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BIDIRECTIONAL NEUROFEEDBACK: A CONTROL CONDITION COMPLEMENTARY TO SHAM?

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ABSTRACT: Neurofeedback (NF) is increasingly used for experimental and therapeutic purposes. However, the lack of proper control about the specificity of NF effects is criticized and hinders the development of reliable and efficient NF procedures. Bidirectional NF is based on the self-regulation of the targeted brain activity in opposite directions and might be better suited than other typical control conditions (e.g., sham) for assessing the link between modulations of brain activity and behavior. The present study aimed to determine if bidirectional regulation of a specific pattern of brain activity, namely motor beta power, can be achieved within a single session. Thirty participants performed several NF trials aiming to either down- or up-regulate their motor beta power. Results showed that participants significantly modulated their motor beta power in opposite directions with bidirectional NF. This modulation was constrained in space (central electrodes) and frequency (alpha/beta band). Overall, bidirectional NF appears as a valid method to probe brain-behavior relationships within a single session.

INTRODUCTION

Neurofeedback (NF) consists of a brain-computer interface in which brain activity is measured and presented online to the participant through a sensory stimulus, for the purpose of enabling self-regulation of specific patterns of brain activity [1]. NF can be used as an experimental tool for studying brain-behavior relationships and as a potential therapeutic strategy for a variety of neurological diseases [2]. Yet, the lack of appropriate control condition in NF studies has been criticized and precludes its implementation as a valid experimental and clinical procedure [2–4]. One of the most commonly employed control condition in NF studies is a sham NF, which consists of presenting a NF whose features are independent from the participant's targeted brain activity (e.g., replay of prerecordings). Sham NF is well suited for assessing the specificity of NF on the effects found on the targeted brain activity and behavior because participants are supposedly not aware of this sham condition, so that they should apply similar mental strategies when presented with the sham NF as with the real NF. However, using sham NF is not adequate for determining whether the changes in brain activity induced by NF are causally involved in the reported behavioral effects. Indeed, sham NF can lead to modulations of the targeted brain activity that do not differ significantly from the ones observed with real NF (e.g., [5]). Establishing the causality of brain-behavior relationships requires at least two NF conditions inducing significantly different changes in the targeted brain activity, such that it can be used as an independent variable. This can be achieved using bidirectional NF, that is implementing two NF conditions aiming to train participants to regulate the targeted brain activity in opposite directions (i.e., down- and up-regulate the targeted brain activity). Thus, opposite patterns of behavioral effects are expected in the two NF conditions. An additional sham-passive condition can be implemented to determine if each active NF condition led to significant change in brain activity in comparison to a "baseline" level without real NF nor mental strategy applied. Assessing whether behavioral effects remain significant when comparing active NF conditions to the sham-passive condition can then allow us to determine whether NF led to significant behavioral change compared to a "baseline" condition, without active modulation of brain activity. Overall, bidirectional NF comprehensively addresses numerous confounding factors associated with NF paradigms, including the ones that are purposely controlled with a sham NF such as placebo effects and global, spatially non-specific effects [6], while avoiding the ethical and time issues associated with sham NF. Indeed, a sham NF condition requires either a fairly high number of participants to ensure sufficient statistical power in the analyses when using a between-group experimental design (i.e., two separate groups of participants, real vs sham NF, that are compared to each other), or a long-lasting experiment if one chooses a within-group experimental design, because each participant will have to perform several sessions of each condition (real and sham NF). In each case, the ex-

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perimental protocol will most likely be time-consuming. In addition to this, the use of a sham NF can bring some ethical issues in studies conducted on patients (e.g., only the group receiving the real NF will see their symptoms improving). Yet, there remains some gray areas regarding the feasibility of bidirectional NF, especially about the required time for learning to modulate a specific pattern of brain activity in opposite directions. Indeed, alternating up- and down-regulation can induce carry-over effects that might impair learning [7].

The present study aimed to determine whether efficient bidirectional regulation of a specific pattern of brain activity, namely the power of brain oscillations in the beta-band (β; 13-30 Hz) over the motor cortex, can be achieved within a single experimental session using NF. Motor cortical β power was chosen as the target for the bidirectional NF protocol in the present study because it has been associated with changes in movement initiation and execution speed in non-invasive neurostimulation studies [8], as well as in a recent NF study using a sham control [5]. Motor cortical β power has also been widely used as a neural marker for decoding movement intention in the field of brain-computer interfaces. Therefore, the present study could provide replication of the results from the studies cited above, while assessing the feasibility of bidirectional NF within a single session. The frequential (frequency band) and spatial (electrodes) specificity of the effects on brain activity induced by the NF were also assessed.

