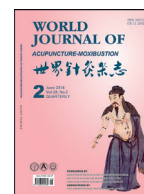




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## Clinical Research

Study on “liver-soothing and mind-regulating” acupuncture manipulation in regulating the blood-oxygen concentration in cerebral cortex of PTSD rats<sup>☆</sup>

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## ABSTRACT

**Objective:** To explore the brain function mechanism of “liver-soothing and mind-regulating” acupuncture manipulation in intervening post-traumatic stress disorder (PTSD).**Methods:** According to random number table method, 60 SD rats were randomly divided into blank group, model group, grabbing group, paroxetine group and acupuncture group. Except for the blank group, all the rats were established into PTSD models through electric shock and incarceration, with model replication for 7 days in total. The rats were given gavage, acupuncture intervention and grabbing fixation 1 h before modeling, with 6 days as 1 course of treatment. Grabbing treatment was performed for 2 courses, with 12 days in total. After modeling, functional near-infrared spectroscopy (fNIRS) system was adopted to collect and record the changes of concentration of Oxy-Hb, Deoxy-Hb and Total-Hb during 3 min in related brain regions of rats in each group after treatment for 5 consecutive days, and the brain function was evaluated.**Results:** According to the comparison of the time series of blood-oxygen concentration, there were significant differences between model group and blank group as well as grabbing group and blank group ( $P < 0.01$ ,  $P < 0.01$ ), no significant difference was found between model group and grabbing group ( $P > 0.05$ ); there were significant differences between paroxetine group and grabbing group as well as acupuncture group and grabbing group ( $P < 0.05$ ,  $P < 0.05$ ), no significant difference was found between paroxetine group and acupuncture group ( $P > 0.05$ ).**Conclusion:** “Liver-soothing and mind-regulating” acupuncture manipulation has a benign regulatory effect on the blood-oxygen concentration in cerebral cortex of PTSD rats, which may be the important brain function mechanism of “liver-soothing and mind-regulating” acupuncture manipulation in intervening PTSD.

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## 1. Introduction

Post-traumatic stress disorder (PTSD) refers to the delayed and persistent psychosomatic disorders of the body caused by super-normal sudden, threatening or catastrophic traumatic events. The clinical manifestations include re-experience of traumatic events, increased alertness and reactivity, and persistent anxiety and avoidance behavior [1]. In recent years, the incidence of PTSD is on the rise with the frequent occurrence of natural disasters,

wars, diseases and major traffic accidents at home and abroad [2]. For the past few years, notable curative effects of acupuncture-moxibustion have been obtained in treatment of PTSD patients after Wenchuan earthquake, Dingxi earthquake and Zhouqu debris flow, and it has been recognized in medical field [3]. Therefore, by taking acupuncture as the basic means, the close correlation between PTSD and heart, brain and liver was summarized in this study from the perspective of the whole view of traditional Chinese medicine, syndrome differentiation idea and meridian points theory through combining with modern studies. The basic pathogenesis of PTSD is the loss of nourishment of brain and mind, and liver failure of free flow of *qi*. According to this study, “liver-soothing and mind-regulating” acupuncture theory was put forward, namely the acupuncture treatment principle of mind-regulating and brain-awakening, as well as liver-soothing and

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qi-rectifying. However, there is so far rare study of brain function mechanism of acupuncture in intervening PTSD [4]. fNIRS is a new, safe and noninvasive indirect brain imaging method, which can be used to analyze and evaluate the neuron activity in related brain regions, cellular energy metabolism and hemodynamics-related functions through detecting the hemodynamic indexes of cerebral cortex, namely, the levels of Oxy-Hb, Deoxy-Hb and Total-Hb, and based on the neurovascular coupling mechanism, that is, the brain activity is associated with the optical property of brain tissue, and optical parameters are closely related to cell activity, energy metabolism and hemodynamics [5]. Therefore, the activities such as brain structure, function and pathology can be further reflected. fNIRS is a new neuroimaging technique, and it can make cerebral function monitoring come true through dynamic detection of neuronal activity. This study aimed to reveal the brain function mechanism of acupuncture manipulation in intervening PTSD by adopting fNIRS, and the study result will be great importance in the selection of clinical plans in the future.

