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Evaluation of Central Fatigue in Post-stroke Rehabilitation: A Pilot Study

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Abstract— **Central fatigue induced by excessive rehabilitation training would limit motor activity or even damage the post-stroke motor function recovery. However, the central fatigue progress during training is unclear and ignored in post-stroke rehabilitation. In this study, we tried to investigate the changes in central fatigue with fractal dimension (FD) of electromyography (EMG) at different peripheral fatigue levels based on the intracerebral haemorrhage (ICH) model. Ten Sprague-Dawley rats with ICH and EMG electrodes implantation were randomly distributed into two groups: the forced training (FOR) group with exhausted peripheral fatigue level (n=5) and fatigue-controlled (FAT) group (n=5) with peripheral fatigue constrained in moderate level. A higher central fatigue level was found in the FOR group (P<0.0001), and the central fatigue could be alleviated by peripheral fatigue-based modulation in the FAT group. The FAT group with less central fatigue achieved significantly better motor function recovery (P<0.0001), and it might be related to the recovery in the ability of motor unit recruitments.**

I. INTRODUCTION

Stroke is a major cause of death and disability globally [1]. The motor deficit due to stroke significantly limits the activities and deteriorates the quality of daily living. Motor recovery is highly relied on post-stroke rehabilitation [2].

Physical training is an effective and widely used way to reduce motor impairments in stroke survival [3]. However, the fatigue caused by sustained physical exercise would lead to a reduced capacity to produce a voluntary force that typically outlasts the exercise bout and affect motor recovery [4]. The source of this fatigue can be divided into central and peripheral. Central fatigue is defined as a reduction in the capacity of the central nervous system to activate muscles [4] and can originate from any structure above the neuromuscular junction, from the central nervous system to the peripheral nerves [5, 6]. The synchronization of motor units (MUs) during central fatigue could increase the mechanical output when the whole MU pool is recruited [7]. Peripheral fatigue can be due to the local changes at or distal to the neuromuscular junction [8] and hampering the execution of descending central commands [9]. It decreases the muscle fiber conduction velocity and reflects in the frequency-domain as a scaling of the power density function of the EMG signal towards lower frequencies [7, 10]. A drop of mean power frequency (MPF) in EMG could be captured in a fatiguing muscle, which had been used as a biomarker of peripheral fatigue [11].

The potential mechanism of central fatigue is owing to increased brain 5-hydroxytryptamine activity caused by increased amino acids muscle depletion during prolonged exercise [12]. 5-hydroxytryptamine showed inhibitory effects on brain activity resulting in drowsiness, lack of attention and depression. For stroke survivors, post-stroke fatigue and depression would increase mortality and reduce recovery [13]. So, it is necessary to take central fatigue into consideration during training to avoid or reduce central fatigue and achieve more effective post-stroke rehabilitation. However, there are very few investigations on central fatigue after stroke, and how the central fatigue changes during post-stroke rehabilitation training are not clear.

Fractal dimension (FD) is an index used to describe shapes or structures which exhibit the property of complexity and detail, which is retained with successive levels of scaling or magnification [14]. It can be used to quantify and capture the essence of the 'complexity' of motor unit recruitment patterns [14]. Decreases in FD may be considered as indicators of progressive MU synchronization [5], which is a significant feature along with central fatigue. Since the FD is little affected by conduction velocity changes and most related to the level of MU synchronism [7], it would be a promising index of central fatigue-free from the disturbance of peripheral fatigue [5, 7].

Hence, in this study, we adopted the FD of EMG as an indicator of central fatigue to find out (1) how the central fatigue changed during post-stroke rehabilitation training at different peripheral fatigue levels, (2) the relation between central fatigue and motor function recovery in post-stroke rehabilitation.

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II. METHOD

A. Surgeries of intracerebral haemorrhage (ICH) and EMG electrodes implantation

Twelve Sprague-Dawley adult rats weighted from 270g to 310g were included in this study. They were housed in a 12/12h light/dark vivarium with ad lib access to food and water except for experimental periods. A three-day consecutive treadmill adaption training (16m/min, 30min/day) was applied before surgeries [15].

ICH disrupts the blood vessels of the brain and leads to contralesional hemiplegia in rats [16]. The surgery was guided by the method in [17]. Briefly, the rat was secured prone onto a stereotaxic apparatus (68005, RWD Life Science, China) with striatum located (0.2 mm anterior, 3.0 mm lateral, 6.0 mm ventral to the Bregma). Type IV collagenase (1.2 μL, 0.25 U in 1μL NaCl 0.9%, C5138, Sigma, USA) was infused into the striatum by a micro-infusion pump (Micro 4, World Precision Instruments, Inc., USA) for 5 minutes. After injection, the syringe remained there for 10 minutes and was subsequently withdrawn slowly to avoid backflow [18]. Then the hole was sealed by medical glue.

