Event-Related Beta EEG Changes Induced by Various Neuromuscular Electrical Stimulation: A Pilot Study

Yun Zhao, Jun Yao, Xiaoying Wu, Lin Chen, Xing Wang, Xin Zhang, and Wensheng Hou

***Abstract*—Previous results demonstrated that neuromuscular electrical stimulation (NMES) with various configurations could induce different activity at both the central and peripheral levels. Although NMES generating different peripheral movements have been studied, it is still unclear whether the difference in NMES-induced cortical activity is due to movement- or stimulation- related differences. Because NMES-induced cortical activity impacts motor function recovery, it is essential to know when NMES with various configurations evoke the same movement, whether the induced cortical activity is still different. Four NMES configurations: 1) Eight-let Frequency Trains, 2) Doublet frequency trains (DFT), 3) Constant-frequency trains with narrow-pulse, and 4) wide-pulse, were delivered to the right biceps brachii muscle in nine healthy young adults. We adjusted the intensities of these NMES to evoke the same elbow flexion and compared the cortical activities over sensorimotor regions. Our results showed that the four NMES patterns induced different beta-band Event-Related Desynchronization (ERD), with the DFT providing the strongest ERD value given the same NMES-induced elbow flexion ($p < 0.05$). This difference is possibly due to NMES with different configuration activated in the amount of afferent proprioceptive fibers. Our pilot study suggests that the NMES-induced beta-band ERD may be an additional factor to consider when selecting the NMES configuration for a better motor function recovery.**

***Index Terms*—Neuromuscular electrical stimulation, doublet frequency trains, constant-frequency trains, brain activity.**

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I. INTRODUCTION

NEUROMUSCULAR electrical stimulation (NMES) not only increases muscle function, promotes blood flow and decreases muscular spasm, it also causes sensory input to the spinal cord and cortex [1]. Due to this sensory input, recent evidence has shown that NMES increases cortical excitability and induces reorganization in sensorimotor cortices for patients with physical impairments [2]–[5]. Further research on chronic stroke patients confirmed that changes in sensorimotor areas were accompanied by commendable hand recovery [6]–[8]. All these previous findings suggest that NMES-induced cortical activity impacts human behavioral restorations following rehabilitation.

Although NMES has been widely applied in the rehabilitative intervention [4], the influence of stimulation parameters on NMES-induced cortical activities is still an open question. A few studies have investigated brain changes induced by different stimulation parameters such as stimulation intensity [4], pulse frequency [9], pulse width [10] or current rate [11] in either healthy subjects or stroke patients. These studies demonstrated that NMES configuration influenced its induced cortical activities and may also impact the potential clinical outcomes.

The optimal selection of stimulation configuration for better clinical outcomes has been an open question for a long period. In clinical practice, the widely used NMES configuration is constant-frequency trains (CFT) of a single pulse with a fixed inter-pulse interval (IPI) [12], and more often with a narrow (about 250μs) pulse width as compared to a wide ($\sim$500μs) one. Therefore, previous NMES-induced cortical activity studies have also focused on NMES with CFT. More recently, NMES configurations with variable-frequency trains (VFT) have attracted increased attention due to the advantage of reducing muscle fatigue [13], [14]. NMES with VFT usually have a stimulation set of two to multiple pulses with short IPI (250$\sim$500 μs) and then a long IPI (20$\sim$50ms) between different sets. When comparing VFT-NMES with a different number (N) of pulses within a stimulation set (called N-lets), a few studies reported doublet-frequency train (DFT, N = 2) as one of the most successful configurations in force improvement in healthy subjects [12], [15]. To explain the underlying mechanisms, previous studies mostly focused on the response in muscle contractions. It is possible that DFT also enhances changes at the cortical level.

Furthermore, although previous studies showed that NMES configuration could modulate brain activities, they did not monitor the NMES-induced movements. As we know, the movements inspired by neuromuscular electrical stimulation can induce different sensory feedback at the cortex, making the stimulation configuration's role in generating the same or different brain activity unclear. Beta-band Event-Related Desynchronization (ERD) of EEG signal can reveal the integrated cortical excitability related to sensorimotor input and motor commands generation during active, imagined, and robot-assisted passive movements [16]–[18]. It has been used to quantify sensorimotor cortical activities during NMES-evoked limb movements in healthy subjects [19] and stroke patients [20].