## 2. Materials

### 2.1. Laboratory animals and grouping

Sixty healthy male SD rats with the age of 6 weeks [weight ( $180 \pm 20$ )g], provided by Gansu University of Chinese Medicine, SPF-grade Laboratory Animal Center [License No.: SCXK (Gansu) 2016-0001], were randomly divided into blank group, model group, grabbing group, paroxetine group and acupuncture group according to random number table method, with 12 rats in each group.

### 2.2. Laboratory apparatus and drugs

Electric shock and incarceration modeling box and electric shock power (including circuit) made by research group, stereotaxic apparatus (Shenzhen Hanix), fNIRS acquisition and analysis system (US NIRX Company, model NIRStar13.0), paroxetine hydrochloride tablets (Zhejiang Jianfeng Pharmaceutical Co., Ltd., batch No. 150104, specification  $20 \text{ mg} \times 12 \text{ s}$ ), disposable sterile acupuncture-moxibustion needles, Hwato $\phi 0.25 \times 25 \text{ mm}$  (Suzhou Medical Appliance Factory).

## 3. Methods

### 3.1. Animal models establishment

After grouping, the rats in model group, grabbing group, paroxetine group and acupuncture group were established into PTSD rats models by adopting electric shock and incarceration method.

According to the modeling method mentioned in literature [6]: the modeling boxes were washed and 75% ethanol solution was sprayed in boxes in order to dispel peculiar smell. Backing boards were placed in the boxes, and rats were grabbed and placed in the boxes with 1 rat in each box. Then the boxes were covered by boards with weight on the boards in order to create a dark and confining environment, which can guarantee that the rats cannot escape from electrical stimulation and the boxes. The rats were confined in boxes for 30 min at first, then AC60V and 8 mA power supply was connected to the electric palisades of boxes in order to impose inescapable electrical stimulation on the feet of rats. The electrical stimulation lasted for 4–8 s in each time with random interval, and the number of times of electrical stimulation was 30 times in total. Then the rats were taken out from the boxes and placed in the cages according to grouping. The time of modeling was recorded. Modeling was conducted for once in the morning and evening, respectively (30 min) with an interval of 4–8 h.

"Electric shock and incarceration" method was applied for modeling for 7 consecutive days.

Model group: models were duplicated; grabbing group: model were duplicated, and rats were fixed through grabbing which was the same as that in other groups; paroxetine group: orally given paroxetine hydrochloride solution by gavage; blank group: normal feeding without treatment.

### 3.2. Intervention methods

#### 3.2.1. "Liver-soothing and mind-regulating" acupuncture manipulation group

"Bǎihuì (百会GV 20)", "Nèiguān (内关 PC 6)", "Shénmén (神门 HT 7)" and "Tàichōng (太冲 LR 3)" were selected. The corresponding acupoint location was determined according to the distribution characteristics of acupoints in rats, and by reference to the acupoint location method of rats in *Experimental Acupuncture Science* [7] and *Sectional Anatomical Atlas of Sprague-Dawley Rat*.

After correct grabbing and effective fixation, a cotton swab with iodine was used for disinfection on "GV 20" at first, then the skin was lifted and pinched, backward transverse insertion was performed with a filiform needle with a depth of 4–5 mm, and then the needle was retained; conventional disinfection was conducted on "PC 6" and "HT 7" in upper limb, oblique insertion with filiform needles was performed with a depth of 2–3 mm, and then the needles were retained; finally, conventional disinfection was conducted on "LR 3" in lower limb, oblique insertion with a filiform needle was performed with a depth of 2–3 mm, and then the needle was retained. During needle retention, basic needling manipulation was carried out persistently at the above-mentioned four acupoints successively with minor lifting and thrusting and twirling as the main manipulations. Needling manipulation was conducted for 1 min at each point, and all the needles were withdrawn after 4 min. Dry cotton swabs were used for hemostasis by compression, and then the rat was put back in the cage. Six days was 1 course of treatment. Grabbing treatment was performed for 2 courses, with 12 days in total.