After the ICH surgery, the intramuscular electrodes were implanted on the affected (AF) and unaffected (UN) medial gastrocnemius muscles (MG) [19]. A differential electrode configuration was adopted for the measurement of EMG activity of the target muscles. After separating the skin from the muscular layer through blunt dissection, two Teflon-coated stainless steel wires (AS632, Cooner Wire, USA) with insulation stripped were inserted and looped around the belly and cauda of the MG, respectively [11, 20]. The common ground was a screw on the skull (0.0 mm anterior and 0.0 mm lateral to Lambda). The EMG electrodes were tunneled subcutaneously from both hindlimbs to the exposed skull and soldered with a head connector. The connector was fixed on the skull by screws with dental cement. After suturing of the wounds, the rat was put in a warm box with ad lib access to food and water till waking up. Two rats died mainly due to severe cerebral haemorrhage. All surgeries and experimental procedures conformed to the Guide for The Care and Use of Laboratory Animals (China Ministry of Health) and were approved by the Animal Care Committee of Zhejiang University, China (ZJU20200129).

B. Training protocol

The rest ten rats were divided into the forced training group (FOR, n=5) and the fatigue-controlled training group (FAT, n=5) randomly. The different treadmill training was conducted daily from Day3 post-stroke to Day14. The motor impairments were assessed through modified Neurological Severity Scale (mNSS) daily (from post-stroke Day2 to Day14) by operators blindly. Neurologic function was graded on a scale of 0–18, with 0 indicating normal neurologic function and 18 maximum functional deficits [18].

For the FOR group, the rats were forced to run on the treadmill for 30 minutes to achieve an exhausted peripheral fatigue state. For the rats in the FAT group, the peripheral fatigue level of the AF hindlimb was monitored and constrained below the moderate fatigue threshold. Once the fatigue level exceeded the threshold, the rat would get a 3-min rest to alleviate peripheral fatigue [15]. The accumulated running duration was 30min/day and speed was 16m/min for both groups.

C. Peripheral fatigue-controlled training system

In this study, we integrated the treadmill with an EMG analysis system based on a customized MATLAB graphical user interface (GUI) (Matlab, 2016a) to facilitate the fatigue-controlled treadmill training system [15]. The drop rate of EMG MPF was monitored as an indicator of peripheral fatigue. Once the MPF drop rate exceeded a pre-set moderate fatigue threshold, a reminder of 3-min rest would be triggered by the software [15].

The EMG signals were amplified with a gain of 1750 by a neural signal acquisition system (OmniPlex Neural Signal Acquisition System, Plexon Inc., USA) with a sampling rate of 40 kHz. The EMG signal was band-pass filtered with a 4th order Butterworth filter (60-2000 Hz). Moving average window (25ms) was applied to get the envelope of the rectified EMG data and the burst duration related to muscle contraction were identified by the threshold, which was defined as the mean value of the enveloped EMG plus 1.5 standard deviations (SD) during the resting period [19]. GUI-based software visualized the MPF drop rate by calculating the following,

$$\mathrm{MPF}=\frac{\int_0^{\infty} f\cdot s(f)\,df}{\int_0^{\infty} s(f)\,df} \quad (1)$$

where s(f) was the power spectrum density of the EMG signal. The MPF value was calculated every 4 seconds during treadmill training.

The MPF drop rate was defined as [11],

$$\text{MPF drop rate}=\frac{\mathrm{MPF_{baseline}}-\mathrm{MPF_{running}}}{\mathrm{MPF_{baseline}}}*100\% \quad (2)$$

where the baseline MPF was the average MPF values in the first 20 seconds in the 30-min treadmill training. The running MPF was the MPF values calculated based on the EMG of the target hindlimb during treadmill training.

D. Fractal Dimension

The FD of the EMG signal is a promising index of central fatigue, which was estimated by the 'box-counting' method [14]. The EMG signals were segmented into 10s segments and mapped to square box with size R. The minimum number of boxes can outline the EMG signal was N. With the size R increased, the minimum number of boxes N would decrease. The log of the number of boxes (log N) versus the log of the inverse of the box size (log 1/R) was linear, and the slope of the line was the FD. The box sizes were ranged from 1 to 1000.