In this study, we designed experiments to test whether NMES with various configurations but inducing the same movements would cause different cortical responses. Specifically, we studied four NMES configurations, including two CFT-NMES configurations: one with narrow (250 μs) and the other with wide (500 μs) pulse width, and two VFT-NMES configurations: one with two wide (500μs) pulses and the other with eight narrow (250μs) pulses (called 'doublet' or 'eight-let', respectively, see Fig. 1). We adjusted the intensities of these four NMES configurations to generate the same elbow flexion in nine healthy individuals. The cortical activity induced by NMES were evaluated with Beta-band ERD at the beta band (15-35 Hz).

II. Methods

A. Subjects

Eleven healthy right-handed subjects (3 females and 8 males, 24$\pm$2 years old) were recruited. Due to the low quality of the recorded electroencephalographic (EEG) data, data from two subjects were excluded from further analysis. All subjects were confirmed with no history of former cardiovascular disease, neurological disorders, or orthopedic problems in arms. Subjects were also free of upper limb resistance training in the past 6 months and no NMES treatment experience before. The study was approved by the ethical committee of Chongqing Cancer Hospital. All subjects signed the informed consent before the experiments.

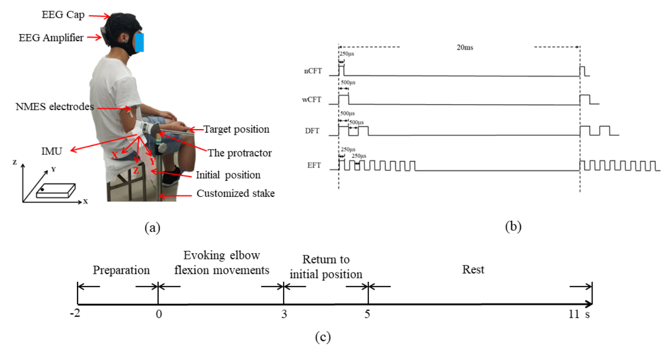

Fig. 1. Experimental design. (a) the experimental set up, (b) the NMES configurations, (c) the experimental paradigm of each trial.

B. Experimental Setup and Protocol

1) The 1st Visit: Subjects visited the laboratory on 2 separate days with a 1-day interval. During the 1st visit, we determined the stimulation position and the current intensities that resulted in a targeted elbow flexion at 50°, and 0° representing the initial forearm position with the arm sagging naturally. The general experimental setup is illustrated in Fig. 1(a). A long-handle protractor was placed near the subjects' right arm, with its center at the right cubital fossa. One of the handles was parallelly fixed on a customized stake perpendicular to the ground, and another handle was positioned at the target position. This target position required the NMES to induce elbow flexion angle of 50° from initial arm position.

To determine the stimulation electrode position, we first prepared the skin using an alcohol pad. Then round hydrogel electrodes (3 cm in diameter) were placed on the top of the right biceps brachii (BIC) muscle. An above-motor-threshold stimulation was delivered using Programmable Stimulator (Master-9, AMPI, Jerusalem, Israel) with isolated cables (ISO-Flex, AMPI, Jerusalem, Israel) to achieve an elbow flexion motion with the forearm in a semi-pronated position. We adjusted the stimulation placement until the desired elbow flexion was evoked. Once determined, the position was marked and fixed using medical adhesive tape.

Subsequently, the intensities of the 4 NMES configurations were tested (see Fig. 1(b)), including Eight-let Frequency Trains (EFT with 8 pulses per set in the train), Doublet frequency trains (DFT with 2 pulses per set in the train), CFT-NMES with narrow-pulse (nCFT), and wide-pulse (wCFT). Specific configurations for each of these four stimulation patterns are listed in Table I. Given one NMES configuration, the current intensities kept increasing until the elbow reached the target position, and the final stimulation intensities were recorded. Subjects were blinded to the stimulation configurations and instructed to avoid any voluntary movement during the stimulation phase.