#### 3.2.2. Paroxetine group

The rats in paroxetine group were orally given paroxetine hydrochloride solution by gavage. According to the gastric volume of  $5 \text{ mL/kg/time}$ , 5 mL syringe was selected to connect with gavage needle (length: 6–8 cm,  $\phi 1\text{--}2 \text{ mm}$ ) [8]. Six days was 1 course of treatment, with 12 days in total.

#### 3.2.3. Grabbing group

The rats in grabbing group were only grabbed and fixed but not treated, and the fixation method was the same as that performed in paroxetine group and acupuncture group. The rats were grabbed for 4 min at each time, and then put back in the cage.

### 3.3. Course of treatment

In this study, 6 days was 1 course of treatment. Grabbing treatment was performed for 2 courses, with 12 days in total. Since model establishment was conducted in the morning of 1st–7th day, the grabbing treatment was performed in the afternoon of 1st–7th day, and then in the morning from the 8th day to the end of treatment.

### 3.4. Index testing

The major test indexes of fNIRS included the concentration of Oxy-Hb, Deoxy-Hb and Total-Hb. The study of fNIRS-related laboratory animals indicated that the change of Oxy-Hb concentration was the most sensitive marker of local cerebral blood flow change



**Fig. 1.** Sequence of light source and detector. Note: the figure on the right was the data model diagram involving the sequence of light source and detector, the light source (S) was in front of the detector (D). The figure on the left was the physical map of installment of S and D based on the model diagram.

in fNIRS test. Therefore, Oxy-Hb was taken as the analysis index in most fNIRS studies. In this study, Oxy-Hb was taken as the main index with Deoxy-Hb and Total-Hb as the auxiliary indexes in order to strengthen the credibility of Oxy-Hb as the main index [9].

### 3.5. Data acquisition

#### 3.5.1. Processing before data acquisition

Processing before data acquisition included anesthesia disposal, head disposal and the location of stereotaxic apparatus (after the head fur was disposed of, the rat was placed on the stereotaxic apparatus on an even keel, the height of the nose clip was adjusted to keep the anterior fontanel and lambdoidal suture at the same level; the bilateral ear bar scale was adjusted to make the rat in the middle position, and the rat head was fixed closely after adjustment), the placement of light source and detector and detection (before the experiment, the sequence of light source (8) and detector probes (12) was set up as the following figure, which covered the rat's head as close as possible to the skin, at the same time, the acquisition software was started to detect whether the light source and detector run normal) (Fig. 1).

#### 3.5.2. Data acquisition

Rats were grabbed randomly, and data acquisition was carried out for 3 min in each rat during which no intervention was given. US NIRStar13-0 software was used for data acquisition. After data acquisition, the time and rat number were recorded in order to prepare for data analysis.

#### 3.5.3. Statistic analysis

During statistical analysis, measurement data result (measured value) was expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm S$ ); all data conformed to normal distribution with homogeneous variance, and intergroup One-way ANOVA was adopted for analysis. SPSS 19.0 statistical analysis software was adopted for statistical analysis of corresponding data result. In all tests, when  $P \leq 0.05$ , the difference was statistically significant; when  $P \leq 0.01$ , the difference was statistically significant and remarkable.

