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A novel training-free externally-regulated neurofeedback (ER-NF) system using phase-guided visual stimulation for alpha modulation

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ABSTRACT

The efficacy of neurofeedback is a point of great controversy, because a certain proportion of users cannot properly regulate their brain activities and thereby fail to benefit from neurofeedback. To address the neurofeedback inefficacy problem, the present study is aimed to design and implement a new neurofeedback system that can more effectively and consistently regulate users' brain activities than the conventional way of training users to voluntarily regulate brain activities. The new neurofeedback system delivers external visual stimuli continuously at a specific alpha phase, which is real-time decoded from ongoing alpha wave, to regulate the alpha wave. Experimental results show that the proposed training-free externally-regulated neurofeedback (ER-NF) system can achieve consistent (effective in almost all sessions for almost all users), flexible (either increasing or decreasing peak alpha frequency and alpha power), and immediate (taking or losing effect immediately after stimulation is on or off) modulation effects on alpha wave. Therefore, the ER-NF system holds great potential to be able to more reliably and flexibly modulate cognition and behavior.

1. Introduction

Neurofeedback is aimed to guide people to voluntarily regulate their brain activities to desired patterns by measuring and showing their relevant brain activity patterns (Hammond et al., 2007). The most commonly regulated brain activity patterns used in neurofeedback are electroencephalographic (EEG) rhythms. Jasper and Shagass (Jasper and Shagass, 1941) first showed that human subjects could be instructed to voluntarily regulate alpha wave, which laid the foundation for neurofeedback. Nowadays, neurofeedback has been used as a therapeutic intervention for the treatment of a range of brain diseases and disorders, such as attention-deficit/hyperactivity disorder (ADHD) (Albrecht et al., 2015), epilepsy (Tan et al., 2009), stroke (Mihara et al., 2013), autistic spectrum disorder (ASD) (Coben et al., 2010), and emotional disorders (Linden et al., 2012).

However, the efficacy of neurofeedback is still a point of great controversy. For example, although many empirical studies supported neurofeedback's efficacy in the treatment of ADHD (Fuchs et al., 2003; Monastra et al., 2002), a few well-designed and -controlled studies reported either absent or reduced effects (Moriyama et al., 2012; Holtmann et al., 2014). Even clinical effects of neurofeedback do exist, it still remains unknown whether the effects are caused by neurofeedback itself or just placebo effects mediated by expectancy (Lofthouse et al., 2012). Neurofeedback inefficacy is also manifested by the fact that a significant proportion of users cannot benefit from neurofeedback (Alkoby et al., 2018). For example, Doehnert et al. reported that about half of their subjects did not succeed in regulating brain activity in their neurofeedback training with ADHD patients (Doehnert et al., 2008). In another study, Lubar et al. found that about 40% of their subjects were not able to regulate EEG to the desired pattern even after 40 sessions of neurofeedback training (Lubar et al., 1995). Neurofeedback inefficacy could be attributed to many factors, such as psychological characteristics and physiological states (Alkoby et al., 2018). One well-recognized reason underlying neurofeedback inefficacy is the great difficulty for users (at least, a certain proportion of users) to master the skills necessary to self-regulate their certain brain activities to match desired patterns. As a consequence, those people who are unable to regulate their brain activities fail to achieve any positive effects. Because of the limitation of self-regulation, a new regulation technique that can modulate brain

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Abbreviations

ER-NF	Externally-Regulated Neurofeedback (the proposed neurofeedback protocol)
SR-NF	Self-Regulated Neurofeedback (the traditional neurofeedback protocol)
REST	resting-state EEG with eyes-open
VEP	visual-evoked potentials
SSVEP	steady-state visual-evoked potentials
F_{rest}	the peak frequency of alpha wave (8–12 Hz) in REST
I_{LED}	the light intensity of LED used in ER-NF
P_{rest}	the peak power of alpha wave at F_{rest} in REST
F_{mod}	the main frequency of the modulation function (alpha power against phase) in ER-NF

activities without users' active participation is highly desired in developing new neurofeedback protocols.

In the present study, we proposed a new neurofeedback protocol that uses external visual stimulation, which is generated based on real-time decoded phases of alpha wave, to regulate the frequency and power of alpha wave. By using external sensory stimulation to regulate users' brain activities, users' active participation is not necessary and they do not need to master any learning skill or experience of self-regulation. Therefore, the new neurofeedback protocol based on such an external regulation of EEG activities is expected to achieve universal and consistent regulation effects. Hereinafter, the new neurofeedback protocol is referred to as externally-regulated neurofeedback (ER-NF), while the traditional neurofeedback based on self-regulation is referred to as Self-Regulated neurofeedback (SR-NF). The key novelty of the proposed ER-NF protocol is that, the delivery time of visual stimuli used to modulate alpha wave is determined by the phases of ongoing alpha wave. It makes the new neurofeedback protocol largely different from conventional visual evoked potential (VEP) protocols using prespecified delivery time. The phase-guided visual stimulation can regulate alpha wave in a more adaptive and flexible manner, and its principle and advantages are explained as follows.

The idea of using phase-guided visual stimulation to regulate EEG comes from the observation that, the timing of stimulation (which corresponds to the phase of certain EEG rhythms when the stimulation is delivered) has a huge impact on brain responses. For example, visual stimuli delivered at different phases of alpha wave evoke different alpha dynamic responses (McSayers and Beagley, 1974; Trimble et al., 1975; Jervis et al., 1983). In another word, the latency and amplitude of evoked potentials are sensitive to the phase of the alpha wave at the stimulation time. This observation inspires us to continuously deliver visual stimuli at a specific alpha phase to modulate the alpha wave to expected dynamic behaviors, which is the basis of the proposed new ER-NF protocol. The principle of phase-guided visual stimulation is illustrated in Fig. 1, where we simplify the alpha oscillation behavior as the motion trajectory of a simple pendulum. Without damping, the simple pendulum system will execute a simple harmonic motion with the frequency and amplitude unchanged (Fig. 1a). However, if we exert a force on the single pendulum at a specific phase, the amplitude of the single pendulum would increase or decrease, depending on the phase of pendulum at which the force is exerted (Fig. 1b and c). Correspondingly, the system frequency would also be changed. Hence, if we can keep delivering a series of visual stimuli at one specific alpha phase, we could change the pattern of the alpha wave (i.e., the amplitude and the frequency of the alpha wave).

There are still a number of difficulties to be addressed in the design and implementation of such an ER-NF system using phase-guided visual stimuli. It is vital to precisely real-time decode the alpha phase for the determination of delivery time of visual stimuli, and it is important to optimize stimulation parameters for each user to maximize the regulation effects. The present study addressed above difficulties and we showed that a proof-of-concept real-time ER-NF system could effectively increase or decrease the power and the frequency of alpha wave. More importantly, the regulation effects of the ER-NF system can be reliably observed in almost all experiments and from almost all users, even users were not trained to master any regulation skills. Hence, this new training-free ER-NF protocol holds great potential to be able to more effectively and consistently modulate cognition and behavior.

2. Methods

2.1. System design

The schema for the proposed ER-NF system is shown in Fig. 2. The system consists of four modules: (1) EEG recording, (2) phase decoding, (3) stimulation sequence generation, (4) visual stimulation. Raw EEG signals were recorded and then the phase of alpha wave was estimated and used to guide the generation of visual stimulation sequence (i.e., the exact time to deliver visual stimuli). Visual stimuli were delivered by LED to provide feedback to users. Because the sequence of visual stimuli was generated based on the alpha phase and then, in turn, modulated the alpha wave, a closed-loop control of the alpha wave was formed. The details of the four modules are introduced as follows.

2.1.1. Module 1: EEG recording

Raw EEG was recorded by a BrainAmp system (Brain Products GmbH,

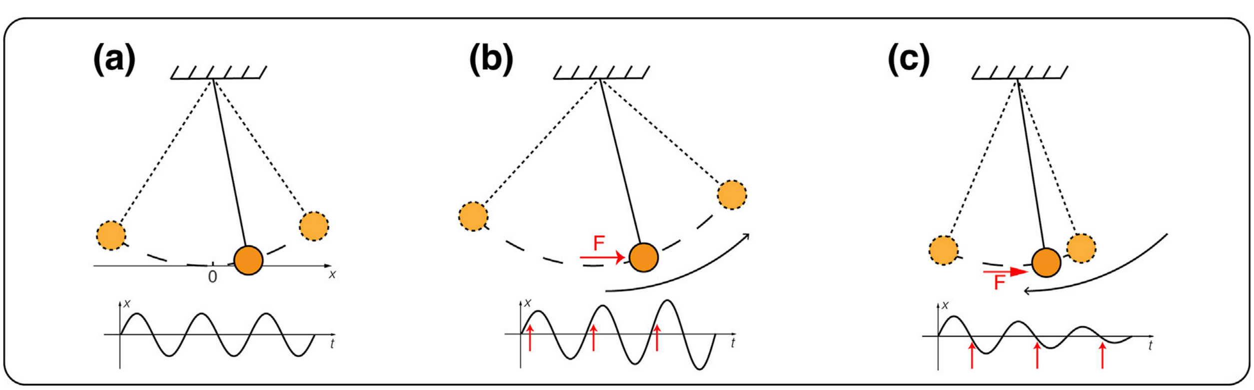

Fig. 1. The principle of the proposed Externally-Regulated Neurofeedback (ER-NF) protocol. (a) The alpha oscillation behavior is simplified as the motion trajectory of a simple pendulum without damping. The motion trajectory of the simple pendulum is a sinusoidal function with fixed frequency and amplitude. The amplitude indicates horizontal displacement of the ball. (b) If a force (the red arrow F in the figure) is exerted at a phase where the pendulum moves in the same direction as the force, the amplitude of the pendulum would be increased. (c) On the contrary, if the force is exerted at the phase where the pendulum moves in the reverse direction as the force, the amplitude of the pendulum would be decreased.