To quantify the NMES-induced movements, an inertial measurement unit (IMU) (MPU6050, Vit motion, China) with a tri-axial accelerometer and a tri-axial gyroscope was placed on

TABLE I
THE PARAMETERS OF FOUR TYPES OF STIMULATION PATTERNS

	Pulse width	Burst frequency of pulse trains	Pulses per train	Current amplitude
EFT	250 µs	50Hz	8	6.5±1.09mA
DFT	500 µs	50Hz	2	5.3±1.04mA
nCFT	250 µs	50Hz	1	7.3±0.86mA
wCFT	500 µs	50Hz	1	5.9±1.08mA

the dorsal forearm of subjects approximately 10 cm proximal to the wrist joint. The positive Y-axis of the IMU was placed along the line from the right cubital fossa to the midpoint of the medial wrist crease. The positive Z-axis and X-axis were confirmed based on a right-handed coordinate system: the positive Z-axis perpendicular to the dorsal forearm's plane toward the dorsal side, and the positive X-axis perpendicular to the YZ plane toward the ulna side (see Fig. 1).

2) The 2^nd Visit: During the second visit, subjects sat comfortably with their right arm sagging naturally in a relaxed state (i.e., with the elbow almost fully extended). The stimulation electrodes and IMU were placed back to their corresponding positions as marked on the first day. Furthermore, 8 Ag/AgCl scalp Electroencephalographic (EEG) electrodes (STARSTIM-8, Neuroelectrics, Inc, Spain) were placed on the subject's head based on the international 10/20 system. The dual reference EARCLIP was placed on the right ear of subjects.

Once set up, 15 trials for each of the four types of NMES were delivered in the sequence of EFT, DFT, nCFT, and wCFT using the pre-determined intensities in the 1st visit. Each trial started with a 2- second preparation phase, after which a computer triggered the stimulator to evoke the right biceps brachii muscle contraction for the desired elbow flexion for 3 seconds. During stimulation, the subjects were instructed to keep relaxing and avoid any voluntary movement. After the stimulation, subjects were instructed to move the arm back to the initial position within 2 seconds. Finally, there was a 6-second resting period before the next trial (see Fig. 1c). During the entire 15 trials for one stimulation configuration, subjects were instructed to close their eyes to avoid observation interferences. A 10-minute resting period was given between two stimulation configurations to prevent muscle fatigue. During the experiment, the protractor was used to monitor the NMES-induced elbow flexion angle. If an NMES induced an elbow flexion less than 40°, the subjects were offered an extra 15 min break before restarting the task. Conversely, when the NMES-evoked elbow flexion angle was more than 60°, which might indicate subjects' voluntary contribution to the evoked movement, the subjects were reinstructed and offered a 5 min break to relax before restarting the task.

C. Data Collection and Processing

Kinematic data about elbow flexion angles were sampled at 100 Hz, and EEG data was high-pass filtered with 0.1Hz and sampled at 500Hz. In addition, current intensities used to evoke the required elbow flexion were recorded for all NMES configurations.

All experimental data were processed in MATLAB2018b (MathWorks, Natick, MA) environment. Kinematic data were segmented in trials according to Fig. 1(c). The angular data in Y-axis direction (i.e., elbow flexion direction) across all 15 trials using the same NMES configuration were averaged and then smoothed by a 20-point moving average filter. The angular range was defined as the angle difference between the initial position and the NMES-evoked maximal elbow flexion postion, and the movement duration was defined as the time between movement onset and the moment corresponding to the maximal elbow flexion angle.

EEG signals were firstly band-pass filtered (2 to 40Hz) by a Butterworth filter in EEGLAB. Independent component analysis (ICA) algorithm was then adopted to remove the ocular artifact from EEG data [26]. EEG signals were then re-referenced to the Cz electrode and segmented from 0 to 7s, with 0s aligned to the onset of the preparation cue in the beginning of each trial (see in Fig. 1c).