## 4. Results

### 4.1. Comparison of the changes of concentration of Oxy-Hb, Deoxy-Hb and Total-Hb in channel CH4, CH33 and CH48 (mmol/L) (Fig. 2)

It can be seen from the figures that the waveform of blank group was dense, regular and consistent, the waveform amplitude was small with a small difference between the maximum and the minimum; the fluctuation in model group and grabbing group was more obvious than that in blank group, many sharp peaks were

**Table 1**

Changes of concentration of Oxy-Hb, Deoxy-Hb and Total-Hb in 10 channels of rats in each group ( $\bar{x} \pm s$ , mmol/L).

| Groups      | Rats | Oxy-Hb               | Deoxy-Hb             | Total-Hb             |
|-------------|------|----------------------|----------------------|----------------------|
| Blank       | 12   | $2.83 \pm 0.37$      | $4.65 \pm 1.17$      | $3.57 \pm 1.04$      |
| Model       | 12   | $4.76 \pm 0.74^{1)}$ | $2.65 \pm 0.57^{1)}$ | $5.95 \pm 1.14^{1)}$ |
| Grabbing    | 12   | $4.75 \pm 0.69$      | $2.61 \pm 0.55$      | $5.94 \pm 1.09$      |
| Paroxetine  | 12   | $3.57 \pm 0.75^{2)}$ | $3.41 \pm 0.83^{2)}$ | $4.53 \pm 0.97^{2)}$ |
| Acupuncture | 12   | $3.84 \pm 0.77^{2)}$ | $3.64 \pm 0.79^{2)}$ | $4.63 \pm 1.01^{2)}$ |

Note: Compared with blank group, 1)  $P < 0.01$ ; compared with model group, 2)  $P < 0.05$ .

found, and the waveform amplitude was wider with obvious difference between the maximum and the minimum as well as obvious extent of variation; the fluctuation in paroxetine group and acupuncture group was milder than that in grabbing group, sharp peaks decreased, only one peak with wide waveform amplitude was found, and the extent of variation was mild (Fig. 2).

### 4.2. Changes of concentration of Oxy-Hb, Deoxy-Hb and Total-Hb in 10 channels of rats in each group

Compared with blank group, the Oxy-Hb and Total-Hb concentration increased, and Deoxy-Hb concentration decreased in model group, and the differences were significant ( $P < 0.01$ ). Compared with model group, the concentration of Oxy-Hb, Deoxy-Hb and Total-Hb did not change significantly in grabbing group, and the differences were not statistically significant ( $P > 0.05$ ). Compared with model group, the Oxy-Hb and Total-Hb concentration decreased, and Deoxy-Hb concentration increased in paroxetine group, and the differences were statistically significant ( $P < 0.05$ ). Compared with model group, the Oxy-Hb and Total-Hb concentration decreased, and Deoxy-Hb concentration increased in acupuncture group, and the differences were statistically significant ( $P < 0.05$ ). Compared with paroxetine group, the concentration of Oxy-Hb, Deoxy-Hb and Total-Hb did not change significantly in acupuncture group, and the differences were not statistically significant ( $P > 0.05$ ) (see Table 1 and Fig. 3).