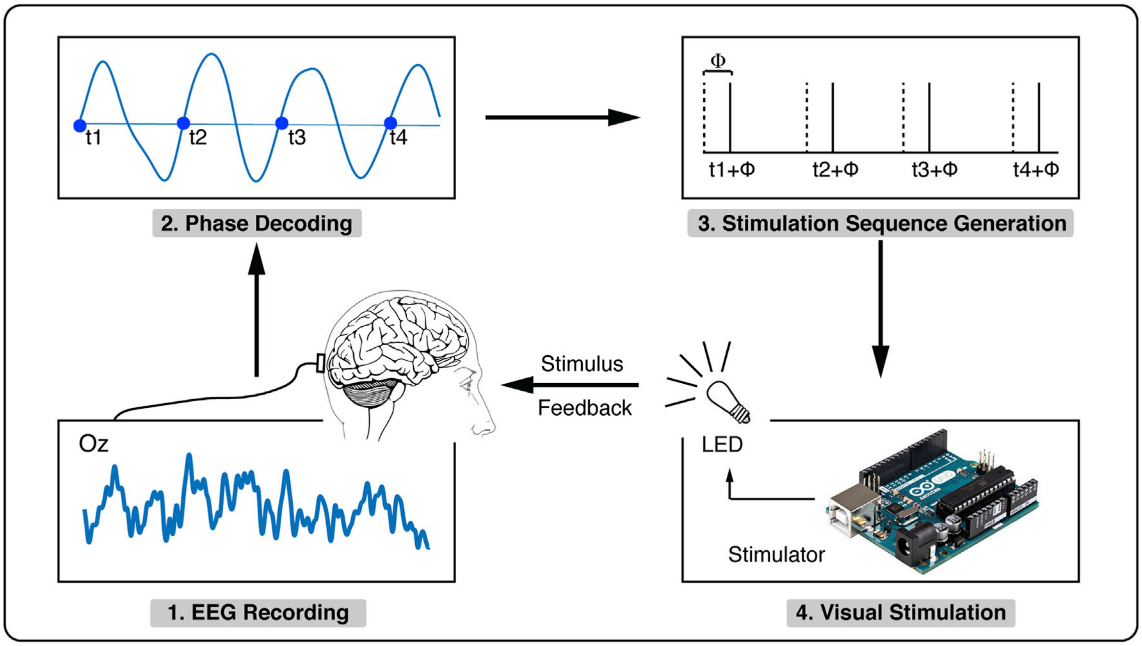

Fig. 2. The schema of the Externally-Regulated Neurofeedback (ER-NF) system.

Germany) from Oz (referenced to FCz) with a sampling rate of 5000 Hz. The impedance for both Oz and the reference electrodes were kept lower than 5 kΩ in the experiments.

2.1.2. Module 2: phase decoding

This module was developed in C++ using BrainAmp SDK. Because fast and accurate estimation of the alpha phase is of key importance to the modulation effect (i.e., how and to what extent the alpha wave is modulated) of ER-NF, we used a bandpass filter and a zero-cross point detection method for phase estimation. First, raw EEG was bandpass filtered online by a second-order Butterworth filter with a bandwidth of 2 Hz to separate alpha wave. The center frequency of the bandpass filter was user-dependent and it was equal to the peak frequency of the user's alpha wave at resting state with eyes-open. Hereinafter we used F_{rest} to denote the peak frequency of alpha wave at rest and it was estimated as the frequency with the maximum power in the range of 8–12 Hz. Note that the Butterworth filter introduced a phase delay of around 240 ms, which may influence modulation effect of ER-NF (see Discussion for details). Next, we need to detect one certain alpha phase for the generation of visual stimuli. Here, the alpha phase at $\varphi = 3\pi/2$ was estimated as the upward zero-crossing of the filtered signal. The zero-crossing method was adopted here because its low complexity and effective phase estimation under noise were suitable for online processing. Note that stimuli delivered at different phases would lead to different alpha dynamic behaviors (as explained in the next paragraph), which could counteract with each other so that the overall modulation effect is reduced or even disappears. Hence, we need to deliver visual stimuli around the same alpha phase, which was generated based on the detected phase of $3\pi/2$, to guarantee modulation effects on alpha wave.

2.1.3. Module 3: stimulation sequence generation

Further, we need to generate a sequence of visual stimuli to modulate the alpha wave. The modulation effect depends on the alpha phase when a visual stimulus is perceived, as illustrated in Fig. 1. Thus, we examined the modulation effects of visual stimuli delivered at different alpha phases, which was achieved by adding a time lag Φ after the decoded phase of $3\pi/2$. Twenty different values of time lag Φ (ranging from 0 to 190 ms with a step of 10 ms) were examined and they correspond to 20 phases of alpha wave. Because F_{rest} is around 10 Hz and the corresponding period is close to 100 ms, the range of Φ (0–190 ms) roughly covers 2 cycles of the alpha wave. The actual delivery time of visual stimuli is around the phase $[3\pi/2 + (\text{system delay} + \Phi) \times 2\pi F_{rest}]$. Since the system delay was a constant (see Discussion for details), we can use the time lag Φ as a phase index. By examining the alpha power at each phase index Φ, we had a modulation function describing how alpha power varied with phase. Based on the simple pendulum model, we expect to see that the modulation effect is periodical and the period is the same as F_{rest}.

2.1.4. Module 4: visual stimulation

Visual stimuli were delivered by LED, which was controlled by a microcontroller (Arduino UNO, Arduino) and placed 45 cm away from subjects' eyes. Ten exponentially increased levels of LED intensity (5, 10, 19, 37, 71, 145, 285, 546, 1074, 1998 Lux, denoted as Level 1 to Level 10) were tested to determine the optimal LED intensity for each subject (see Section 2.3 for details about the selection of light intensity). The light intensity was measured by a light meter (TES-1332A, TES). It should be noted that the light intensities tested in this experiment were in general small. At low levels of light intensity (specially for Level 1 and Level 2), a few subjects could not perceive whether the light was on or off. Even at the highest level of light intensity (Level 10), some subjects still had no clear EEG responses, i.e., VEP.

2.2. Experimental design

Twenty-one healthy subjects (5 females and 16 males) aged 18–26 years (mean 23.57 ± 2.11), without a history of epilepsy, participated in the study. To validate the reproducibility of modulation effect, these subjects took part in two experiments, which were almost the same and were arranged in two different weeks within a month (the interval between one subject's two experiments ranged from 5 to 31days, mean 15.7 ± 7.50). One subject was excluded from further analysis because he did not take part in the second experiment. As a result, we have totally 20 subjects and 40 experiments. In the following, we use the suffix 'a' and 'b' to denote the first and second experiments, respectively. For example, the second experiment of subject 02 is labeled as Sub02b. The experiments were in accordance with the Declaration of Helsinki. Ethical approval of the study was sought and obtained from the Bioethics Committee, Shenzhen University Health Science Center. Each subject was given the written informed consent prior to the experiments.

Each experiment consisted of two parts: a calibration part and an evaluation part. In the calibration part, two important parameters, I_{LED} (the light intensity of LED) and F_{rest} (the peak frequency of the alpha wave in the resting state with eyes-open) were respectively obtained from VEP and REST (resting-state EEG with eyes-open). In the evaluation part, we evaluated the modulation effect of the proposed ER-NF system in six consecutive sessions. To compare the modulation effects of different types of visual stimulation, SSVEP (steady-state visual-evoked potentials) was also recorded in users' second experiments. The experimental paradigm is illustrated in Fig. 3 and more details are provided below.

2.2.1. Part 1: calibration

- **VEP**: There were ten VEP sessions in the calibration part. In each session, a subject received continuously flashing visual stimuli via LED with random time intervals ranging from 80 ms to 120 ms, so that VEP had similar stimulation frequency (around 10 Hz) as in ER-NF and SSVEP. Each session lasted 2 min. One level of light intensity was used once in a session in a random order. More details about the light intensity were provided in Section 2.1.
- **REST**: There were four resting state sessions: two with eyes open and two with eyes closed. Four sessions were carried out alternately in turn and each session lasted one minute. Only resting state EEG data with eyes open, referred as REST below, were used in subsequent analyses.

2.2.2. Part 2: evaluation

- **ER-NF**: There were six ER-NF sessions. In each session, ER-NF was performed with 20 different alpha phases (Φ) of the alpha wave in a random order, and visual stimulation at each phase lasted 20 s. Since visual stimuli continuously delivered at different phases could not be discriminated by eyes, both the subjects and the experimenter did not know which phase was performed during the experiment. Hence, the ER-NF experiments were double-blind.
- **SSVEP**: Flashing light at the frequency of 10 Hz was used in SSVEP for 30 s. The I_{LED} was determined in the calibration part of each experiment. The stimulus frequency was fixed as 10 Hz (see Discussion for details).

2.3. Parameter selection

Two important parameters used to generate visual stimulation in ER-NF are F_{rest} and I_{LED}, and they can be estimated from REST and VEP data, respectively. To estimate these two important parameters, an offline analysis was run immediately after the calibration part, in which REST and VEP were recorded. A MATLAB script was written for the offline analysis, which lasted less than 2 min. The subjects took a rest during the time.

To detect the F_{rest} for individualized ER-NF, we located the maximum of the power spectrum of REST data (concatenated from EEG of two REST sessions with eyes open) in the alpha band (8–12 Hz). The Welch's method (with a window of 2 s and 50% overlap) was used for power spectral density estimation. Because the alpha wave was variable within subjects, the detected F_{rest} in two separate experiments of the same subject varied slightly, especially when the alpha wave was weak.

