for this study, 4 of them (2 in PLWNT group and 2 in control group) were excluded because their head motion was more than 2.5 mm translation (FD standard) during the scanning process. Finally, 15 in the PLWNT group and 15 in the control group were finished tested using fMRI in a randomized controlled trial before and after the study. The clinical and demographic characteristics and the intergroup differences are shown in Table 1. There were no significant differences between PLWNT group and control groups in terms of age, weight, height, gender and education (p>0.05), which confirmed the two groups were comparable.
Table 1

Demographic and clinical characteristics of the patients.

|                  | PLWNT (n=15)         | Control (n=15)        | P value |
|------------------|----------------------|-----------------------|---------|
| Age (year)       | 37.94±11.3447        | 37.34±9.864           | 0.935   |
| Weight (kg)      | 59.80±10.893         | 61.94±12.061          | 0.557   |
| Height (cm)      | 163.51±6.679         | 165.00±7.376          | 0.209   |
| Gender (M:F)     | 7:8                  | 6:9                   | 0.420   |
| Education (year) | 11.82±3.25           | 11.23±2.86            | 0.641   |
| MFI-20           | 10.55±2.896          | 10.93±2.872           | 0.513   |
| SF-36            | 45.02±8.266          | 45.40±8.082           | 0.828   |

3.2 ALFF changes

We observed significant activation of ALFF neuronal activity in CFS patients (p<0.05). Compared with the control group, the brain areas with significantly enhanced ALFF value in the PLWNT group were the right superior frontal gyrus (SFG) and left median cingulate gyrus (DCG). In contrast, the areas with decreased ALFF value in the PLWNT group included the left middle occipital gyrus (OG) and left middle temporal gyrus (MTG). These regions were all corrected by FWE, with voxel level p < 0.001 and cluster level p < 0.05 (Table 2, Figure 2).

Table 2

Compared with the control group, the brain areas enhanced and reduced ALFF value in the PLWNT group. These regions are all corrected by FWE, with voxel level p<0.001 and cluster level p<0.05

| Cluster | L/R | Regions | X   | Y   | Z   | Voxel | T-values |
|---------|-----|---------|-----|-----|-----|-------|----------|
| Cluster 1 | L   | OG      | -24 | -81 | 12  | 78    | -4.7812  |
| Cluster 2 | R   | OG      | 21  | -90 | 6   | 55    | -5.0478  |
| Cluster 3 | R   | SFG     | 6   | 51  | 36  | 35    | 4.6676   |
| Cluster 4 | L   | DCG     | 0   | -18 | 45  | 35    | 5.0678   |
| Cluster 5 | L   | MTG     | -39 | -63 | 15  | 197   | -6.6237  |

3.3 FC changes

To study the changes in the brain network, we took the brain regions with significant differences in ALFF as the regions of interest (ROI) for whole-brain FC analysis, and finally obtained two ROIs: OG and DCG.
Compared with the control group, the FC values between the DCG and MTG (Table 3, Figure 3), and those between the left OG and the right OG were enhanced (Table 3, Figure 3).

Table 3  Compared with the control group, the FC values between the DCG and MTG.

| ROI  | Regions             | X    | Y    | Z    | Voxel | T-value | P-value |
|------|---------------------|------|------|------|-------|---------|---------|
| ROI-1| DCG  MTG            | 51   | -39  | -6   | 47    | 5.83    | <0.05   |
| ROI-2| OG  right middle occipital gyrus | 30   | -81  | 39   | 76    | 4.92    | <0.05   |

3.4 Correlation between the rs-fMRI parameters and the clinical features

Since fatigue and quality of life were the focus of the study, the additional correlation analysis between the scales and brain activation areas outcomes were performed. The Pearson correlation coefficient was used for calculation to test the relationship between the scales of total score of the Multidimensional Fatigue Inventory (MFI-20), Health Survey Short Form (SF-36) and the brain activation of OG, SFG, and DCG. PLWNT interfered with neuronal activity and had a significant impact on the scores of SF-36 and MFI-20. The clinical symptoms in SF-36 were positively with the left OG (r=0.542), SFG(r=0.517) and DCG(r=0.533), and clinical symptoms in MFI-20 were negatively with the left OG (r=-0.583), SFG(r=-0.542) and DCG(r=-0.578). P-values were all less than 0.05. The results of the correlation analysis are shown in Figure 4 (a-f).