MATERIALS AND METHODS

Participants: Thirty participants (15 females, 15 males; age (mean $\pm$ standard deviation (SD)): 22 $\pm$ 3 years old) were recruited for the experiment. All participants were right-handed (mean Edimburgh score (mean $\pm$ SD): 94 $\pm$ 5%), had normal or corrected-to-normal vision and were free of any known neurological or psychiatric condition. All subjects gave their written informed consent before participation in the study, which had been approved by the French committee for the protection of individuals (CPP) number 18-INSB-01. This study conformed to the standards set by the latest version of the Declaration of Helsinki. One participant was removed from the analyses because of excessive noise in the EEG data.

Experimental design: The experiment consisted of a bidirectional NF training coupled with a force task. Each participant performed a total of 125 trials, including 5 familiarization trials that were not considered in the analyses. Each trial started with the appearance of a fixation cross on a screen for 3 s. The cross was then replaced by a gauge, representing the NF based on the recorded online changes in motor β activity (see NF section below) for 2 to 10 s. This NF phase was followed by a hand grip task, subjective effort rating on an analog scale and written feedback about the performance at the hand grip task (Fig. 1C). Force data from the hand grip task and effort ratings from the analog scale were not analyzed in the present article, as it focuses on modulations of β activity across NF conditions.

Data acquisition and calibration: At the beginning of the experiment, participants were comfortably seated in front of a screen (60 x 34 cm) with their right hand holding a dynamometer (K-Force Grip, Kinvent). They were asked to not exert any pressure on the dynamometer with their hand unless receiving an explicit instruction to do so. A 32-channel EEG cap (EEGo sports, ANTneuro) was placed on the participants' head and the EEG signal was recorded continuously for the duration of the experiment with a 500 Hz acquisition rate. Stimuli presented on the screen were synchronized with EEG and force recordings through an open-source software toolkit (lab streaming layer; LSL). The ground and reference electrodes were AFz and CPz respectively. The first EEG recording of the experiment was performed in a resting state to calibrate NF parameters in an individualized fashion. A white fixation cross was presented at the center of the screen and participants were asked to maintain their gaze on the cross and remain still as long as the cross was on. The cross was displayed for 1 min but only the last 30 s were recorded to ensure that participants were already in a resting state when starting EEG recordings. The distribution of beta power values during those recordings was used to set individualized NF thresholds (see NF section). The participants' maximal force for hand grip was also determined individually at the beginning and the middle of the experiment.

NF: The NF was implemented using OpenViBE (3.3) and Unity C# (2020.3.17f1). It was represented on the screen as a gauge (vertical rectangle cut by a horizontal midline) whose level varied as a function of motor β power. More precisely, the level of the gauge was refreshed every 250 ms based on the mean β power (squared amplitude of the EEG signal between 15 and 25 Hz, computed using a 4th order Butterworth filter) recorded at C3 electrode during the last 500 ms (i.e., sliding window of 500 ms per 250 ms step). This averaging procedure has been used by previous studies to avoid difficulties in reading the gauge because of excessive flickering. Spatial noise was attenuated using a Laplacian filter including 6 neighboring electrodes of C3 (FC5, FC1, F3, CP5, CP1, P3). Participants were trained to downregulate and upregulate their motor β power in two separate experimental conditions: β-down and β-up respectively. Participants were encouraged to fill up the gauge in both conditions. In β-down, the lower the recorded β power, the higher the level of the gauge, whereas in β-up, the higher the recorded β power, the higher the level of the gauge. The gauge was calibrated according to β power detected at C3 electrode per 250 ms windows of the 30 s preliminary resting-state recording (120 values in total). The inferior boundary of the gauge corresponded to the median of resting-state β power in the two conditions. The gauge started to fill up if the recorded β power was below that median in β-down and above that