As the electrode C3 corresponds to primary sensorimotor cortex projecting to the right upper limb, the event-related desynchronization (ERD) value within beta band (15-30Hz) of C3 was selected to evaluate the cortical activities during stimulation. To calculate ERD, we first quantified the Event-Related Spectral Perturbation (ERSP) of EEG signals in time-frequency domain [21], as follows:

$$ERSP\left(f,t\right)=\frac{1}{N}\sum\nolimits_{n=1}^{N}\left(F_n\left(f,t\right)\right)^2, \quad (1)$$

where $F_n\left(f,t\right)$ is the spectral estimation of the nth trial at the frequency f and the time t, which was computed using wavelet transform with Morlet wavelets applied in EEGLAB.

Then, we quantified the averaged ERD value, ERD_{mean}, in the beta band (15-30Hz) during the stimulation period (0s $<$ t $\leq$ 3s), as following:

$$ERD_{mean}=\frac{1}{K}\sum_{0<t\leq 3,15\leq f\leq 30}10\log \times\left(\frac{ERSP\left(f,t\right)-\mu_B\left(f\right)}{\mu_B\left(f\right)}\right), \quad (2)$$

where $\mu_B\left(f\right)$ is the mean of the power during the baseline ($-2 < t_{baseline} \leq 0$) at frequency f across all 15 trials, K is the number of the time-frequency bins in the beta band (15-30Hz) during the stimulation phase (0s $<$ t $\leq$ 3s). By definition, the unit of ERD_{mean} is Decibel (dB).

Since the four NMES configurations evoked the same elbow flexion, the phase charge Q [22] (i.e., the current-time integral of the pulses during a trial in μC) was calculated to compare the efficiency of these configurations in generating the desired movement, with a less required phase charge indicating higher efficiency. To evaluate the efficiency of each NMES configuration in inducing beta-band ERD changes, we calculated the $\mathrm{ERD_{charge}}$, an index reflecting the ERD changes caused by a unit stimulation energy as

$$\mathrm{ERD_{charge}}=\frac{-ERD_{mean}}{\mathrm{Q}}, \quad (3)$$

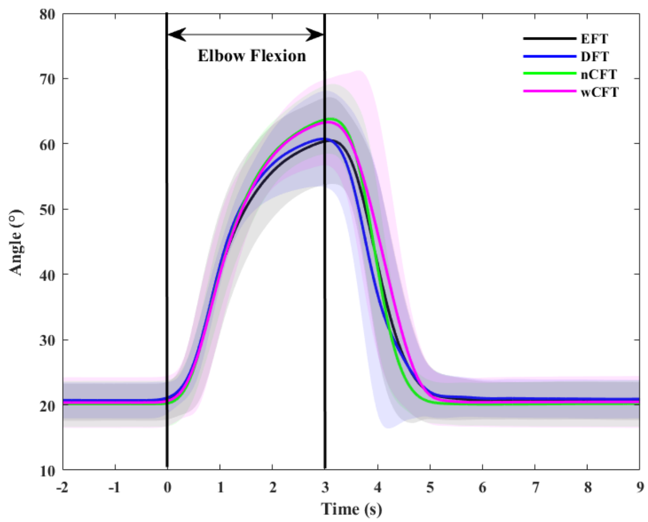

Fig. 2. Angle curves of NMES-evoked elbow flexion tasks. The solid lines represent the mean values, and the corresponding shaded areas represent the standard deviations.

where a higher $\mathrm{ERD_{charge}}$ indicating a higher efficiency in inducing the cortical activity.

D. Statistical Analysis

Kinematic parameters (including angular range and movement duration), EEG activities (ERD_{mean}), and the efficiency measures (i.e., the phase charges Q, and $\mathrm{ERD_{charge}}$) were analyzed with one-factor (NMES configurations) repeated measures ANOVA respectively to assess NMES configuration-related differences. The sphericity assumption was evaluated by Mauchly's test, and the Greenhouse–Geisser procedure was used to correct the degrees of freedom if necessary. The post-hoc pairwise comparisons using the Least Significant Difference (LSD) correction were performed. Statistical analyses were performed using SPSS 22 (SPSS Inc., Chicago, Illinois), and the significance level was set at $p < 0.05$ for all procedures.