## 5. Discussion

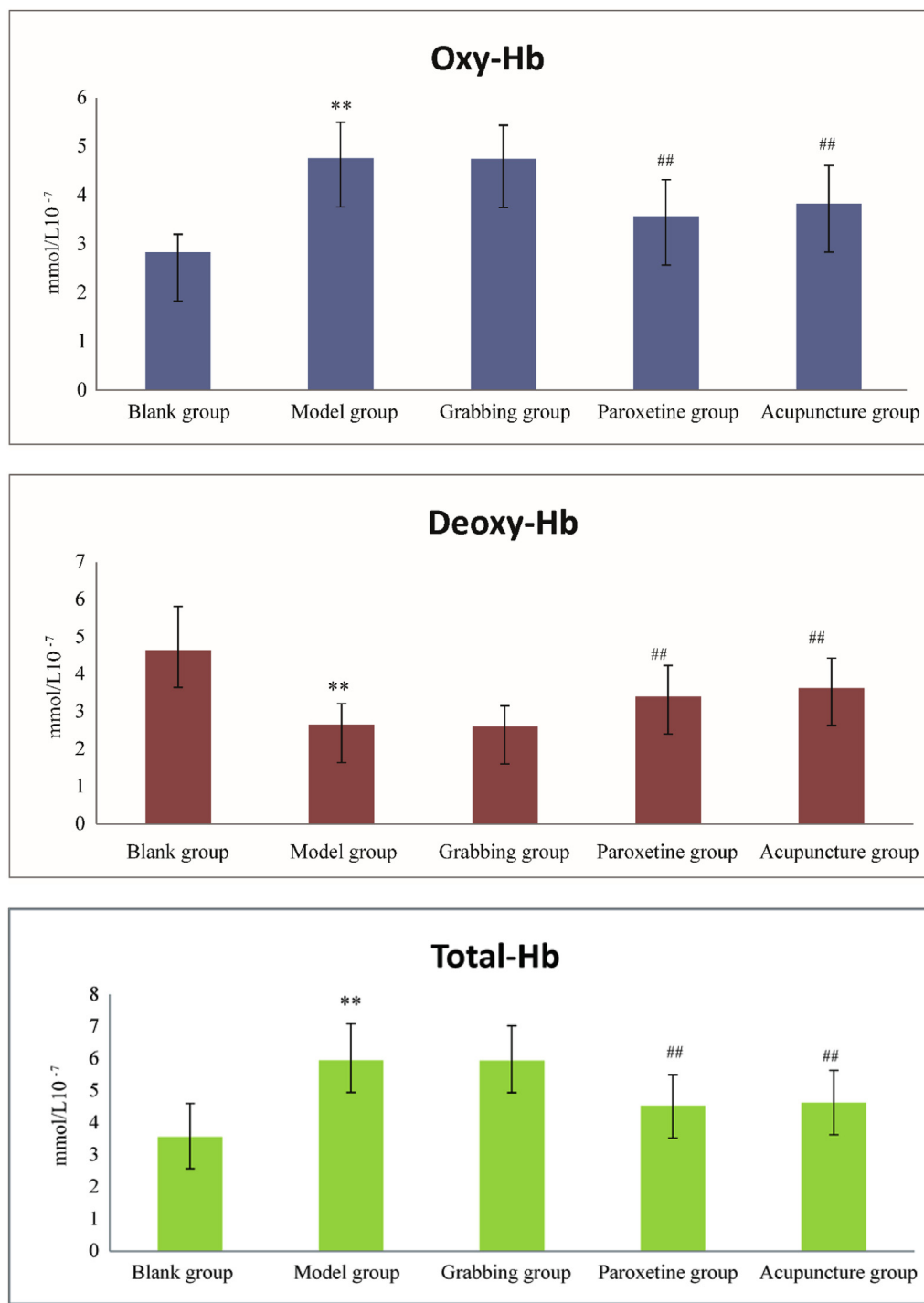
The pathogenesis and symptoms of PTSD have been recorded as early as in *Huángdì Nèijīng* (《黄帝内经》, *The Yellow Emperor's Inner Classic*). PTSD belongs to the emotional disease in traditional Chinese medicine. The disease is located in the heart, brain and liver, and is closely related with other *zang-fu* organs. It was said in *Sùwèn* (《素问》, *Plain Questions*) that "Anger causes *qi* to rise, excessive joy causes *qi* to slacken, sorrow consumes *qi*, fear causes *qi* to sink, fright causes *qi* to be chaotic, and excessive thinking causes



**Fig. 2.** Comparison of the changes of concentration of Oxy-Hb, Deoxy-Hb and Total-Hb in channel CH4, CH33 and CH48. Note: channel connection and representation, D1-S4 is channel CH4. The hemodynamic data (Oxy-Hb, Deoxy-Hb and Total-Hb) obtained by fNIRS were closely related to tissue oxidation and metabolism, so the study of cerebral cortex function and activity by using fNIRS has a certain physiological basis. The fluctuation signal of fNIRS was characterized by mitigative and smooth peak, and sharp trough of wave.