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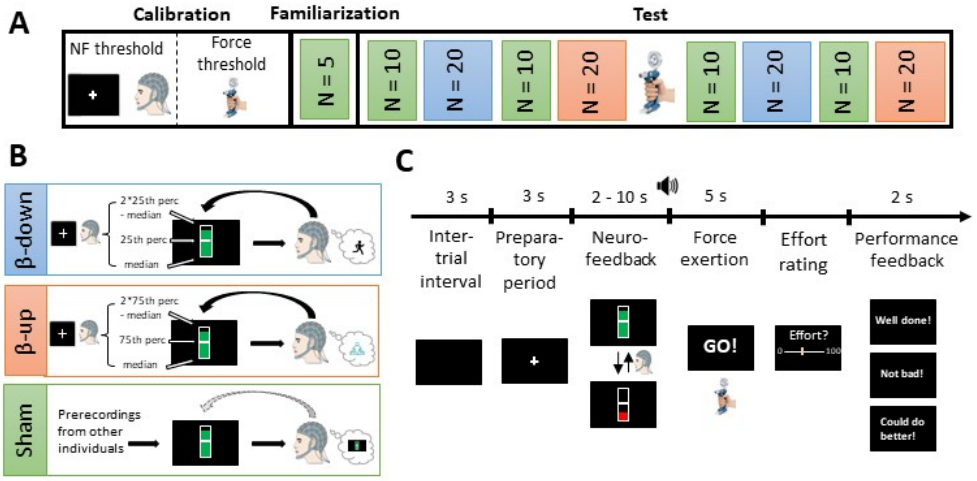

Figure 1: Methods. A. Overview of the experimental design. Blue, orange and green boxes indicate β-down, β-up, and sham-passive blocks respectively. N refers to the number of trials included in each block. The dynamometer's picture indicates the moments when the maximal force was (re)calculated. B. Neurofeedback conditions. The individualized values that were used for calibrating the level of the gauge are indicated on the left of the gauge. The images inside of the thought bubbles illustrate mental strategies that participants were advised to use in each condition. C. Trial timeline. Depiction of the name, duration and visual stimuli associated with each phase of a trial, in a chronological order.

median in β-up. As explained in Fig. 1, the gauge was half-filled/completely filled when β power reached the 25^{th} percentile/2*25^{th} percentile-median of the resting-state distribution in β-down, or the 75^{th} percentile/2*75^{th} percentile-median in β-up. The filling color of the gauge was red if its level was below midline and turned green if its level reached above midline. If the gauge remained green for 2 consecutive seconds (i.e., β power was inferior to the 25^{th} percentile in β-down/superior to the 75^{th} percentile in β-up for 2 s), the NF stopped and the gauge was replaced by a go cue. In cases where this criterion was not met, the NF was automatically replaced by a go cue after 10 s.

To improve self-regulation of motor β power, participants were given mental strategies before starting the trials. In β-down, participants were advised to perform motor imagery, that is mentally representing themselves performing movements without executing actual movements. Indeed, motor imagery has been shown to reduce β power to an extent that can equal or even exceed the β event-related desynchronization observed for actual movements when combined with NF [9]. Conversely, relaxation strategies (e.g., relaxing body parts, conscious breathing, task-unrelated thinking) have been shown to increase β power [10], and were thus suggested to the participants in β-up. Those mental strategies were not mandatory, participants were told that they were free to use any mental strategy they found efficient for filling up the gauge. A reminder of the recommended mental strategy (motor imagery or relaxation) was presented on the screen for 5 s before the beginning of each block.

A sham passive condition was also implemented as a control condition with similar sensory inputs as in β-down and β-up (i.e., gauge) but without any mental strategy nor congruent NF. In this condition, participants were asked to keep their gaze on the gauge but not to try controlling it. The level of the gauge varied according to fluctuations in β power in prerecordings from other subjects, such that the gauge was not informative of the actual online changes in β power of the tested participants. Blocks of 10 sham passive trials were interspersed with blocks of 20 β-down or β-up trials (Fig. 1A). The presentation order of β-down and β-up blocks was counterbalanced across participants.

Data processing: Data processing was conducted on Matlab (R2018B, MathWorks). β power values computed in OpenViBE (squared amplitude of EEG signal comprised between 15 and 25 Hz at C3 electrode after applying a Laplacian filter, see NF section above for details) for updating the NF were averaged during the last 2 s of the NF phase for the analyses. Resting-state median β power was subtracted from average β power at the end of the NF phase individually to account for interindividual variability in baseline β power. Outliers were calculated separately for each participant and condition and were defined as values inferior to median-3*absolute deviations around the median (MADs; [11]) or superior to median+3*MADs, and were removed from the analyses.