III. Results

A. Elbow Flexion Movements Evoked by All NMES Configurations

Fig. 2 shows the mean and standard deviations of the angular curves induced by all the 4 NMES configurations. The statistical results showed no significant difference among the 4 NMES-evoked elbow flexion in either angular range ($F(3, 24) = 0.354$, $p = 0.787$) or movement duration ($F(3, 24) = 1.643$, $p = 0.206$). Our results confirmed that all NMES configurations evoked the same elbow flexion.

B. The Effect of Four NMES Configurations on ERD Values of Sensorimotor Cortical Activities

The averaged time-frequency maps of EEG data at the C3 electrode cross all trials and all subjects for each of the 4 stimulation configurations are shown in Fig. 3. As shown

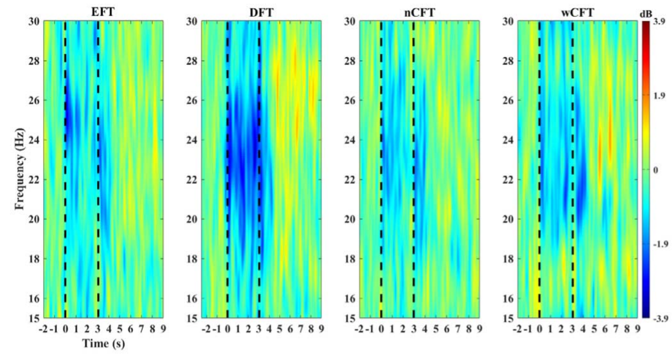

Fig. 3. The averaged time-frequency maps at the electrode C3 for all trials of all subjects. The color bar indicates the magnitude of *ERSP*(*f,t*), and the blue color indicates the magnitude lower than zero, representing ERD. The dashed vertical line denotes the NMES onset.

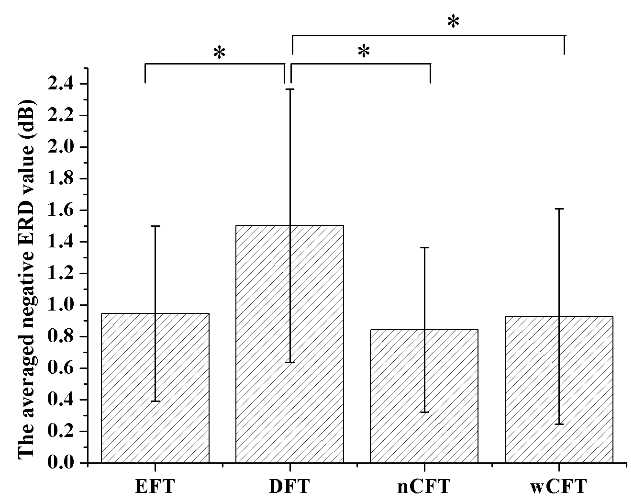

Fig. 4. The averaged negative beta ERD values at contralateral sensorimotor cortex (C3) induced by the 4 different NMES configurations.

in this figure, although all the NMES evoked the same elbow flexion, the induced sensorimotor cortical activities, as measured by ERSP, varied across the 4 stimulation configurations.

Fig. 4 shows the negative ERD value, $-ERD_{mean}$, during the NMES on-time ($0s < t \leq 3s$). The $-ERD_{mean}$ was significantly affected by the NMES configuration ($F(3, 34) = 7.881$, $p = 0.001$). The post-hoc comparison showed that the DFT evoked a significantly higher beta-band $-ERD_{mean}$ than the other 3 stimulation configurations ($p < 0.05$).

C. The Phase Charge Efficiency of Four NMES Configurations Inducing ERD Values

Repeated measures ANOVA showed a significant effect of NMES configuration on the phase charge ($F(1.104, 8.833) = 258.409$, $p < 0.001$). As shown in Fig. 5a, the post-hoc testing showed that: 1) the phase charge required by EFT was significantly higher than that by other 3 configurations ($p < 0.001$); 2) the phase charge of DFT was significantly greater than that of the two CFT configurations ($p < 0.001$); and 3) the phase charges of wCFT was also significantly higher than that of nCFT ($p < 0.001$).