The light intensity I_{LED} is also an important parameter. It should be large enough to produce an evident modulation effect but cannot be too large so that users may feel uncomfortable. From the analogy of the simple pendulum in Fig. 1, we can see that a small force is sufficient to change the system's dynamic behavior while a large force might make the system unstable. Therefore, I_{LED} was selected as the minimum light intensity which can evoke VEP in the present study. In our experiments, I_{LED} was determined as the minimum light intensity which evoked a clear VEP response different from the background ongoing EEG. To improve the consistency of this selection criteria, we first made sure all the experiments were performed by the same operator. Moreover, all the light intensity selection results were double-checked by two people (the operator and another one) in offline analyses, and there was no difference between the offline selection of intensity and the intensity used in the experiments. In case there is no clear VEP response for a subject, the highest light intensity will be selected for this subject. An example was provided in Fig. 4 to illustrate how we determine I_{LED} for Sub01b. Because the intervals between consecutive stimuli, 80–120 ms, was too short, it would be difficult to detect VEP from a single visual stimulus by averaging. Hence, we firstly filtered the raw EEG by 8–12 Hz bandpass filter, and then calculated the mean absolute value of the filtered signal under different levels of light intensity. After baseline correction with the interval -500 – 0 ms, the Hilbert transform was applied on the signal. Finally, the amplitudes of the Hilbert transformed VEP signals are shown in Fig. 4 with ten different light intensities for Sub01b. The amplitudes of VEP (measured as the averaged values in the interval of 50–300 ms) are displayed in Fig. 4. In this example, the light intensity at level 7 was selected as the I_{LED} in ER-NF, because VEP with the light intensity at this level had a clear response different from ongoing EEG while VEP evoked by the light intensity from Level 1 to Level 6 did not.

2.4. Data analyses

2.4.1. Single-subject analyses of modulation effects

To evaluate the modulation effect of ER-NF at a range of alpha phases, the power spectral density of regulated alpha wave was estimated using the Welch's method (the window length is set to be 2 s with 50% overlap). Because ER-NF was expected to modulate the pattern of alpha wave (i.e., the distribution of alpha power over frequency), we mainly checked how the alpha power was modulated at one specific frequency F_{rest} and also examined how the peak alpha frequency was modulated. The power of the alpha wave was estimated as the averaged spectral power over

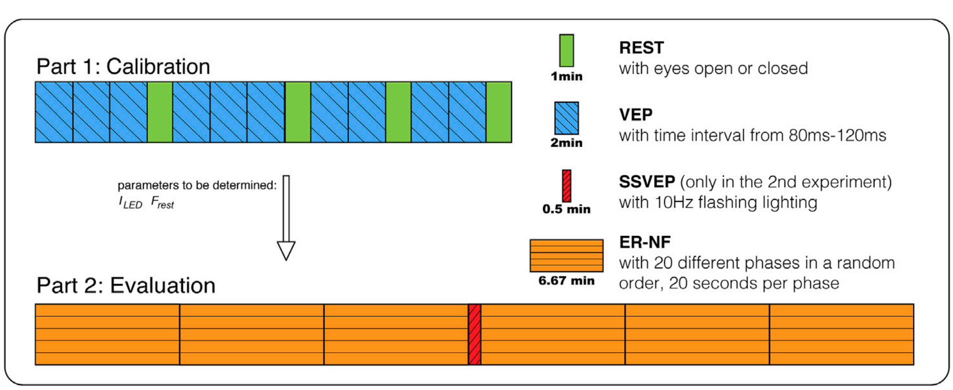

Fig. 3. Experimental paradigm. All subjects took the experiment for two times.

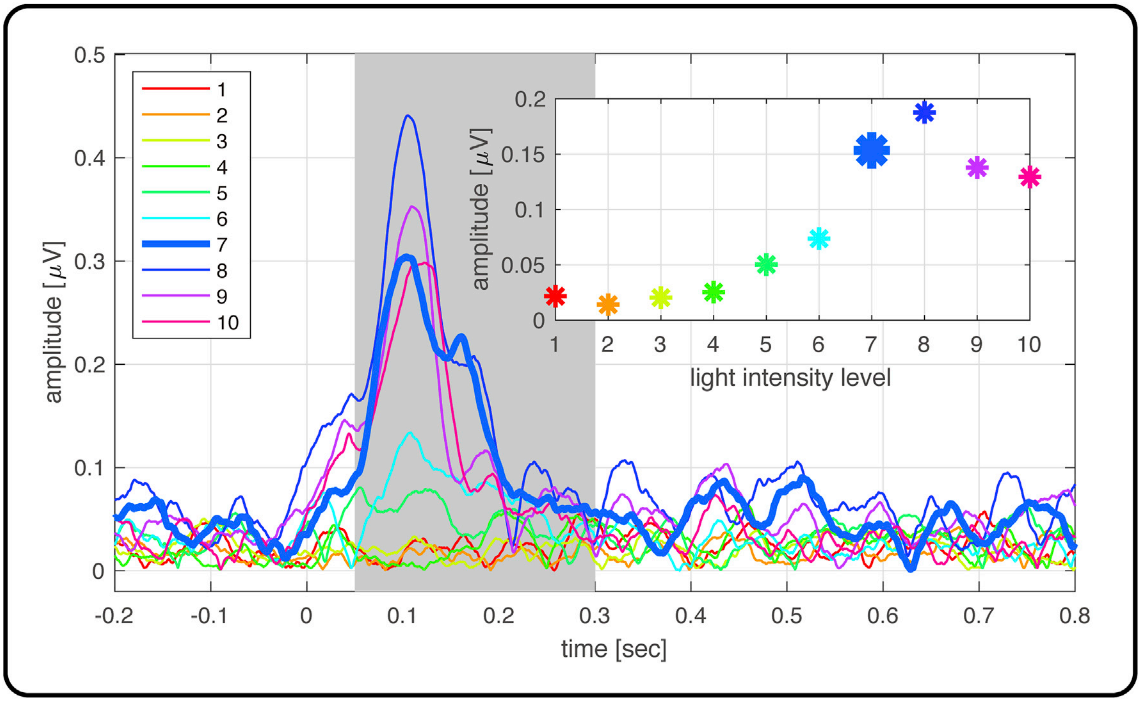

Fig. 4. The procedure to determine the I_{LED} used in ER-NF in one experiment (Sub01b). With the light intensities varying from Level 1 to 10, the VEP waveforms (the mean absolute values of the filtered signal after baseline correction and Hilbert transform) are illustrated with different color and their mean amplitudes in the interval of 0.05–0.3 s are displayed in the upper right plot. In this case, when the light intensity was at Level 7 (as marked by a large blue asterisk), the mean amplitude of VEP was substantially increased, as compared with that at Level 1–6. So, a duty cycle of 0.128 (Level 7) was selected as the I_{LED} used for ER-NF in this experiment.

6 ER-NF sessions. A modulation function to describe how the alpha power at the F_{rest} varies with respect to the phase index (time lag) Φ was estimated to illustrate ER-NF's modulation effect at different alpha phases. A 1024-point Fast Fourier transform (FFT) was applied to estimate the periodicity (i.e., the main frequency) of the modulation function, which was abbreviated as F_{mod} below. If the proposed ER-NF system does really work, the modulation function should be periodical and the period should be same with the alpha wave.

To further illustrate the modulation effect of ER-NF along time, Short-time Fourier Transform (with parameters: a window length of 2 s, a moving step of 20 ms) was applied on modulated EEG during ER-NF. For clarity, we only showed the modulation functions with phase indices Φ corresponding to the maximal and minimal power values in the modulation function (denoted as Φ-Max and Φ-Min). The time-varying spectral power of modulated EEG were averaged over 6 sessions. The peak alpha frequency at each phase index Φ was detected from the time-varying spectral power to depict how ER-NF modulated a subject's peak alpha frequency.

Based on the simple pendulum model, visual stimuli at different phases could either increase or decrease the alpha power and the frequency. Hence, the modulation functions of the alpha power were compared with the P_{rest} (the peak power of resting-state EEG). The modulation function was also compared with the peak power of SSVEP, because ER-NF and SSVEP used visual stimuli to regulate alpha wave in different ways (see Discussion for details).

2.4.2. Group analyses of modulation effects

At the group level, point-wise *t*-test was firstly applied to detect significant modulation effects (with respect to zero) along time from −20s to 20s. For each experiment, we calculated the instantaneous EEG power with the phase indices Φ-Max and Φ-Min corresponding to the maximal and minimal values in the modulation function. Considering the multiple comparison problem, the cluster-based permutation test (Maris and Oostenveld, 2007) was used with the cluster-threshold setting to 0.05 and permutation for 20000 times.

Then, the correlation between F_{mod} (the main frequency of the periodic modulation functions) and F_{rest} across all subjects was calculated for each experiment to examine whether the periodicity of the modulation function agreed well with the alpha peak. Next, since each subject took participant in the experiment for two times, we calculated the correlation coefficient separately for each experiment. To validate the repeatability of modulation effect, the Fisher r-to-z transformation was used to check whether there was significant difference between correlation coefficients of two experiments.

2.4.3. Comparison of modulation effects among different regulation protocols

To check whether the ER-NF system could significantly increase or decrease the alpha power, we compared the maximum and minimum value in the modulation function with P_{rest}. Further, to compare modulation effects between closed-loop and open-loop visual stimulation protocols, the maximum value of ER-NF's modulation function was also compared with that of SSVEP. Hence, in total four types of EEG alpha power were compared, and they are from the following four protocols:

- ER-NF (Φ-Max): ER-NF with the stimuli delivered at the phase Φ-Max,
- ER-NF (Φ-Min): ER-NF with the stimuli delivered at the phase Φ-Min,
- REST: Resting-state with eyes-open,
- SSVEP: SSVEP in which stimuli were delivered at 10 Hz.