*qi* to knot...", the basic pathogenesis lies in the loss of nourishment of brain and mind, liver constraint and *qi* stagnation, which may finally result in many symptoms of PTSD. PTSD is located in the brain, heart and liver, and is closely related with other *zang-fu* organs. The basic pathogenesis lies in the loss of nourishment of brain and mind, and liver fails to regulate free flow of *qi*, which cause the failure of spleen to transport, and may finally result in *yin-yang* and *qi*-blood disharmony. The primary function of liver to govern the free flow of *qi* is regulating *qi* movement. It was said in *Lingshū* (《灵枢》, *The Miraculous Pivot*) that "Liver *qi* deficiency will cause fear"; it was also recorded in *Xuèzhènglùn* (《血证论》, *Treatise on Blood Syndromes*) that "Wood can govern the free flow of *qi*. After *qi* enters the stomach together with food,

liver wood is responsible for the free flow, thus water and grain can be transformed", namely, the precondition of normal *qi*-blood and body fluid circulation is smooth *qi* movement which is also the precondition of normal functions of *zang-fu* organs. *Qi*-blood and body fluid are the material bases of emotional activities, and *zang-fu* organs are also the base of emotional activities. The functions of *zang-fu* organs lie in smooth *qi* movement; therefore, emotional activities are closely related with the liver to govern the free flow of *qi*. PTSD is also directly related to the change of brain and mind. The brain is also called "the house of original spirit", which dominates human vital activities, and governs human mental activities. It was proposed as early as in *Plain Questions* that "The head is the house of bright essence", and "The house of original



**Fig. 3.** Histogram of Oxy-Hb, Deoxy-Hb and Total-Hb concentration-time changes in 10 channels of rats in each group. 3-1 Histogram of Oxy-Hb concentration-time change in 10 channels of rats in each group. Note: compared with blank group, \*\*  $P < 0.01$ ; compared with model group, ##  $P < 0.05$ . 3-2 Histogram of Deoxy-Hb concentration-time change in 10 channels of rats in each group. Note: compared with blank group, \*\*  $P < 0.01$ ; compared with model group, ##  $P < 0.05$ . 3-3 Histogram of Total-Hb concentration-time change in 10 channels of rats in each group. Note: compared with blank group, \*\*  $P < 0.01$ ; compared with model group, ##  $P < 0.05$ .

spirit" was firstly mentioned in *Běncǎo Gāngmù* (《本草綱目》, *The Grand Compendium of Materia Medica*), which indicated that brain is the hub of spiritual activities, the normal function of brain to govern the mental activities can guarantee full of spirit and energy, quick-wittedness and good memory, otherwise, abnormal thinking and emotion may be found [10]. Modern TCM clinical studies have confirmed that the damage of heart and spirit is the key factor of the pathogenesis of emotional diseases [11]. The brain and liver are the main regulating objects for emotional change. The loss of

nourishment of brain and mind, and the liver failure of free flow of *qi* are the basic pathogenesis of emotional diseases [12]. Based on the contents mentioned above, the basic pathogenesis of PTSD is the loss of nourishment of brain and mind, and the liver failure of free flow of *qi*. "Liver-soothing and mind-regulating" acupuncture manipulation can regulate the spirit and awaken the brain, soothe the liver and rectify *qi*. In most cases, the acupoints of heart, brain and liver are selected clinically, including GV 20, HT 7, PC 6 and LR 3, in order to focus on cerebral acupoints, regulate the heart and

spirit, soothe the liver *qi*, smooth the emotion, harmonize *qi*-blood and unblock meridians.