Statistical analyses: A within-subject experimental design was conducted. A repeated-measures ANOVA was computed for comparing β power (value used for the NF in OpenViBE) across NF conditions (3 levels: β-down, β-up and sham-passive). An additional ANOVA including NF conditions and block number (2 levels: 1, 2) was performed to test if the effects differed across blocks. Greenhouse-Geisser's correction was applied to p-values when sphericity assumption was violated (Mauchly's test p-value < 0.05). Pairwise comparisons were conducted with paired Student's t-tests when observations were normally distributed (p-value from Shapiro-

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Wilk test ≥ 0.05), and Wilcoxon's rank tests when normality assumption was violated (p-value from Shapiro-Wilk test < 0.05). Bonferroni's correction was applied on p-values for multiple comparisons. Effect sizes were reported as partial eta squared for ANOVAs (eta_p^2), Cohen's d (d) for Student's t-tests and rank biserial correlation (r) for Wilcoxon's rank tests. Cluster-based permutation tests were performed using Fieldtrip to identify cluster of electrodes that were behaving differently between β-down and β-up [12]. Clusters were defined as adjacent electrode/time pairs whose test statistic exceeded the threshold for statistical significance (alpha = 0.05, two-tailed paired t-tests). In the present analysis, a cluster was composed of at least two electrodes showing statistically significant t values within a radius of 4 cm. These tests were conducted from -2 to 0 s before the presentation of the go cue, in the theta (4-7 Hz), alpha (8-12 Hz), beta (15-25 Hz), and low-gamma (30-49 Hz) frequency bands separately.

RESULTS

β power during NF was significantly decreased as compared to resting-state β power in β-down (W(28) = 82, p = 0.003, r = -0.62, mean difference = -19.5%). Conversely, a trend toward an increase in β power during NF in comparison to resting-state β power was observed in β-up (W(28) = 301, p = 0.072, r = 0.38, mean difference = +9.3%). β power in the sham passive NF condition was not significantly different from resting-state β power (W(28) = 156, p = 0.190, r = -0.28, mean difference = -3.5%). Direct comparison of average β power across NF conditions showed a significant difference (F(1.4, 39.5) = 16.2, p = 10^{-4}, $\eta_p^2 = 0.37$). Post-hoc analysis revealed that β power was significantly decreased in β-down in comparison to β-up (W(28) = 33, p = 10^{-5}, r = -0.85) and sham-passive (W(28) = 51, p = 10^{-4}, r = -0.77), whereas it was significantly increased in β-up as compared to sham-passive (W(28) = 372, p = 0.001, r = 0.71; Fig. 2, top left panel). Single-subject analysis showed that 79% (23/29) of participants significantly decreased their β power in β-down as compared to β-up, 14% (4/29) did not significantly modulate their β power and 7% (2/29) inversely modulated their β power (i.e., increased their β power in β-down in comparison to β-up). When comparing β-down to sham-passive, results showed that 72% (21/29) of participants significantly decreased their β power in β-down as compared to sham-passive, 14% (4/29) did not significantly modulate their β power and 14% (4/29) inversely modulated their β power (i.e., increased their β power in β-down in comparison to sham-passive). Finally, 69% (20/29) of participants significantly increased their β power in β-up as compared to sham-passive, 14% (4/29) did not significantly modulate their β power and 17% (5/29) inversely modulated their β power (i.e., decreased their β power in β-up in comparison to sham-passive).

A two-way ANOVA for repeated measures showed a significant effect of NF condition (β-down, β-up and sham-passive; F(1.4,39.7) = 16.0, p < 0.001p = 10^{-4}, $\eta_p^2 = 0.36$) but no significant effect of block (1 and 2; F(1,28) = 0.49, p = 0.489, $\eta_p^2 = 0.02$) nor interaction between NF condition and block (F(1.5,43.3) = 0.15, p = 0.804, $\eta_p^2 = 0.01$) on β power. This suggests that NF performance did not improve throughout the experiment as β power did not significantly change with time across NF conditions (Fig. 2, top right panel). NF performance was also measured by the percentage of time spent within criterion (i.e., $< 25^{th}$ percentile of resting-state β power for β-down and $> 75^{th}$ percentile of resting-state β power for β-up) during the NF phase, and the duration of the NF phase. There was a trend toward longer time spent within criterion in β-down as compared to β-up (t(28) = 1.83, p = 0.078, d = 0.34; Fig. 2, bottom right panel). Additionally, the duration of the NF phase was significantly shorter in β-down than β-up (t(28) = -2.79, p = 0.009, d = -0.52; Fig. 2, bottom left panel). This suggests that NF performance was significantly better in β-down than β-up as participants reached the criterion for 2 s more often, leading to shorter trials.