Alpha powers from these four paradigms were compared using repeated measured one-way ANOVA, and then paired-sample *t*-test is performed between each pair of paradigms for post-hoc tests using Bonferroni adjusted significance level of ($0.05/6 = 8.33 \times 10^{-3}$) per test. Because SSVEP sessions were only available in the second experiments, only the results in the second experiments were compared when SSVEP was in the comparison. More precisely, 20 samples of REST, ER-NF(Φ-Max) or ER-NF(Φ-Min) obtained from the second experiments and all 20 samples for SSVEP were compared, if a comparison included SSVEP.

3. Results

In section 3.1, we firstly took one experiment of one subject as an example to demonstrate the modulation effects of the proposed ER-NF system. Then, group-level results are illustrated in section 3.2. Last, the comparison of modulation effects between different visual stimulation/regulation protocols is presented in section 3.3.

3.1. Single subject analyses of modulation effects

The second experiment of subject 1 (Sub01b) was selected because the results were clear and representative. For Sub01b, the detected F_{rest} was 11 Hz. Hence the bandwidth setting of the Butterworth was 10–12 Hz. The I_{LED} in ER-NF was Level 7 (as explained in Fig. 4).

Fig. 5a shows the modulation effects of ER-NF at F_{rest} when the phase index (time lag) Φ is 0 ms (Φ-Min; blue curve) or 50 ms (Φ-Max; red curve). For both two alpha phases, the modulation took effect from 0 s and plateaued for 20 s until the experiment was switched to the next phase.

Actually, the modulation effects at the phase Φ = 50 ms and Φ = 0 ms respectively achieved the maximal and the minimal values of the modulation function, and these two phases were marked in red and blue circles in Fig. 5b, which shows the modulation function of the alpha power at F_{rest} = 11 Hz against the phase index Φ. The modulation function showed a clear periodicity, and its frequency (F_{mod}) was 10.94 Hz, which was very close to the F_{rest}. For comparison, the power of rest EEG (P_{rest} = −10.36 dB) is marked in yellow dash line, and the power of SSVEP (7.76 dB) is marked in violet dots line. Alpha power values of both SSVEP and REST were lower than the maximal power of 9.32 dB in the modulation function of ER-NF, while alpha power values of REST was larger than the minimal power of −20.99 dB in the modulation function.

Further, Fig. 5c shows that, with the increase of the phase index Φ, the peak frequency of the modulated alpha wave moved towards the lower frequency band (marked as white dots in Fig. 5c). The result indicated the proposed ER-NF protocol could not only modulate the power of the alpha wave, but also modulated the peak alpha frequency. In another word, ER-NF could modulate the pattern of alpha wave. It also agreed with the model assumption of the simple pendulum, in which a force exerted at a specific phase could influence not only the amplitude but also the frequency of the simple pendulum.

The modulation effects of ER-NF in all experiments are illustrated in Fig. 6. Similar with Fig. 5b, in each experiment the power of the

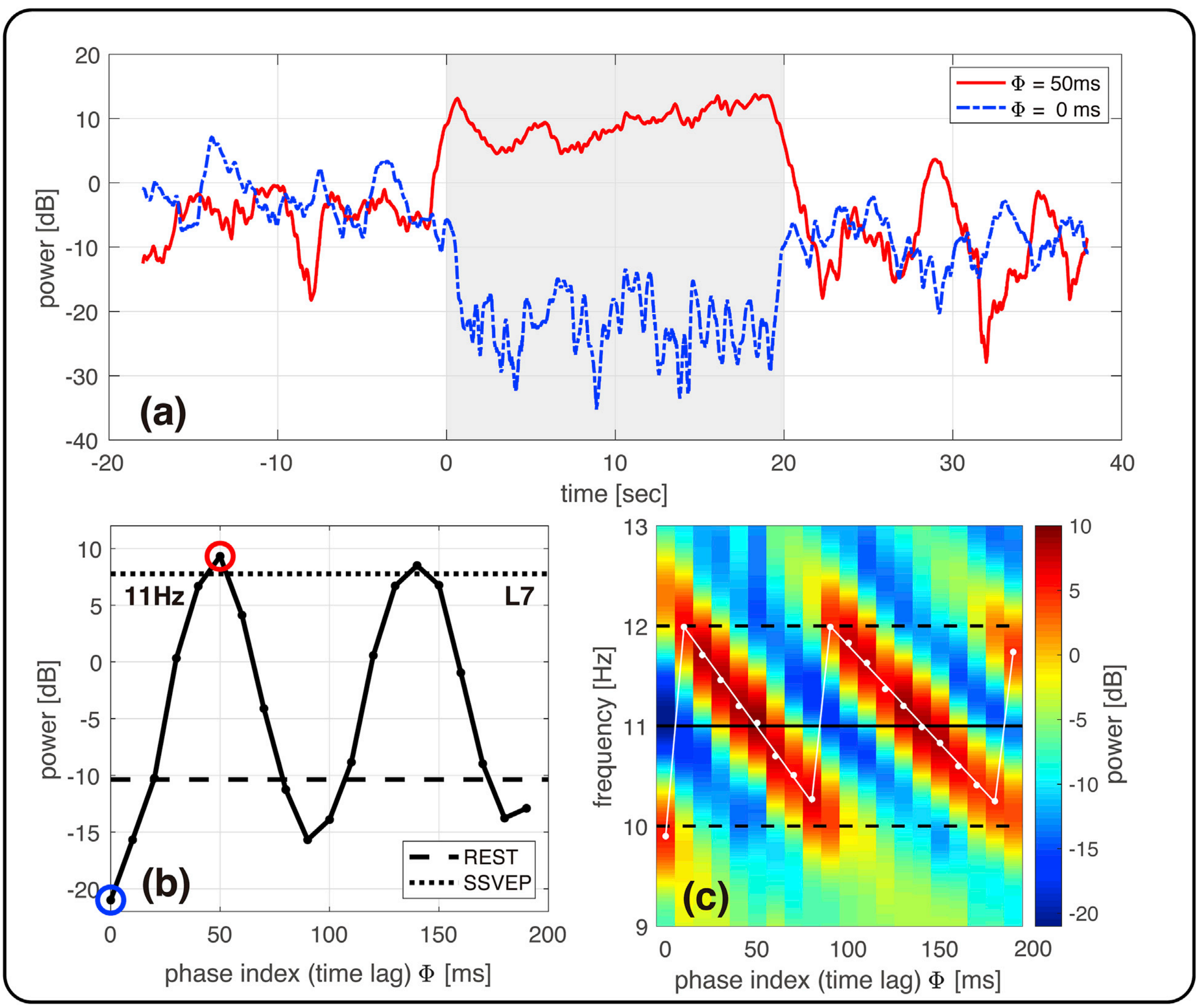

Fig. 5. The modulation effect of ER-NF in the second experiment of Subject 1 (Sub01b). (a) The time response of the modulation effect with the phase index (time lag) Φ corresponding to the maximal (Φ = 0 ms) and minimal (Φ = 50 ms) power in the modulation function. The shadowed interval (0–20 s) indicates the modulation interval with the target phase index Φ. (b) The modulation function against the phase index (time lag) Φ, in which 11 Hz is the value of F_{rest} and L7, short for Level 7, is the value of I_{LED}. The dash line indicates the P_{rest}. The dots line indicates the power of the SSVEP at 10 Hz. The valley and peak of the modulation function are marked by blue and red circles. (c) Power spectra of the alpha waves regulated by visual stimuli delivered at different values of Φ. The solid line and the dash line indicate the central frequency and bandwidth setting of the online filter. The white dots and lines stand for the peak frequencies at different Φ.