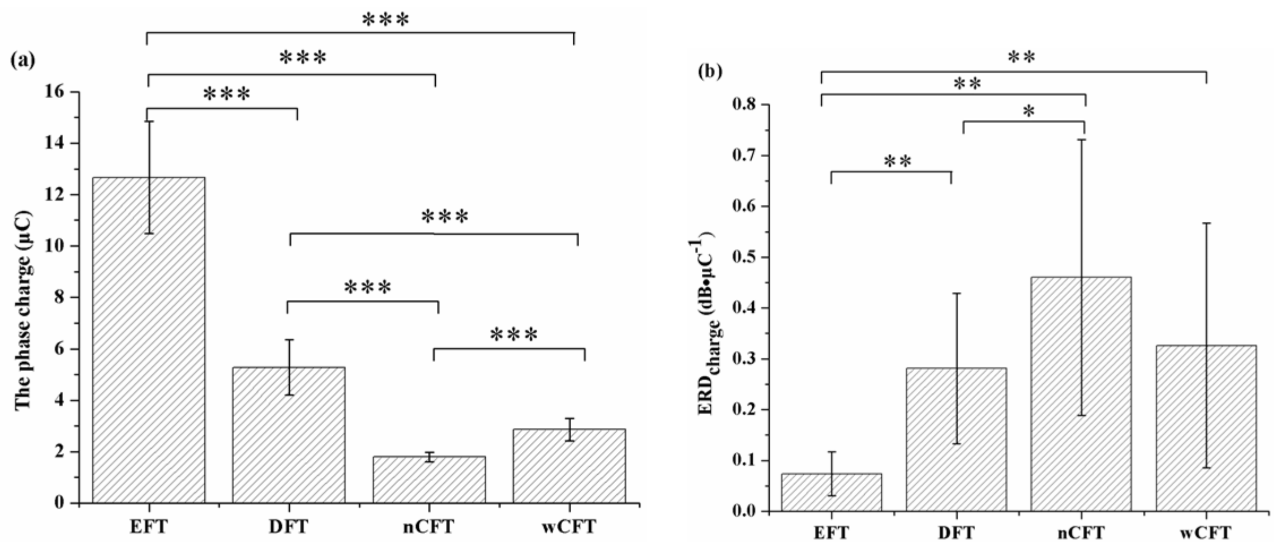

Fig. 5. The phase charge and its efficiency of the 4 NMES configurations. Stars indicate significance: * = p-value $<$ 0.05, ** = p-value $<$ 0.01, and *** = p-value $<$ 0.001.

Moreover, the NMES configuration also significantly influenced the ERD_{charge} ($F(3, 24) = 13.359$, $p < 0.001$). As shown in Fig. 5b, the nCFT is the most efficient in inducing beta-band ERD, as demonstrated by the ERD_{charge} in nCFT was significantly higher than that in both EFT ($p < 0.01$) and DFT ($p < 0.05$). The EFT has the least efficiency, which is significantly lower than the ERD_{charge} of DFT, nCFT and wCFT ($p < 0.01$).

IV. Discussion

The results in this study showed that the four tested NMES configurations induced different beta-band ERD values when evoking the same elbow flexion.

Our results may reflect that the four NMES configurations activated different amount of afferent proprioceptive fibers, resulting in the difference in the induced event-related beta EEG changes in sensorimotor cortex. The event-related beta EEG changes induced by NMES are mainly resulted from NMES-evoked afferent inputs, including both cutaneous afferent inputs by activating cutaneous receptors (i.e., tactile sensations) [23] and afferent proprioceptive inputs by depolarizing proprioceptors such as muscle spindle, Golgi tendon organs, and Joint Afferents et al (i.e., proprioceptive sensations) [1]. Previous studies have reported that NMES-evoked tactile sensations induce mu-band rather than beta-band ERD [24], while beta oscillations in sensorimotor cortex are related to afferent proprioceptive inputs from the muscles to the primary motor cortex and somatosensory cortex [17], [18], [25]. Results in this study may indicate that different NMES configurations depolarize different amount of afferent proprioceptive fibers, even they result in the same elbow flexion.