At present, many studies have confirmed that "the attack of PTSD may be the result that the stress injury on the functions and structures of related brain regions caused by intense trauma stimulation exceeds a certain limit" [13]. Acupuncture at points, as an external stimulus, may first activate the corresponding central nervous system and regulate the neural, endocrine and humoral networks through the central nervous system, and then affect the target organs [14]. The development of neuroimaging has promoted the visualization of the central effect of acupuncture, in which fNIRS is a new, safe, noninvasive and continuous indirect brain imaging method, which explores the effect of acupuncture at points on the hemoglobin in cerebral cortex, and further analyzes the brain function mechanism of acupuncture effect [15]. It has been found [16] that to find out the corresponding relationship between acupuncture at points and the blood flow changes in cerebral cortex by using the mid and far-infrared imaging to detect the effect of acupuncture at points on the activation area of cerebral cortex of animals provided a new method for the study of central nervous mechanism of acupuncture effect. This may be a response to the sympathetic nerve. Acupuncture changes the degree of excitement of sympathetic nerve, thus resulting in a series of responses to blood vessels - circulation - metabolism - temperature, and etc. [17] Studies have found that acupuncture caused the changes in blood-oxygen saturation, blood flow and glucose metabolism in some central regions of brain [18]. Zhang et al. [19] have studied the effect of electroacupuncture on the glucose metabolism in patients with post-traumatic stress disorder by using PET-CT imaging technique. The results preliminarily showed that the brain region with metabolic disorders associated with PTSD may be the target of electro-acupuncture treatment, in particular, the reduced mechanism in ACC and MPFC brain regions may be one of the mechanisms of electro-acupuncture treatment of PTSD.

At present, a number of studies have confirmed that "the attack of PTSD may be the result that the stress injury on the functions and structures of related brain region caused by intense trauma stimulation exceeds a certain limit" [20]. In order to further study the effect mechanism of acupuncture in intervening PTSD, the distribution and change of blood volume and blood oxygen in cerebral cortex were measured to understand the activity of the brain by utilizing fNIRS technology on the basis of neurovascular coupling mechanism, thus further analyzing and exploring the brain function mechanism of "liver-soothing and mind-regulating" acupuncture manipulation in the intervention on PTSD. There was paradoxical discharge of neurons, increased cellular energy metabolism, increased local oxygen consumption, increased local blood flow, and elevated Oxy-Hb concentration in PTSD-related brain regions. It has been found according to the study that compared with blank group, model group showed increased Oxy-Hb and Total-Hb concentration, and decreased Deoxy-Hb concentration, and the differences were significant, suggesting that the activity of neurons in cerebral cortex of electric shock and incarceration models increased, the demand for cellular energy metabolism increased, the local oxygen consumption increased and the blood flow elevated, thus resulting in the increased concentration of Oxy-Hb and Total-Hb and decreased Deoxy-Hb concentration. Compared with grabbing group, acupuncture group showed decreased Oxy-Hb and Total-Hb concentration and increased Deoxy-Hb concentration, and the differences were statistically significant, indicating that "liver-soothing and mind-regulating" acupuncture manipulation can inhibit abnormal neuron activity in cerebral cortex of rats, stabilize the demand for cellular energy metabolism, restore the local

oxygen consumption, thus resulting in the increased concentration of Oxy-Hb and Total-Hb and decreased Deoxy-Hb concentration.

Acupuncture can improve the injury of brain function after trauma stress. The early studies have shown that "liver-soothing and mind-regulating" acupuncture manipulation can promote the recovery of spatial-temporal mode of neural information encoding in hippocampal CA1 and CA3 regions of rats, and the repair of tissue ultrastructure to a greater extent when compared with paroxetine hydrochloride treatment. It has been found according to the study that "liver-soothing and mind-regulating" acupuncture manipulation has a benign regulatory effect on the blood-oxygen concentration in cerebral cortex of PTSD rats, which may be the important brain function mechanism of "liver-soothing and mind-regulating" acupuncture manipulation in intervening PTSD.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.wjam.2018.09.010.

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