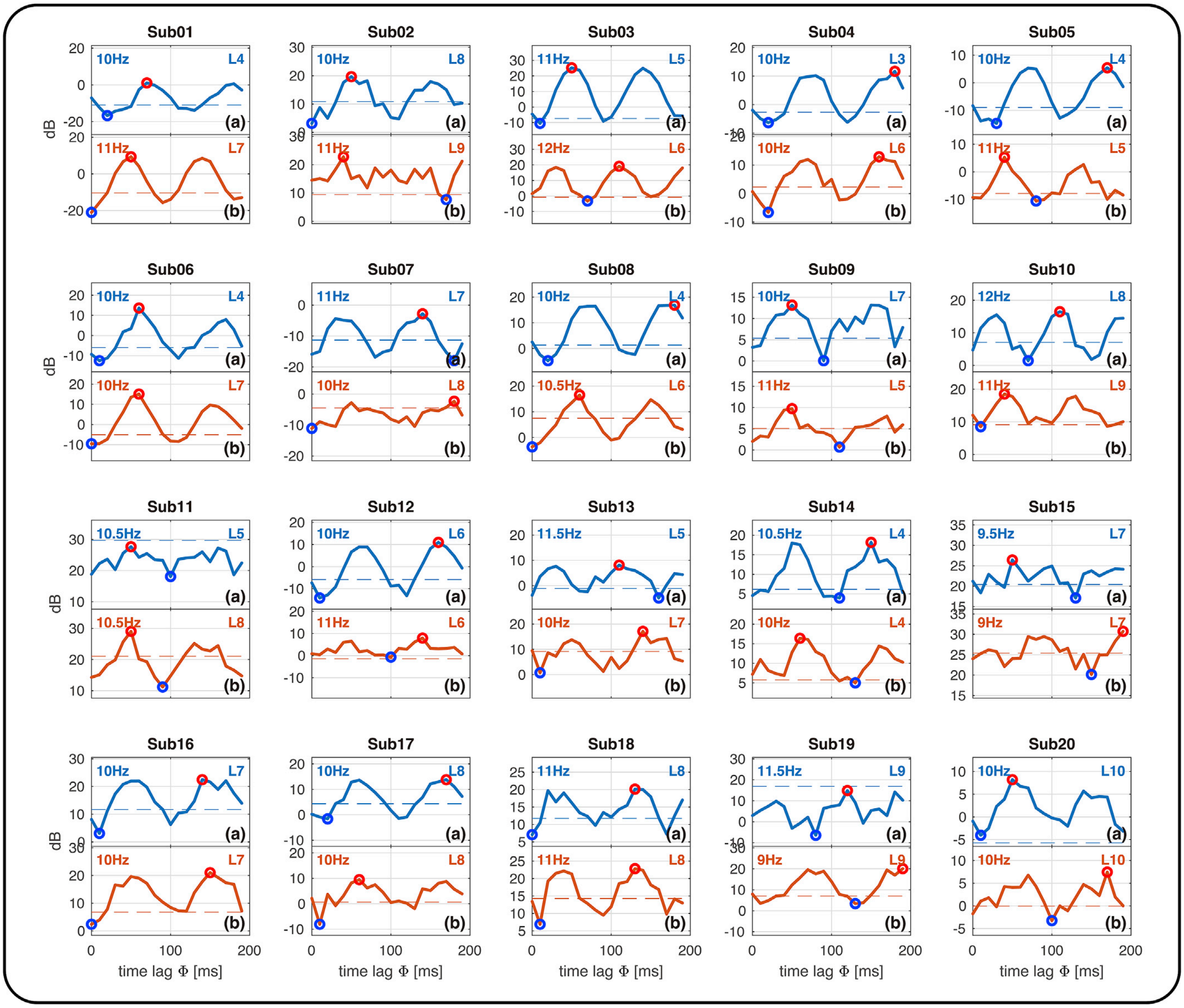

Fig. 6. The modulation effects of the ER-NF in all experiments. For each subject, the power of the alpha wave at its F_{rest}, is shown as a power modulation function against the phase index (time lag) Φ, which corresponds to different phases of the alpha wave. The valleys and peaks of the modulation functions are marked by blue and red circles. Two important parameters, F_{rest} and I_{LED}, are labeled in the upper part of each subfigure. The dash line stands for P_{rest}. All subjects took participant in the experiment for two times (blue for the first time, orange for the second time) to test the within-subject repeatability of the ER-NF.

modulated EEG at F_{rest} is shown as a power modulation functions against the phase index Φ. The results for two experiments are respectively shown as blue and orange curves and their parameter settings (F_{rest} and I_{LED}) are also labeled. On average, F_{rest} was 10.35 ± 0.76 Hz, and I_{LED} was Level 6.51 ± 1.75. It should be stated that, even with the I_{LED} of Level 10, some experiments (Sub02b, Sub07a, Sub07b, Sub09b, Sub10b, Sub18a, Sub20a and Sub20b) did not have clear VEP responses. In these cases, the I_{LED} that evoked the maximal VEP was used in the evaluation part of the experiment.

Similar with the modulation effect of ER-NF of Sub01b in Figs. 5 and 6 shows that clear periodic modulation functions (modulated power of EEG signal at F_{rest} with respect to Φ) could be observed from almost all experiments. The time response of the modulation effect and the power spectra of the alpha waves regulated by visual stimuli delivered at different values of Φ in all experiments is arranged in Figs. S3 and S4. Bad modulation effect, such as that of Sub02b, could be explained by the subject's mental state. The experimenter reported that Sub02 was drowsy in the second experiment (Sub02b), but not in the first experiment (Sub02a), suggesting that drowsiness may have an impact on the modulation effects of ER-NF. Pairwise comparisons between ER-NF at Φ-Max or Φ-Min and REST can be found in Fig. S5 in the Supplementary Materials.

3.2. Group analyses of modulation effects

The mean modulation effects along the time axis are displayed in Fig. 7a. Using point-wise t-test with cluster-based permutation test to correct the family-wise error rate, it was found that the alpha power of ER-NF (Φ-Max) and ER-NF (Φ-Max) at their F_{rest} were significant different in the whole modulation period. The significant interval, from −0.46–20.44 s, was a little bit wider than the modulation window ([0, 20] second, marked in a gray shadow), which was caused by the moving window (2 s) used in power spectral estimation.

F_{mod} (the main frequency of the periodic modulation functions) was significantly correlated with F_{rest} across subjects (black curve in Fig. 7b with $r = 0.86$, $p = 1.99 \times 10^{-12}$ in both experiments 1 and 2. Sub02b

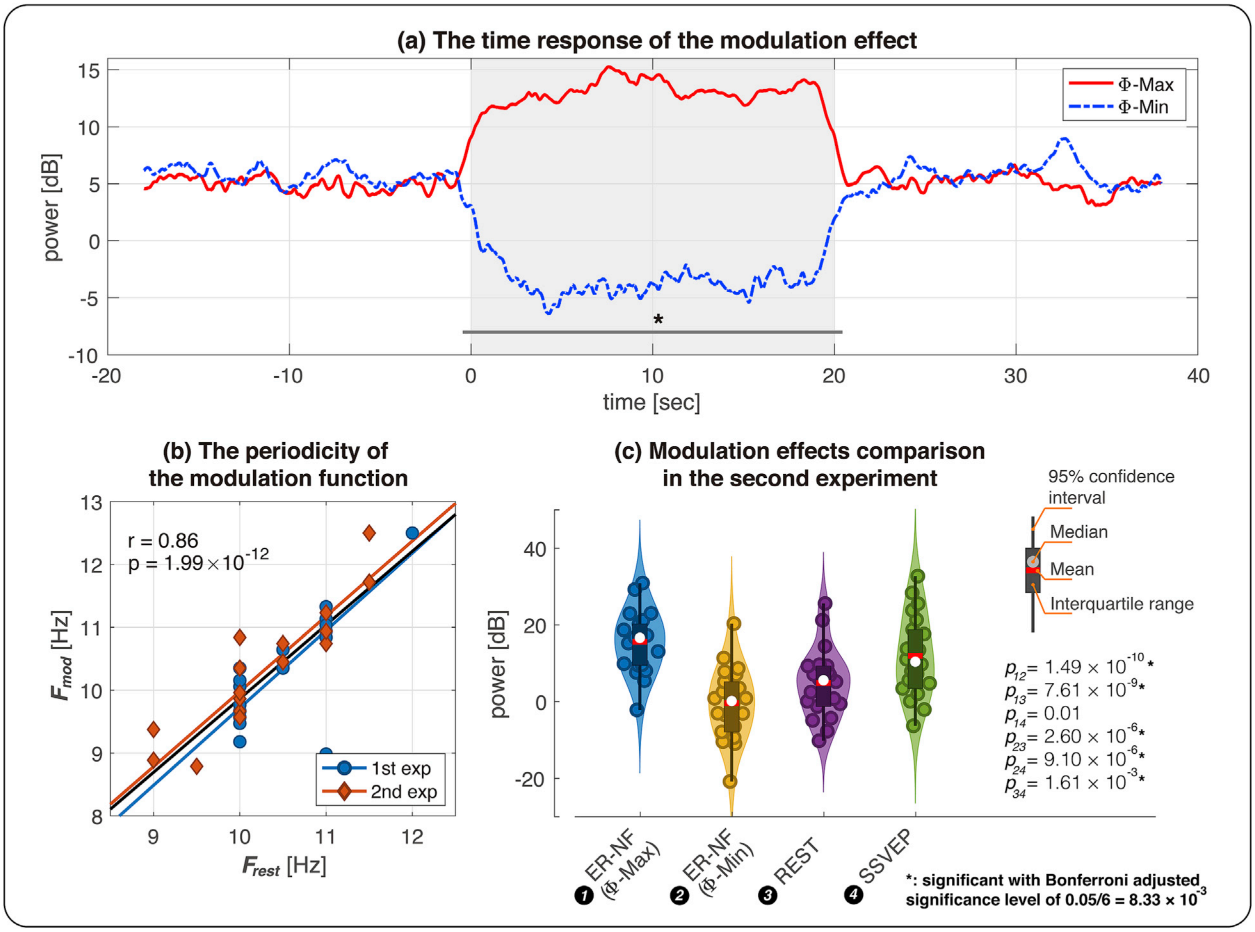

Fig. 7. (a) Time responses of the modulation effects at the phase indices Φ-Max and Φ-Min (corresponding to the maximal and minimal power in the modulation function). The shadowed interval (0–20 s) indicated the modulation interval with the target phase Φ. There is significant difference between the two conditions in the interval of the asterisk from −0.46–20.44 s. (b) The peak frequency of the modulation function is significantly correlated with F_{rest} ($r = 0.86$ and $p = 1.99 \times 10–12$). (c) The violin plot for the alpha powers of ER-NF (Φ-Max), ER-NF (Φ-Min), REST and SSVEP in the second experiment. Since SSVEP data is only recorded in the second experiment, all the statistical analysis is done based on the second experiment. There is significant difference between alpha powers of the four paradigms ($F(3,19) = 13.95$ and $p = 2.11 \times 10^{-15}$). Post-hoc comparisons show that all the pair-wise comparisons, except the comparison between ER-NF (Φ-Max) and SSVEP, had significant difference (i.e., they survived the Bonferroni adjusted significance level of $0.05/6 = 8.33 \times 10^{-3}$).

with $F_{mod} = 19.43$ was excluded in the correlation analysis, because it was detected as an outlier by the criterion that an outlier has a value more than three scaled median absolute deviations away from the median (Leys et al., 2013; see Fig. S6). We also performed correlation analysis separately for the two experiments. The blue and red curves in Fig. 7b show the significant correlation between F_{mod} and F_{rest} in the first experiment ($r = 0.84$, $p = 4.07 \times 10^{-6}$) and the second experiment ($r = 0.91$, $p = 9.39 \times 10^{-8}$), respectively. By comparing the two correlation coefficients with the Fisher r-to-z transformation, we got the z-value $z = -0.84$ ($p = 0.40$), which indicated there was not significant difference between the two experiments.