Specifically, DFT induced greater sensorimotor cortex activities than the other three NMES configurations did. Previous studies have reported that DFT could improve muscle force and reduce muscle fatigue, with the underlying mechanisms as that DFT activates more afferent fibers and results in an increased asynchronous recruitment of motor units (MU) through afferent pathway. This is similar to the MU's recruitment during voluntary contractions, where asynchronous MU's recruitment is seen by activating spinal motor neurons via afferent inputs to the spinal cord [26] and results in fatigue-resistant contraction. Differently, NMES recruit motor units through both a direct activation of motor axons (efferent pathway) and an indirect recruitment of motoneurons in the spinal cord by depolarizing the sensory fibers (i.e., afferent pathway) [26], with the former one leading to synchronous MU recruitment and more muscle fatigue. Our results provided new evidence shown that DFT activates more afferent fibers that not only result in an increased asynchronous recruitment of motor units through afferent pathway, but may also correspondingly contribute to greater beta band ERD in sensorimotor cortex.

In the present study, we introduced the new idea of using cortical activity as an indicator to choose the optimal NMES configuration. When selecting the NMES configuration, possible indices presented in this paper include: the efficiency in inducing movement (i.e., using Q index in this study since movements are controlled to be the same), the efficiency in inducing the beta band ERD, and its strength given the same movements. Currently, a more widely used index is probably the efficiency in inducing movement, as the targeted movement is usually set as an observable and measured goal. Our results demonstrated that nCFT with the shortest stimulation duration is the most efficient one in inducing the elbow flexion and the beta band ERD (see Fig. 5). These results agree with previous findings that NMES with various configurations can selectively activate different fibers based on the strength-duration curve [27]–[29]. NMES configurations with short duration of charge injection (the whole burst duration) have been demonstrated to be more charge efficient to activate fibers [30]. This may be one reason for nCFT to be more widely used in the current clinical practice. In addition, because the pulse interval between stimulation trains was shorter than the refractory period of fibers, NMES configurations with multiple pulse trains may generate a charge buildup at the axon membrane. In this case, fibers depolarized by the first pulses will be in the refractory period and not activated by the subsequent pulses [28]. Therefore, EFT with multiple pulse trains showed the lowest phase charge efficiency in the present study.

On the other side, a new point of successful intervention is to increase beta oscillatory modulation on the sensorimotor cortex as a therapeutic target for restorative training approach [20]. Based on this new point, we argue that the efficiency in energy consuming or generating movements is less important, and the strength of the induced cortical activity is more critical. According to this rule, DFT outperforms the rest 3 tested NMES configurations. Interestingly, our results are in line with previous results, suggesting DFT not only induces more beta band ERD in sensorimotor cortex, but also creates stronger force and less fatigue.

The present study is based on a limited number of healthy subjects. Whether our results can be generalized to pathological population needs further confirmation. To avoid the observation interferences and ocular artifacts, subjects in this study were required to close their eyes during the experiment. This design increased the alpha band EEG signals. Because the present study focused on beta-band ERD, the increased alpha-band activities may have limited impact on our results. In addition, in this study, the four stimulation configurations were applied in the fixed order for all subjects. This may cause the confounding impact from certain factors, such as muscle fatigue. Although a 10-minute resting interval between the NMES configurations was provided to reduce muscle fatigue, it could be better to exclude this confounding factor through randomizing the order of the four tested NMES configurations in different subjects. In addition, another confounding factor may be the gravity of the arm, which was not considered in our experiment design. Changes in gravity conditions have been demonstrated to influence brain hemodynamics as well as neuronal activity [31]. In the future, an experimental setup with the arm placed on a haptic table that is created by a robot can be used to investigate the cortical responses of NMES-evoked elbow flexion in the horizontal direction without the gravity factor. Finally, only EEG signal at Electrode C3, a representative electrode for the classical sensory and motor homunculus [32], was used to evaluate the cortical cortex in this study. Maximal beta ERD changes have been reported in electrode C3 during NMES-evoked right wrist movements [33]. Therefore, the results based on the electrode C3 in this study may also reveal the sensorimotor cortical activities. Cortical analysis based on high-density EEG measures will provide more accurate and complete picture of the NMES-induced changes at the cortex.

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