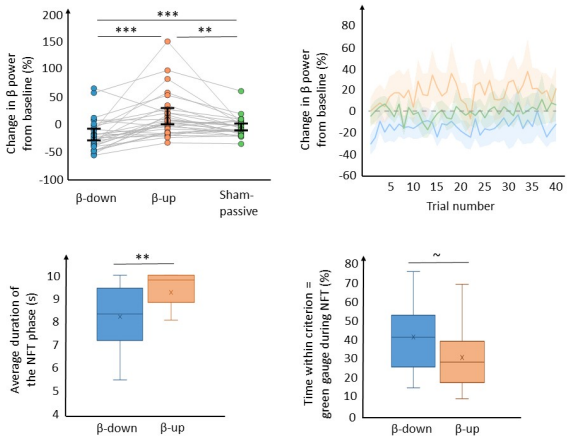

Figure 2: Effects of bidirectional NF on motor cortical β power. Top, left: β power change from baseline according to NF condition. Colored dots indicate individual data. Light gray lines connect dots pertaining to the same participant. Black error bars illustrate 95% confidence intervals around the mean. Top, right: β power change from baseline according to NF condition. Data is averaged across participants. Trials are represented in their chronological order of presentation during the experiment. Blue, orange, and green lines illustrate the β-down, β-up and sham-passive conditions. Shaded areas represent 95% confidence intervals around the mean. The zero-line (indicating no change from baseline β power) is highlighted with a dotted gray line. Bottom, left to right: average duration of the NF phase and time within criterion (i.e., when NF threshold is reached/the gauge is green) in β-down (blue) and β-up (orange). Median and mean are represented as horizontal line and cross respectively. *** p < 0.001, ** p < 0.01, * p < 0.05, $\sim$ p = 0.05-0.1

The last step of the analysis consisted of assessing the spatial and frequential specificity of the changes in brain activity induced by NF. To do so, the power of the EEG signal was computed in different frequency bands and across all electrodes by means of time-frequency anal-

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ysis (see Methods for details). Signal power was first averaged in different frequency bands at C3 electrode to determine the frequential specificity of NF. Theta (4-7 Hz; $F(2,54) = 1.21$, $p = 0.306$, $eta_p^2 = 0.04$), alpha (8-12 Hz; $F(1.57,42.34) = 2.32$, $p = 0.122$, $eta_p^2 = 0.08$), and low-gamma (31-49 Hz; $F(1.08, 29.11) = 1.05$, $p = 0.319$, $eta_p^2 = 0.04$) power did not appear significantly affected by NF, suggesting that, over the contralateral motor cortex, β power was the only frequency band that was significantly modulated by NF. Spatial specificity was then quantified using cluster-based permutation tests. These tests highlighted a significant cluster of contralateral and midline fronto-central electrodes when comparing β power in β-down and β-up (Fig. 3, top panel). This cluster was centered on C3 and showed significant reduction of β power in β-down as compared to β-up. A significant negative cluster was also found when comparing alpha power in β-down and β-up, though in contrast with β power, alpha power appeared mostly attenuated over ipsilateral fronto-central electrodes (Fig. 3, top panel). No significant cluster was detected when comparing theta nor gamma power in β-down and β-up. Time-frequency maps of the activity recorded at C3 showed that baseline-corrected β power appears decreased in β-down and β-up, but the magnitude of this decrease appeared greater in β-down than in β-up.

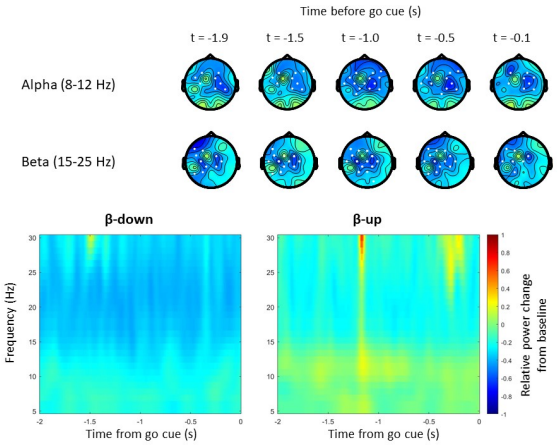

Figure 3: Spatial and frequential specificity of NF. Top: topographical maps representing changes in alpha (top) and beta (bottom) power between β-down and β-up, at different times before go cue onset (t). White dots highlight significant negative cluster of electrodes. Bottom: time-frequency maps of the signal recorded at C3 in β-down (left) and β-up (right).