3.3. *Comparison of modulation effects between different stimulation protocols*

The power of ER-NFs with phases Φ-Max and Φ-Min were compared with the maximum EEG power in REST and SSVEP (Fig. 7c). Since SSVEP was only recorded in the second experiment, all the statistical comparisons including SSVEP were based on the second experiment. On average, the power for ER-NF (Φ-Max), ER-NF (Φ-Min), REST and SSVEP was 15.46 dB, −0.55 dB, 4.68 dB and 11.78 dB. There is a significant difference among the four protocols ($F(3,19) = 13.95$ and $p = 2.11 \times 10^{-15}$). Paired-sample *t*-test results are provided in Fig. 7c. Results showed that, all the pair-wise comparisons, except the comparison between ER-NF (Φ-Max) and SSVEP, had significant difference, which shows the capability of the proposed ER-NF protocol in the regulation of alpha wave. Note that, no sample was excluded as outlier in this comparison.

When comparing modulation effects, REST stands for the resting state EEG with eyes-open. The paired-sample *t*-test result between ER-NF (Φ-Max) and the resting state EEG with eyes-closed was not significant ($p = 0.09$), so the result of EEG with eyes-closed was not illustrated in Fig. 7c to keep the result concise and clear. As compared with REST, the proposed ER-NF either increased or decreased the alpha power at the frequency F_{rest} ($p = 7.61 \times 10^{-9}$ for ER-NF (Φ-Max) vs. REST and $p = 2.60 \times 10^{-6}$ for ER-NF (Φ-Min) vs. REST and), depending on the stimulation phase (i.e., alpha phase at which the visual stimuli were delivered). In the experiments shown in Fig. 6, we got ER-NF (Φ-Max) > REST > ER-NF (Φ-Min) in the alpha power in most cases. But there were some exceptions: the whole modulation functions for Sub11a and Sub19a were below P_{rest}, and the whole modulation functions for Sub12b and Sub20a were above P_{rest}. In Fig. S5 of the Supplementary Materials, we provided more detailed information about the comparison between REST and ER-NF (Φ-Max/Φ-Min). SSVEP also evoked higher EEG power than P_{rest} ($p = 1.61 \times 10^{-3}$). With the same I_{LED}, ER-NF (Φ-Max) could evoke marginally significantly higher alpha power than SSVEP ($p = 0.01$, which cannot survive the Bonferroni correction for multiple comparison in the post-hoc tests of ANOVA), while ER-NF (Φ-Min) could achieve significantly lower alpha power than

SSVEP ($p = 9.10 \times 10^{-6}$).

4. Discussion and conclusion

A proof-of-concept system of a new Externally-Regulated Neurofeedback (ER-NF) protocol was designed, implemented, and validated in this study. The main novelty of the ER-NF system is the fact that it is able to regulate the alpha wave by continuously delivering visual stimuli at a specific alpha phase. By using this new ER-NF protocol, users do not need to learn how to regulate their brain activities and the modulation effects are more consistent and flexible.

4.1. Externally-regulated vs. self-regulated neurofeedback

The efficacy of traditional neurofeedback protocols depends on the users' capability to regulate their brain activities in a self-paced voluntary manner. Because of the substantial inter-individual variability in user's skills and experience in self-regulation, the effects of neurofeedback vary hugely. To ensure all users could benefit from neurofeedback, a new EEG regulation method, which is free of user's active participation and training, is desired.

The proposed new ER-NF protocol uses phase-guide visual stimulation to regulate EEG, and it does not rely on users' active participation. As a result, the new protocol can achieve consistently good regulation performance for all users. It is important to note that, external stimuli are not delivered to users according to the operators' predefined specification (such as the delivery time in evoked potential experiments), and they are actually guided by users' EEG but without users' intention. In another word, users do not need to intentionally regulate their brain activities in the new protocol, because the system can decode their brain activities (i.e., to estimate the alpha phase) and accordingly generate external stimuli for users.

An important advantage brought by the ER-NF protocol is that no training is required for new users. In the classical neurofeedback, training is an essential part. Normally, users have to be trained for several weeks or even a couple of months to be able to "voluntarily control" their EEG (Gruzelier, 2014). But in the proposed ER-NF system, users need not regulate EEG by themselves, so that training is not necessary. In this study, users were not trained to regulate their EEG, but their alpha waves were effectually regulated even without any training.

The new ER-NF protocol also has advantages in its capability to modulate alpha wave in a flexible and immediate fashion. The proposed ER-NF can either increase or decrease the alpha power, while SSVEP can only increase the alpha power. Also, note that ER-NF actually used exactly the same stimulation intensity, and it is the timing for stimulation (phase index Φ) that makes the difference in the modulation effect. On the other hand, SSVEP increases alpha power by increasing the stimulus intensity, but higher stimulus intensity can cause users' discomfort. In addition, SSVEP evokes EEG responses at the target frequency and its harmonics, while ER-NF affects a user's individualized alpha frequency band. Last, ER-NF can achieve its modulation effect immediately. As soon as the stimuli are delivered, the modulation effect is on; once the stimuli are withdrawn, the modulation effect is gone.

ER-NF also has a merit in its rigorously controlled experiment, which is actually double-blind. A double-blind experiment should eliminate subjective, unrecognized biases carried by the subjects and operators. Most of conventional neurofeedback studies are not double-blind, which makes the efficacy of neurofeedback controversial (for example, some studies argued that neurofeedback efficacy actually comes from placebo effect) (Arnold et al., 2013). Therefore, double-blind placebo-controlled studies should be designed to validate the efficacy of neurofeedback (Heinrich et al., 2007). In ER-NF, since visual stimuli continuously delivered at different phases cannot be discriminated by eyes, both the user and the experimenter did not know which alpha phase was being used to generate visual stimulation and whether the user's alpha power would be increased or decreased during the experiment. Hence, the ER-NF experiments are double-blind and placebo-controlled, which provided a rigorous validation of the good modulation effect of the ER-NF system.

4.2. Comparisons with other neural modulation techniques

We further compare the ER-NF protocol with other two neural modulation techniques that can regulate or change the brain activities: evoked-potential (EP) paradigms and brain stimulation (such as deep brain stimulation [DBS], transcranial magnetic stimulation [TMS], transcranial direct current stimulation [tDCS], transcranial alternating current stimulation [tACS]). Table 1 summaries the similarities and differences of four neural modulation techniques.

First, it is clear that, ER-NF, EP, and brain stimulation do not need users' active participation or training, while users of the traditional SR-NF have to be trained to master the skills of self-regulation. So, training is an essential part of conventional neurofeedback systems, and its effect greatly determines the efficacy of neurofeedback.

Second, ER-NF, EP, and brain stimulation techniques have different styles of stimuli and different ways to change the brain activities. Both ER-NF and EP use sensory stimulation (visual stimulation in this study) to change brain signals. But the stimulation parameters used in ER-NF are generated based on decoded brain activities, while the stimulation parameters used in EP are pre-defined by operators. Unlike ER-NF and EP, brain stimulation techniques delivered electrical, magnetic, or acoustic stimulation directly on the brain. Normally, the stimulation parameters used in brain stimulation are defined by operators, though some new brain stimulation techniques can also use decoded brain signals or other physiological signals as feedback to adaptively adjust stimulation parameters (Rosin et al., 2011).

Third, ER-NF and other traditional neurofeedback protocols have a closed-loop, which decodes brain activities to regulate brain activities (via computers and/or other devices or by the subject him/herself). In ER-NF, the decoded phase information is directly used to generate the stimulation sequence. On the other hand, in the traditional neurofeedback, the decoded information is just displayed to users so that they can regulate their brain wave accordingly. EP and brain stimulation techniques modulate the brain in an open-loop fashion: computers or devices deliver pre-defined stimuli to users and there is no feedback.

Fourth, these neural modulation techniques can modulate different types of EEG activities. As a new protocol, ER-NF is found to only modulate the peak alpha frequency and alpha amplitude, which are actually covaried. On the other hand, because the conventional SR-NF has been studied for decades, it has been found to be able to modulate a wide range of EEG activities, from rhythms to brain connectivity. EP paradigms can elicit various types of transient EPs (such as VEP) and steady-state EPs (such as SSVEP), which are reflected as changes in the time-domain morphology or in the spectral characteristics of various frequency bands. Different brain stimulations techniques modulate different types of EEG activities, from time-domain EPs to spectral properties. It must be mentioned that, Table 1 only lists some commonly-used or well-known EEG activities and actually the list is far from exhaustive. Because the brain is a highly dynamic and complex system, external stimulation or self-regulation can change a wide variety of EEG activities. For example, all these neural modulation techniques (including the proposed ER-NF) may be able to alter the functional connectivity and network properties of the brain.

Last but not the least, the underlying neuroscience theories for these four neural modulation techniques are different. The traditional SR-NF is based on learning mechanism of operant conditioning (Rosenfeld et al., 1995; Vernon et al., 2003), which suggests that users can be trained to gain some voluntarily control on their brain wave. ER-NF and EP are based on the theory of neurodynamics, which implies that stimuli delivered at different phases would evoke different dynamic behaviors of neural activities (McSayers and Beagley, 1974; Trimble and Potts, 1975; Jervis et al., 1983). Brain stimulation is normally based on the theory of

Table 1
Comparisons between the ER-NF protocol and other neural modulation techniques.