4. Discussion

This study used resting-state fMRI to analyze the effect of PLWNT intervention on the activation of brain network neurons and FC changes in CFS patients. The change in resting state network (RSN) is related to the lack of mental activity, which seriously affects the quality of life\[54\]. It is currently believed that RSN has strong spontaneous activity, and it is also the most common neural network for evaluating quality of life, involving cognitive control, attention, language processing, and working memory\[55\], including the OG, angular gyrus, MTG, SFG and DCG\[56\]. RSN brain area is related to the maintenance of the brain’s alertness to the outside world and introspection\[57\]. Previous studies have shown that CFS can lead to impaired RSN function, which is manifested when performing externally targeted tasks such as cognitive memory tasks\[58, 59\]. As shown in our study, the OG and MTG of the PLWNT group of patients belong to RSN and have a lower ALFF value compared with the control group. This suggests that long-term fatigue, insomnia, and poor quality of life in CFS patients can cause damage to the brain’s advanced cognitive memory function. The injury of a certain center does not permanently remove the function managed by the center, the function can be compensated by other areas to restore the function to a certain extent after
exercises\textsuperscript{[60]}. This may be a neural compensation mechanism for the functionally damaged brain areas in CFS patients after PLWNT treatment. The ALFF values of the SFG and DCG were all increased. This shows that when CFS patients suffer from fatigue and sleep disturbance that affect their quality of life, there are new strengthened brain areas that continue to complete specific neuronal activities and brain functional activities.

Our study showed that 12 weeks of PLWNT intervention had a positive effect on ALFF and FC of abnormal brain regions of OG, SFG, and DCG in patients with CFS. The FC values between the DCG and MTG, and between the left OG and the right OG were all enhanced. In previous studies, these brain areas have been linked to fatigue and quality of life\textsuperscript{[61–63]}. We used correlation analysis to observe the relationship between ALFF, FC, and the improvement of clinical symptoms. The results of our study showed that among patients receiving Qigong, these brain activation areas positively correlated with the clinical symptoms in SF-36 and negatively correlated those in MFI-20 in terms of fatigue, physical pain, and lack of energy, thereby suggesting that PLWNT may objectively reflect the quality of life of CFS patients through the DCG, SFG, and OG neuronal activity. Compared with other analyses, ALFF analysis can suppress nonspecific signals more effectively, thereby significantly improving the neuron specificity for detecting spontaneous activity in brain regions\textsuperscript{[64]}. The FC analysis focuses on the similarity of spontaneous brain activity within and between regions, with the ALFF activation area as the point of interest\textsuperscript{[65]}. Changes in the ALFF and FC values of DCG, SFG, and bilateral OG suggest that patients with CFS have increased hemodynamic response to local neural activity or the brain's compensatory response to fatigue. These findings provide support that PLWNT Qigong intervention may actively improve the clinical symptoms of CFS patients. DCG, SFG, and OG can reflect the spontaneous neural activity of the brain and the activation of CFS abnormal brain areas. The changes in DCG, SFG, and OG can help to understand the changes in brain nerve function in CFS patients after exercises.