DISCUSSION

Results show that the bidirectional NF paradigm used in the present single-session experimental design effectively led to opposite modulations of motor cortical β power. Most participants (79%) significantly decreased their β power in β-down as compared to β-up. Additionally, participants significantly decreased and increased their β power in β-down and β-up respectively, as compared to in sham-passive. The changes in brain oscillations induced by NF were not specific to the β frequency as a significant decrease in alpha power was also observed in β-down in comparison to β-up. However, this modulation of alpha power was mostly localized over the ipsilateral motor cortex, whereas changes in β power were more on the contralateral side. Taken as a whole, these results suggest that single-session bidirectional NF, including blocks belonging to each direction of regulation presented in an alternated order, constitutes an appropriate method to probe the nature of the relationship between motor cortical β power and behavior.

To our knowledge, the present results represent the first evidence of the possibility to use bidirectional NF for volitionally modulating motor cortical β power within a single session, and studying its effects on motor behavior over several trials using a within-subject experimental design. Two studies [13, 14] already demonstrated that bidirectional NF based on individualized task-specific features of sensorimotor rhythms can significantly affect motor performance. However, targeted features for NF varied across participants (e.g., an alpha and a β power components were included in 4 out of 8 participants, whereas only a β power component was included in the rest of the participants), thereby complicating the identification of the specific EEG patterns that were responsible for the behavioral changes observed. The experimental design presented herein allows the assessment of the specific influence of self-regulating motor cortical β power on motor behavior, and takes into account inter-individual variability in baseline EEG activity by calibrating β power values used for the NF individually. Yet, these β power values are calculated identically for all participants (median, 25^{th} and 75^{th} percentiles of the distribution of resting-state β power). This standardized procedure supposedly enables reliable conclusions about the relationship between a specific EEG pattern and behavior, though it may be inadequate for some participants (e.g., highly variable baseline activity, weak amplitude of movement-related β power changes). This does not appear to be the case in the present experiment as 79% of participants successfully decreased their motor cortical β power in β-down in comparison to β-up. The proportion of non-responders (21%) is in accordance with the numbers reported by previous studies (15 to 30%; [15]).

In addition to successful opposite regulation of motor cortical β power within a single session, the present results also showed that participants significantly decreased and increased their β power as compared to sham-passive in β-down and in β-up respectively. This demonstrates that the present experimental design is particularly well suited to assess brain-behavior relationships, considering that the influence of modulating motor cortical β power on motor behavior can be determined in each direction of regulation (down and up) and compared to a "baseline" level of β power and behavior. This design would enable to extend the results from previous studies that have shown significant effect of regulation of β power with NF

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on motor behavior without control comparison or compared to a sham-passive NF only ([5, 16, 17]).
Some limitations associated with the proposed experimental design should be underlined. First, self-regulation of β power with NF did not significantly improve across trials, suggesting that the single-session design, consisting of blocks of β-down and β-up trials presented in an alternated order, might have interfered with the learning process of self-regulation. An alternative option could be to perform each NF condition (i.e., β-down and β-up) in separate sessions. However, in addition to significantly increase the duration of the experiment, splitting the experiment into distinct sessions brings other issues, such as potential differences in the positioning of the EEG cap, as well as differences in baseline β power values used for setting the NF threshold. Second, NF performance appeared slightly better in β-down than β-up, which could influence the following motor performance (i.e., filling up the gauge faster and more easily could boost motivation and thus lead to better motor performance). Possibilities for remediating to such an effect include modifying mental strategies for increasing β power in β-up, considering that the one used in the present experiment was fairly close to participants' resting state (i.e., relaxation strategy), or setting NF thresholds based on pre-movement β power instead of resting-state, as it should be closer to the baseline activity observed during the NF phase before the motor task.

CONCLUSION

The present study provides evidence that bidirectional NF can be used to determine the effects of modulating brain oscillatory activity with NF, such as up- and down-regulation of motor β power, on behavior. Opposite modulations of brain oscillatory activity was achieved within a single session for most individuals. Therefore, bidirectional NF represents a relevant method for controlled, simple and rapid experimental designs aiming to study the association between a specific pattern of brain activity and behavior.

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