The FD drop rate was calculated as,

$$\text{FD Drop rate}=\frac{\mathrm{FD_{Baseline}}-\mathrm{FD_{end}}}{\mathrm{FD_{Baseline}}}*100\% \quad (3)$$

The baseline/end FD was calculated as the mean FD of the first/last 30s of daily training. The normalized baseline FD was normalized by the maximum and minimum values of baseline FD from Day3 to Day14 for individual rats.

E. Statistical Analysis

The FD drop rates among the AF and UN of the FAT and FOR groups were compared by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc tests. The mNSS of

both groups were evaluated by two-way analysis of covariance (ANCOVA). The covariate was the behavioral score on Day2 post-stroke to exclude the possible deviations of initial motor impairment between the groups. The inter-group changes of mNSS at different time points were evaluated by one-way ANOVA. The normalized baseline FD among the AF and UN of the FAT and FOR groups were analyzed by two-way ANOVA with Tukey's post-hoc tests. $P<0.05$ was adopted as a statistically significant level in this study. Significant levels of $P<0.01$, <0.001 and <0.0001 were also indicated. All statistical analyses were performed using SPSS (Version 20, IBM, USA) or Graphpad Prism (v9.0.0, GraphPad Software, San Diego, California, USA).

III. RESULTS

The mNSS was assessed blindly and mNSS changes during the rehabilitation of FAT and FOR groups were shown in Figure 1. The two-way ANCOVA suggested the mNSS varied significantly with respect to the time point and group factors (2-way ANCOVA, timepoint: $P<0.0001$, group: $P<0.0001$). For the FAT group, a significant reduction of mNSS compared to Day2 appeared from Day4 to Day14 (One-way ANOVA, $P<0.0001$, Day4 to Day14 Tukey's post-hoc, $P<0.0001$), while for the FOR group, significant reduction of mNSS compared to Day2 arose from Day9 to Day14 (One-way ANOVA, $P=0.0212$, Day9 to Day14 Tukey's post-hoc, $P<0.05$). A higher score represents a poorer motor function. The decrease of mNSS suggested the motor function recovery in both the FAT and FOR groups. However, the fatigue-controlled rehabilitation strategy led to an earlier and better motor function recovery than the forced training strategy.

The representative trials on the FD changes during treadmill training in the FAT and FOR groups were shown in Figure 2. The FD in the FOR group showed a decreasing trend with treadmill training. In comparison, the FD in the FAT group showed a smaller slope compared to the FOR group and increased after the interval rest. The drop of FD suggested the MU synchronization, that is, the progress of central fatigue. The results showed that central fatigue appeared in both the FAT and FOR groups. However, the central fatigue in the FAT group was alleviated by 3-min rest and led to a smaller level of central fatigue compared to the FOR group.

The FD drop rates in the AF and UN hindlimb of the FAT and FOR groups from Day3 to Day14 post-stroke were shown in Figure 3. Significant differences in FD drop rate were found among the four groups (One-way ANOVA, $P<0.0001$). Tukey's post-hoc tests showed higher FD drop rates were found in both sides of the FOR group compared to the FAT group (AF: $P=0.0186$, UN: $P<0.0001$). These results demonstrated that a peripheral fatigue-controlled training strategy was able to alleviate central fatigue and achieve smaller central fatigue in both AF and UN sides compared with forced training. Combined with Figure 1, it was implied the lower central fatigue training strategies could achieve better motor function recovery.

The normalized baseline FD of the AF/UN side in the FAT and FOR groups from Day3 to Day14 were shown in Figure 4. The baseline FD suggested the initial status of MU synchronization. We normalized the baseline FD to avoid the deviations of individual brain haemorrhage and focused on the changes of status of MU synchronization caused by different rehabilitation strategies. Significant improvements of normalized baseline FD were found in Day13 and Day14 compared to Day3 in the FAT-AF group (Two-way ANOVA, Timepoint: $P=0.22$, group: $P=0.2272$, Tukey's post-hoc tests: Day13: $P=0.0284$, Day14: $P=0.0356$). The higher baseline FD

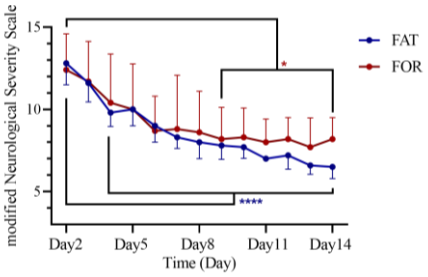

Figure 1. The behavioral assessments evaluated by mNSS in FAT and FOR groups from post-stroke D2 to D14. The values were represented by mean and SD (error bars) at each timepoint. Red line represents the FAT group, blue line represents the FOR group. The significant differences in the FAT group and FOR groups were indicated by "*" and "*", respectively. Significant levels were indicated as, 1 superscript for <0.05, 4 superscripts for <0.0001.