Higher-order level cognitive dysfunctions, such as those of memory and cognition, are well-known in CFS\textsuperscript{[66]}, and recent studies have also documented the effects of basic sensory processing deficits on quality of life\textsuperscript{[67,68]}. In CFS patients, there are also perceptual defects of the visual system\textsuperscript{[67–69]}. In the human brain, the OG is the main brain region of DMN for visual processing, which is involved in memory acquisition. The ratio of occipital neurons to glial cells is the smallest, and the efficiency of removing potassium ions is the lowest, which in turn affects the membrane potential and ultimately reduces excitability, reduces exercise capacity, and includes symptoms such as fatigue, which reduces the quality of life. Therefore, the OG is the most common site of CFS\textsuperscript{[70]}. Bilateral OG cortex contains topographic maps of size and orientation preference, in which neural responses to stimulus sizes and stimulus orientations are modulated by intrarregional lateral connections. We propose that these lateral connections may underlie the selective influence of PLWNT Qigong on visual perception\textsuperscript{[71,72]}. Using diffusion-tensor imaging, researchers have found that the white matter of the right suboccipital tract of Gulf War syndrome veterans with visual neglect was damaged in connection with the occipital cortex, which was manifested by severe fatigue, sleep, and decreased quality of life\textsuperscript{[73]}. A resting-state ASL-fMRI study also pointed out that the functional connection between the OG structure and the cerebral cortex of
CFS patients was damaged, which was related to the degree of fatigue and quality of life[46]. In our study, the OG structure (middle occipital gyrus, supraoccipital gyrus) of CFS patients showed decreased neuronal activity. These convergent results emphasize the possibility that memory decline, unrecoverable fatigue, and the decreased quality of life in CFS patients may be related to OG dysfunction. Apart from the increase in OG neural activity, this study revealed that long-term Qigong exercises actively increased FC between the bilateral OG. These effects may be related to the ability of Qigong to change the brain's functional networks related to the processing of external visual stimuli[74, 75]. To our knowledge, the enhancement of FC in OG has not been reported to play a role in CFS quality of life, which may suggest that the FC of the OG dysfunction may affect the quality of life of CFS patients and may also be involved in the pathogenesis of CFS.

The defects of the somatic motor center seem to be related to the higher levels of fatigue in CFS, somatic pain, energy disorders, and other aspects of the quality of life[76–78]. Researchers have early recognized the importance of the motor function of the somatic motor center in explaining mental fatigue, but the structure of the somatic motor center and OG is not sufficient to explain the model. Subsequently, brain area networks including SFG, DCG, and MTG have also been shown to be related to fatigue[79, 80]. SFG corresponds to the somatosensory center, which is mainly responsible for processing spatial information, attention control, and somatosensory information. SFG is of great significance to the adjustment of the quality of life such as fatigue, anxiety, and depression of CFS patients, as well as for the improvement of functional activities, learning, and memory[74, 81, 82]. A recent study has found that the SFG area is widely activated when CFS patients participate in activities. Although it is not clear whether these activations are caused by positive or negative emotions, it shows that severely fatigued brains need to activate the right frontal lobe and adjacent areas[74]. This may be caused by the accumulation of free radicals caused by excessive neural activity of SFG in chronic fatigue, which induces brain oxidative stress. It is speculated that the overactivity of the SFG area of the brain may be related to the pathophysiological changes of CFS structure, neurotransmitter dynamics, and frontal mitochondrial function[83, 84]. Compared with the control group, the SFG neuron activity in the PLWNT group was abnormally increased. Consistent with the results of our study, research has shown that the white matter of the brain area related to cognition promotes information transmission in the brain and makes the nervous system fast and effective[85]. Any disorder of these neurological functions will affect the quality of life, including memory, attention, energy, and executive function, as shown in CFS[85–87]. In addition, SFG is related to deficits in working memory, impaired attention, poor motor coordination, and inability to concentrate vision. This area plays an important role in connecting the frontal and temporal lobes[88, 89]. The above findings may reflect that PLWNT intervention increased the activation of SFG neurons and the functional integration with MTG. This change may improve higher-level processes such as fatigue and quality of life.

The fatigue symptoms of CFS and the decline in quality of life are closely related to the transition network that connects cognitive and emotional feelings[55, 90]. There is numerous research evidence[91–93] that DCG participates in a series of functions; not only it can process emotions, feelings, and attention, but it can also participate in the regulation of sleep. The gray matter creatine phosphate of insomnia
patients is reduced, indicating that insomnia consumes more energy than normal sleep. The enhancement of these activated abnormal brain regions and the enhancement of the functional connection of MTG may be related to the high-energy compensation mechanism. Beyond that, pain is also a common symptom of CFS and an important factor that affects the quality of life. The decline in quality of life as in patients with CFS has been reported in many types of pain disorders, including chronic back pain, physical pain disorders, and lack of energy\[^{94-96}\]. These pain disorders can occur in multiple locations, from the cerebral cortex to the spinal cord, and is considered to be the damage to the central nervous system may cause the neurotransmitter involved in analgesia to be abnormal release\[^{97}\].