	Proposed Externally-Regulated Neurofeedback	Traditional Self-Regulated Neurofeedback	Evoked-potential paradigms (VEP, SSVEP et al.)	Brain stimulation (DBS/TMS/tDCS/TACS)[a]
Need users' active participation and training?	**No**	**Yes**	**No**	**No**
Need external stimulation?	**Yes** sensory stimulation generated based on decoded EEG	**No** visual and/or auditory feedback is just used to show brain state information	**Yes** sensory stimulation predefined by operators	**Yes** electric/magnetic stimulation predefined by operators and delivered on the brain
Need to decode brain signals to construct a closed-loop?	**Yes (closed-loop)** brain → computer/device→ sensory system → brain	**Yes (closed-loop)** brain → computer/device→ sensory system → brain	**No (open-loop)** computer/device → sensory system → brain	**No (open-loop)** computer/device → brain
Modulated EEG activities	peak frequency and power/amplitude (which are covaried) in the alpha band (based on this study)	peak frequency, power/amplitude spatial distribution (such as asymmetry), connectivity, and other features in various frequency bands (Gruzelier, 2014; Yamashita et al., 2017; Baehr et al., 2001; etc.)	Evoke certain response in time domain and time-frequency domain for VEP; magnitude and phase on certain frequency point with its harmonic frequency point for SSVEP (Luck, 2014)	cortical oscillations in various frequency bands/amplitude and latency for ERP components (Kibleur et al., 2017; Fröhlich, 2015; Vossen et al., 2015; Lenoir et al. 2017; etc.)
Neuroscience theory	Neurodynamics (McSayers and Beagley, 1974; Trimble and Potts, 1975; Jervis et al., 1983)	Operant conditioning (Vernon et al., 2003)	Neurodynamics (McSayers and Beagley, 1974; Trimble and Potts, 1975; Jervis et al., 1983)	Neuroplasticity (Huang et al., 2005)

[a] A few new brain stimulation techniques have used brain activities or other physiological recordings as feedback signals to construct a closed-loop, such as closed-loop DBS (Rosin et al., 2011). But, in general, most of existing brain stimulation are open-loop and do not record and decode brain activities for feedback.

neuroplasticity. For example, repetitive transcranial magnetic stimulation will induce plasticity of both excitatory and inhibitory synapses (Lenz et al., 2016; Huang et al., 2005; Hamada et al., 2012), and paired associative stimulation is based on the theory of Hebbian learning (a synapse between two neurons is strengthened when they have highly correlated outputs) (Ridding et al., 2003; Stefan et al., 2000).

Although the ER-NF protocol is similar to some other neural modulation techniques in some aspects, it also has uniqueness and key improvements. For example, the ER-NF protocol is similar to some new closed-loop brain stimulation systems, such as EEG-guided DBS, which can be used on the patients with essential tremor with movement intention (Herron et al., 2015). The advantage of this ER-NF protocol over closed-loop brain stimulation is that, ER-NF uses natural sensory input and thereby is non-invasive, more accessible and user-acceptable.

4.3. Limitations and future work

The new proof-of-concept system still has some limitations to be overcome.

4.3.1. Modulation effects of ER-NF on alpha wave

The proposed ER-NF protocol is able to modulate the power distribution pattern of alpha wave. The present study main analyzed the modulation effects of ER-NF on alpha power at individually-defined alpha frequency point F_{rest}, not in the whole alpha band. It is because the modulation effects are most significant at F_{rest}. Actually, with the increase of the range of alpha wave, the modulated alpha power exhibited a similar but weaker modulation effect. This phenomenon may be caused by the band-limited feedback signal we used. Because we used the phase of a band-limited EEG signal (which was bandpass-filtered with cutoff frequencies of $F_{rest}\pm1$ Hz) as feedback to modulate the alpha wave, the modulate effect may be only evident in the frequency range of $F_{rest}\pm1$ Hz. In Fig. S1 and Fig. S2 of the Supplementary Materials, we showed the modulation effects of ER-NF in the whole alpha band, and then tried to explain why ER-NF is more effective at individually-defined alpha frequency points. Further, it can be seen from Fig. 5 that ER-NF can modulate the power distribution pattern of alpha wave. When we evaluated the modulation effect at one specific frequency (F_{rest}), the modulation effect was exhibited to be exerted on the alpha power. But we can see from the phase depending spectral power in Fig. 5c that the proposed ER-NF modulates peak alpha frequency as well. With the increase of the phase index Φ, the peak frequency of the modulated EEG moved towards the lower frequency band (marked as white dots in Fig. 5c for Sub01b and Fig. S4 for all the experiments in the supplementary materials). These results suggested that the modulation effects of the proposed ER-NF protocol on alpha wave could be complicated because alpha power and frequency are modulated interdependently. Considering the fact that the modulation effect on alpha power is weaker if alpha power is calculated in a wider frequency large, it is also possible that ER-NF mainly modulates the peak alpha frequency. This speculation should be examined in future by more specifically designed experiments (for example, to check how different bandwidths of bandpass filtering influence the modulation effect) and more sophisticated mathematical models.

4.3.2. Mathematical models

In Fig. 1, we used a simple model of pendulum to illustrate the principle of ER-NF. Such an analogy is easy to understand but may oversimplify the dynamic behaviors of alpha wave. For example, most neurodynamic models describe the alpha oscillation as a limit cycle attractor (Huang et al., 2011; Freeman, 2015; Acedo and Moraño, 2013), not the simple pendulum motion without dumping. In future, we should use mathematical functions to describe how alpha power and frequency are modulated by external visual stimuli delivered at a specific phase. Some sophisticated models, such as neural mass models (Jansen and Rit, 1995) and time-series models (Vijayan et al., 2015), could be used to provide a more accurate description and a comprehensive understanding of the alpha wave regulated by phase-guided visual stimuli in ER-NF.

4.3.3. System delay

The proposed system has an inevitable delay stemming from both hardware and software. The hardware delay is caused by data transmission via the EEG amplifier (BrainAmp), which is a constant (60 ms) in our testing. The software delay comes from the phase delay of the online casual Butterworth bandpass filter used to separate alpha wave. The Butterworth filter used is an Infinite Impulse Response (IIR) filter, which introduced different phase delay values at different frequencies. If the F_{rest} is 10 Hz, the maximum delay for the 2-order Butterworth bandpass filter (9–11 Hz) is 247 ms. The filter parameters (such as the filter order and the bandwidth) determine the tradeoff between quality phase estimation of the alpha wave and the filter delay. A higher filter order would increase the delay, and a wider bandwidth would decrease the accuracy for the phase estimation. Hence, the system delay from both the software and hardware added up to more than 300 ms, which is more than 3 alpha cycles. That is, the alpha phase we estimate is actually the alpha phase at 3 cycles before. Due to the unpredictable dynamic behavior of the alpha wave, the delay of the system may have an influence on the modulation effect. If we can estimate the alpha phase with shorter system delay, the modulation effect may be further improved.

4.3.4. Extensions to other EEG rhythms and other sensory stimuli

This work manipulated alpha wave by visual stimulation. In principle, this ER-NF system can be extended by modulating other EEG rhythms (beta, theta, etc.) and/or using other types of sensory stimulation (such as auditory and somatosensory inputs). We selected alpha band and visual stimulation in this study because alpha wave is strong in EEG and visual stimulation is easy to generate and easy to evoke EEG changes. If we extend the ER-NF system to other EEG rhythms and sensory stimulation, we need overcome the difficulties in precisely and promptly detecting phases of EEG rhythms and in generating user-dependent and phase-guided stimulation sequence. Further, the real time alpha phase estimation technique can also be potentially used in the modulation of sensory perception.

4.3.5. Modulation effects on cognitive and behavioral states

We have used converging results to demonstrate the efficacy of ER-NF in regulating the power and frequency of alpha wave. However, a relationship between alpha wave and mental states does not mean mental states can be altered by modulating alpha wave. Because we did not collect any behavioral and cognitive variables, it is still unknown whether the new system holds the capability to modulate users' behavior and cognition. Alpha wave is closely related to many cognitive and behavioral states, such as attention (Aftanas and Golocheikine, 2001; Klimesch et al., 1998; Klimesch, 2012) and perception (Nunn and Osselton, 1974; Tu et al., 2016; Peng et al., 2015). We believe the proposed ER-NF could regulate perceptual and cognitive variables by modulating alpha oscillation because some other neuromodulation studies have revealed the causal link between alpha wave and perception or cognition. Non-invasive brain stimulation methods, such as TMS, TDCS, and TACS, have shown that, they can modulate the alpha wave and in turn influence perception, cognition and behavior (Herrmann et. al. 2013; and Kuo et. al. 2012), implying a causal relationship between alpha wave and behavior. Since the proposed ER-NF method can also modulate alpha oscillation, it should be able to change certain domains of cognition or behavior. Because the proposed ER-NF method can provide a more individualized and consistent way to modulate alpha wave than non-invasive brain stimulation, we expect it could achieve better performance in modulating cognition and behavior. Of course, the actual effect of ER-NF on users' behavior and cognition should be rigorously examined by well-designed experiments, large-scale validation, randomized trials, and longitudinal study, and be compared with other types of mainstream and advanced neurofeedback techniques.

In summary, we proposed a new ER-NF protocol, which uses phase-guided external stimulation to regulate brain activities, so that no users' active participation or training is required. The modulation effects of the system can be reliably observed from almost all users in a double-blind test. Therefore, the proposed ER-NF system is an important step towards addressing the neurofeedback inefficiency problem and holds great potential to more reliably and flexibly modulate various domains of cognition and behavior.