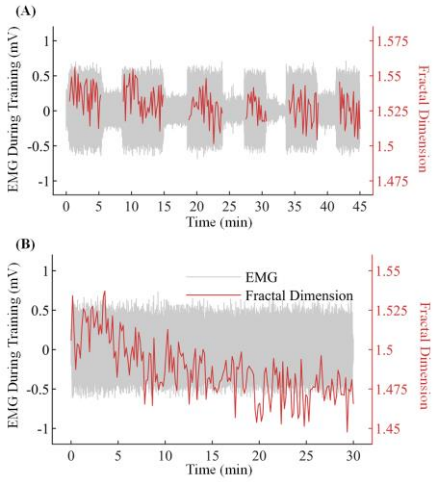

Figure 2. Representative trials of the FD during treadmill training in the FAT (A) and FOR (B) groups. The red lines were FD. The grey parts were EMG thumbnails, and the amplitude around ±0.5 mV stood for scuttle, while the amplitude around 0 mV represented the 3-min rest.

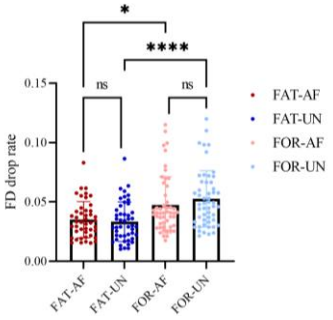

Figure 3. The FD drop rate of the AF/UN hindlimbs in the FAT and FOR groups from Day3 to Day14 post-stroke. The values were represented by mean and SD (error bars) at each timepoint. The significant differences between FD drop rate in the AF/UN hindlimb of FAT and FOR groups were indicated by "*". Significant levels were indicated as, 1 superscript for <0.05, 4 superscripts for <0.0001.

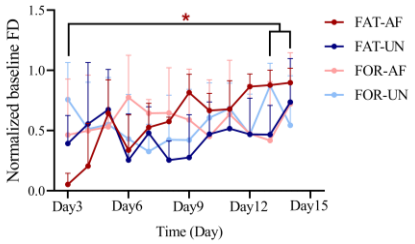

Figure 4. Normalized baseline FD of the AF/UN hindlimbs in the FAT and FOR groups from Day3 to Day14 post-stroke. The values were represented by mean and SD (error bars) at each timepoint. The significant differences between the normalized baseline FD in Day3 and Day13-Day14 in the FAT-AF group were indicated as "*". Significant levels were indicated as, 1 superscript for <0.05.

might suggest more MUs could be recruited along with the peripheral fatigue constrained rehabilitation training and might imply the recovery of controlling in the hindlimb GM muscles.

The correlations of the mNSS score and normalized baseline FD (affected side) in the FAT and FOR groups were shown in Figure 5. A significant negative correlation was found in the FAT group (Spearman r=-0.4713, P=0.0008). While for the FOR groups, no significant correlation between the mNSS score and normalized baseline FD was found (Spearman r=0.09955, P=0.5008). It might imply the motor function recovery in the FAT group was related to the recovery of the central nervous system in MU recruitments while the motor recovery in the FOR group was not.

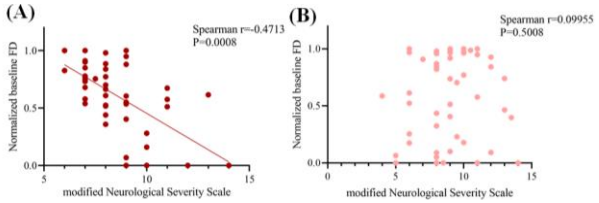

Figure 5. Scatter plot of the normalized baseline FD in the FOR-AF group versus mNSS (light red dots, A) and the normalized baseline FD in the FAT-AF group versus mNSS (dark red dots, B). The r and P values of the Speraman's correlation coefficient are indicated. The dark red line indicated linear regression performed on the dots.

IV. Conclusion

This study investigated how central fatigue changed during post-stroke training and its influences on motor function recovery. The alleviation FD of EMG in the FAT group showed the central fatigue could be constrained through peripheral fatigue-controlled, and it could be alleviated by interval rest during training.

The rehabilitation training with high central fatigue would bring damage to the recovery in MU recruitments, which might inhibit the neuron plasticity and lead to worse motor recovery. In contrast, the limited central fatigue rehabilitation training showed better motor recovery, which might be related to the improvements in the ability in MU recruitments in the affected hemisphere.

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