At the same time, studies have further pointed out that physical pain in CFS patients may be caused by hyperalgesia, that is, the brain area that regulates pain perception information is abnormal\[^{98}\]. If the brain has obstacles in receiving and processing pain information, then it is more sensitive to pain\[^{99}\]. Previous studies have also confirmed that this was mainly related to the core activation of the anterior cingulate gyrus, SFG, occipitotemporal area and DCG in our study, which was typical features of pain management\[^{100}\]. More importantly, Zack et al.\[^{9}\] found that SFG and MOG neuron activities in CFS patients positively correlated with SF-36 by comparing CFS patients with healthy people, which is consistent with our findings that the brain activation areas positively correlate with the clinical symptoms in SF-36. Based on these observations, we can infer that PLWNT can reduce the fatigue symptoms and improve the quality of life in CFS patients by activating related brain areas and regulating the patients’ sleep and physical pain.

Although our findings provide new and objective insights into the effects of PLWNT intervention on the brain function of CFS patients (including fatigue symptoms and quality of life), there are still some limitations that need to be further addressed. First of all, the selection criteria for CFS patients in this study were only based on self-rating scales, and there was no equipment for objectively measuring fatigue, energy, and pain; this may have resulted in irregular requirements for the inclusion of patients. However, we limited the age of participants to 20–60 years to reduce the likelihood of chronic fatigue symptoms and poor quality of life caused by diseases and age. Second, there were potential limitations in the experimental design. Ideally, participants should be blinded, but this is difficult to achieve in non-drug trials. However, we worked hard to ensure that laboratory technicians, data management personnel, and statisticians did not participate in recruitment and data processing, which to a certain extent ensured the authenticity of the data. Finally, our results indicating the brain regions with enhanced neuronal activity and functional connectivity in patients with CFS after PLWNT intervention need to be verified in a larger sample.

**Conclusions**

This study showed that PLWNT can relieve the fatigue symptoms of CFS patients and improve their quality of life. We also found that CFS patients had abnormal regional spontaneous neuronal activity and abnormal functional connections between regions after PLWNT intervention. There were also changes in the activation of the brain regions, improving the quality of life related to fatigue symptoms and physical...
pain, which were linearly related to the clinical symptoms in MFI-20 and SF-36. These findings provide a new perspective for the role of traditional medical interventions such as Qigong in medicine, and may provide guidance for the diagnosis and prevention of CFS.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the participants of this study. The study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine (Ethics Approval Number: 2018-043), and registered in the American Clinical Trial Registry (12/04/2018), Registration Number is NCT03496961.

Consent for publication

All authors agreed to publish this article.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China under Grant 81774443 and 82105038, The funder is the corresponding author Professor Fei Yao and the first author Dr. Fangfang Xie. The funding sources were not involved in study recruitment, data processing and publication of papers.

Authors’ Contributorship

The project was conceived and designed by all the authors. F.F.X. performed the search. F.Y. and Y.L.Y. contributed to data analysis and interpretation F.F.X., the manuscript draft that was revised by all co-authors. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

We are grateful to Guanwu Li for advice relating to the analysis and thanks are due to Ruiping Wang for guidance. We also would like to thank Professor Min Fang from the University of Shanghai university of traditional Chinese medicine for proofreading the manuscript.
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**Figures**

![Figure 1](image)

**Figure 1**

The postures of PLWNT. (A) Press and knead acupoint in Shanzhong. (B) Rubbing from Shanzhong Acupoint to Pubic Symphysis. (C) Rubbing from Pubic Symphysis to Shanzhong Acupoint. (D) Pushing
from Shanzhong Acupoint to Pubic Symphysis. (E) The right hand massages the abdomen by the left
circle. (F) The left hand massages the abdomen by the right circle. (G) Pushing with the right hand from
the left breast to the groin. (H) Pushing with the left hand from the right breast to the groin. (I) Turn left
and right. Every movements will be carried out 21 times. PLWNT, prolong life with nine turn method.

Figure 2

Compared with the education group, the ALFF brain area changes in the PLWNT group. Red shows
enhanced area, green shows reduced area, based on FWE correction, with voxel level p<0.001 and cluster
level p<0.05.
Figure 3

(a) Functional connection enhancement area of DCG and MTG. (b) Functional connection enhancement area of the left OG and the right middle occipital gyrus.
Figure 4

(a~f) The relationship between the changes of neuronal activity (ALFF) in OG, SFG, and DCG brain regions and the scores of patients on the MFI-20 and SF-36 scales.