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Appendix A. Supplementary data

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References

Acedo, L., Moraño, J.A., 2013. Brain oscillations in a random neural network. Math. Comput. Model. 57 (7–8), 1768–1772.

Aftanas, L.I., Golocheikine, S.A., 2001. Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. Neurosci. Lett. 310 (1), 57–60.

Albrecht, B., Uebel-von Sandersleben, H., Gevensleben, H., Rothenberger, A., 2015. Pathophysiology of ADHD and associated problems-starting points for NF interventions? Front. Hum. Neurosci. 9, 359.

Alkoby, O., Abu-Rmileh, A., Shriki, O., Todder, D., 2018. Can we predict who will respond to neurofeedback? A review of the inefficacy problem and existing predictors for successful EEG neurofeedback learning. Neuroscience 378, 155–164.

Arnold, L.E., Lofthouse, N., Hersch, S., Pan, X., Hurt, E., Bates, B., Kassouf, K., Moone, S., Grantier, C., 2013. EEG neurofeedback for ADHD: double-blind sham-controlled randomized pilot feasibility trial. J. Atten. Disord. 17 (5), 410–419.

Baehr, E., Rosenfeld, J.P., Baehr, R., 2001. Clinical use of an alpha asymmetry neurofeedback protocol in the treatment of mood disorders: follow-up study one to five years post therapy. J. Neurother. 4 (4), 11–18.

Coben, R., Linden, M., Myers, T.E., 2010. Neurofeedback for autistic spectrum disorder: a review of the literature. Appl. Psychophysiol. Biofeedback 35 (1), 83.

Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H.C., Drechsler, R., 2008. Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? J. Neural. Transm. 115 (10), 1445–1456.

Freeman, W.J., 2015. Mechanism and significance of global coherence in scalp EEG. Curr. Opin. Neurobiol. 31, 199–205.

Fröhlich, F., 2015. Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. Prog. Brain Res. 222, 41–73.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J.H., Kaiser, J., 2003. Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl. Psychophysiol. Biofeedback 28 (1), 1–12.

Gruzelier, J.H., 2014. EEG-neurofeedback for optimising performance. III: a review of methodological and theoretical considerations. Neurosci. Biobehav. Rev. 44, 159–182.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2012. The role of interneuron networks in driving human motor cortical plasticity. Cerebr. Cortex 23 (7), 1593–1605.

Hammond, D.C., 2007. What is neurofeedback? J. Neurother. 10 (4), 25–36.

Heinrich, H., Gevensleben, H., Strehl, U., 2007. Annotation: neurofeedback–train your brain to train behaviour. JCPP (J. Child Psychol. Psychiatry) 48 (1), 3–16.

Herrmann, C.S., Rach, S., Neuling, T., Strüber, D., 2013. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front. Hum. Neurosci. 7, 279.

Herron, J., Denison, T., Chizeck, H.J., 2015, April. Closed-loop DBS with movement intention. Int IEEE EMBS Conf Neural Eng 844–847.

Holtmann, M., Sonuga-Barke, E., Cortese, S., Brandeis, D., 2014. Neurofeedback for ADHD: a review of current evidence. Child Adolesc Psychiatr Clin N Am 23 (4), 789–806.

Huang, G., Zhang, D., Meng, J., Zhu, X., 2011. Interactions between two neural populations: a mechanism of chaos and oscillation in neural mass model. Neurocomputing 74 (6), 1026–1034.

Huang, Y.Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45 (2), 201–206.

Jansen, B.H., Rit, V.G., 1995. Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. Biol. Cybern. 73 (4), 357–366.

Jasper, H., Shagass, C., 1941. Conditioning of the occipital alpha rhythm in man. J. Exp. Child Psychol. 28 (5), 373.

Jervis, B.W., Nichols, M.J., Johnson, T.E., Allen, E., Hudson, N.R., 1983. A fundamental investigation of the composition of auditory evoked potentials. IEEE Trans. Biomed. Eng. 30 (1), 43–50.

Kibleur, A., Polosan, M., Favre, P., Rudrauf, D., Bougerol, T., Chabardès, S., David, O., 2017. Stimulation of subgenual cingulate area decreases limbic top-down effect on ventral visual stream: a DBS-EEG pilot study. Neuroimage 146, 544–553.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., Schwaiger, J., 1998. Induced alpha band power changes in the human EEG and attention. Neurosci. Lett. 244 (2), 73–76.

Klimesch, W., 2012. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cognit. Sci. 16 (12), 606–617.

Kuo, M.F., Nitsche, M.A., 2012. Effects of transcranial electrical stimulation on cognition. Clin. EEG Neurosci. 43 (3), 192–199.

Leys, C., Ley, C., Klein, O., Bernard, P., Licata, L., 2013. Detecting outliers: do not use standard deviation around the mean, use absolute deviation around the median. J. Exp. Soc. Psychol. 49 (4), 764–766.

Lenz, M., Galanis, C., Müller-Dahlhaus, F., Opitz, A., Wierenga, C.J., Szabó, G., Ziemann, U., Deller, T., Funke, K., Vlachos, A., 2016. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. Nat. Commun. 7, 10020.

Linden, D.E., Habes, I., Johnston, S.J., Linden, S., Tatineni, R., Subramanian, L., Sorger, B., Healy, D., Goebel, R., 2012. Real-time self-regulation of emotion networks in patients with depression. PLoS One 7 (6), e38115.

Lofthouse, N., Arnold, L.E., Hersch, S., Hurt, E., DeBeus, R., 2012. A review of neurofeedback treatment for pediatric ADHD. J. Atten. Disord. 16 (5), 351–372.

Lenoir, C., Huang, G., Vandermeeren, Y., Hatem, S.M., Mouraux, A., 2017. Human primary somatosensory cortex is differentially involved in vibrotaction and nociception. J. Neurophysiol. 118 (1), 317–330.

Lubar, J.F., Swartwood, M.O., Swartwood, J.N., O'Donnell, P.H., 1995. Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in TOVA scores, behavioral ratings, and WISC-R performance. Biofeedback Self. Regul. 20 (1), 83–99.

Luck, S.J., 2014. An Introduction to the Event-Related Potential Technique. MIT press.

Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG-and MEG-data. J. Neurosci. Methods 164 (1), 177–190.

McSayers, B., Beagley, H.A., 1974. Objective evaluation of auditory evoked EEG responses. Nature 251, 608–609.

Mihara, M., Hattori, N., Hatakenaka, M., Yagura, H., Kawano, T., Hino, T., Miyai, I., 2013. Near-infrared spectroscopy–mediated neurofeedback enhances efficacy of motor imagery–based training in poststroke victims: a pilot study. Stroke 44 (4), 1091–1098.

Monastra, V.J., Monastra, D.M., George, S., 2002. The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl. Psychophysiol. Biofeedback 27 (4), 231–249.

Moriyama, T.S., Polanczyk, G., Caye, A., Banaschewski, T., Brandeis, D., Rohde, L.A., 2012. Evidence-based information on the clinical use of neurofeedback for ADHD. Neurotherapeutics 9 (3), 588–598.

Nunn, C.M.H., Osselton, J.W., 1974. The influence of the EEG alpha rhythm on the perception of visual stimuli. Psychophysiology 11 (3), 294–303.

Peng, W., Babiloni, C., Mao, Y., Hu, Y., 2015. Subjective pain perception mediated by alpha rhythms. Biol. Psychol. 109, 141–150.

Ridding, M.C., Uy, J., 2003. Changes in motor cortical excitability induced by paired associative stimulation. Clin. Neurophysiol. 114 (8), 1437–1444.

Rosenfeld, J.P., Cha, G., Blau, T., Gotlib, I.H., 1995. Operant (biofeedback) control of left-right frontal alpha power differences: potential neurotherapy for affective disorders. Biofeedback Self-Regul. 20, 241–258.

Rosin, B., Slovik, M., Mitelman, R., Rivlin-Etzion, M., Haber, S.N., Israel, Z., Vaadia, E., Bergman, H., 2011. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron 72 (2), 370–384.

Stefan, K., Kunesch, E., Cohen, L.G., Benecke, R., Classen, J., 2000. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123 (3), 572–584.

Tan, G., Thornby, J., Hammond, D.C., Strehl, U., Canady, B., Arnemann, K., Kaiser, D.A., 2009. Meta-analysis of EEG biofeedback in treating epilepsy. Clin. EEG Neurosci. 40 (3), 173–179.

Trimble, J.L., Potts, A.M., 1975. Ongoing occipital rhythms and the VER. I. Stimulation at peaks of the alpha-rhythm. Invest. Ophthalmol. Vis. Sci. 14 (7), 537–546.

Tu, Y., Zhang, Z., Tan, A., Peng, W., Hung, Y.S., Moayedi, M., Iannetti, G.D., Hu, L., 2016. Alpha and gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli. Hum. Brain Mapp. 37 (2), 501–514.

Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., Gruzelier, J., 2003. The effect of training distinct neurofeedback protocols on aspects of cognitive performance. Int. J. Psychophysiol. 47 (1), 75–85.

Vijayan, A.E., Sen, D., Sudheer, A.P., 2015. EEG-based emotion recognition using statistical measures and auto-regressive modeling. Int IEEE CICT Conf 587–591.

Vossen, A., Gross, J., Thut, G., 2015. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. Brain stimulation 8 (3), 499–508.

Yamashita, A., Hayasaka, S., Kawato, M., Imamizu, H., 2017. Connectivity neurofeedback training can differentially change functional connectivity and cognitive performance. Cerebr. Cortex 27 (10), 4960–4970.