Selective neuromodulation induced by alpha-based neurofeedback learning: A double-blind randomized study

Fanny Grosselin[a,b,c,*], Audrey Breton[b], Lydia Yahia-Cherif[e,f,g,h], Xi Wang[b,1], Giuseppe Spinelli[b], Laurent Hugueville[e,f,g,h], Philippe Fossati[i,f,g,h,j], Yohan Attal[b], Xavier Navarro-Sune[b], Mario Chavez[f], Nathalie George[e,f,g,h,k]

Affiliations

[a] Sorbonne Université, Institut du Cerveau - Paris Brain Institute (ICM), INSERM U 1127, CNRS UMR 7225, Equipe Aramis, 75013, Paris, France

[b] myBrain Technologies, 75010, Paris, France

[c] INRIA, Aramis project-team, 75013, Paris, France

[e] Institut du Cerveau - Paris Brain Institute - ICM, Centre MEG-EEG, Paris, France

[f] CNRS, UMR 7225, F-75013, Paris, France

[g] Inserm, U 1127, Paris, France

[h] Sorbonne Université, Paris, France

[i] Institut du Cerveau - Paris Brain Institute - ICM, Equipe CIA - Cognitive Control, Interoception, Attention, 75013, Paris, France

[j] AP-HP, Hôpital Pitié-Salpêtrière, Service de Psychiatrie Adulte, 75013, Paris, France

[k] Institut du Cerveau - Paris Brain Institute - ICM, Equipe Experimental Neurosurgery, 75013, Paris, France

* Corresponding author: fanny.grosselin@mybraintech.com

---

[1] Xi Wang is currently a PhD student at Lyon Neuroscience Research Center (CRNL), Neurocampus, 69500, Bron, France

Highlights

- Randomized double-blind study of neuromodulation induced by EEG-neurofeedback (NF)

- Sham feedback (FB) was used for the control group

- Targeted alpha activity increased selectively over the 12 NF training sessions

- This neuromodulation was observed only in the real NF training group

- The feeling of control across sessions increased more for real than sham FB group

Abstract

Background:

The neuromodulation induced by neurofeedback training (NFT) remains a matter of debate. Investigating the modulation of brain activity specifically associated with NF requires controlling for multiple factors, such as reward, performance, congruency between task and targeted brain activity. This can be achieved using sham feedback (FB) control condition, equating all aspects of the experiment but the closed-loop between brain activity and FB.

Objective:

We aimed at investigating the modulation of individual alpha EEG activity induced by NFT in a double-blind, randomized, sham-controlled study.

Methods:

Forty-eight healthy participants were assigned to either NF (n=25) or control (n=23) group and performed 12 NFT sessions of alpha upregulation with a wearable EEG device. Participants of the NF group received FB based on their individual alpha activity. The control group received the auditory FB of participants of the NF group.

Results:

An increase of alpha activity across training sessions was observed in the NF group only ($p<0.001$). This neuromodulation was selective in that it was not observed for theta (4-8Hz) and low beta (13-18Hz) activities. It was associated with an increased feeling of control ($p<0.001$), more marked for NF than control group. Anxiety level decreased and relaxation feeling increased with training in both groups.

Conclusions:

NFT across multiple sessions can induce specific brain modulation, suggesting a neuroplasticity

selective of the targeted brain activity. Our results pave the way to self-learnt, NF-based

neuromodulation with light-weighted, wearable EEG systems for various applications (e.g. epilepsy,

sleep, attention).

Keywords

Neurofeedback; controlled sham condition; alpha oscillations; relaxation; neuromodulation;

wearable EEG

Introduction

Neurofeedback (NF) is a cognitive training that exploits the causal relationship between brain activity and cognitivo-motor abilities. It consists in providing real-time, closed-loop— auditory, visual, or tactile—feedback of a subject's brain activity to train self-regulation of specific brain patterns related to a targeted ability. NF applications have been developed since the 70's in non-clinical [1], [2] and clinical settings, such as epilepsy [3], attention-deficit hyperactivity disorder [4]–[8], autism [9], depression [10], [11], psychopathy [12], [13], and anxiety [10], [14]–[16]. However, the understanding of the neurocognitive mechanisms and effects of NF training (NFT) remains elusive [17].

NF can be considered as a particular case of reinforcement learning, by which the subject is rewarded through the feedback for modulating the targeted brain activity. This modulation is usually learnt through a cognitive strategy enforced by task instruction and related to the cognitivo-motor ability to be improved or restored. The ensuing cognitive or motor improvements are typically used as the primary outcome measures to assess NFT efficiency, in particular in clinical applications [14], [18], [19]. Control conditions are quite variable, not only aiming at the closed loop between brain activity and feedback but also varying the task or the procedure [20]. For example, in clinical NF application studies, where NFT aimed at reducing behavioral symptoms associated with various disorders (anxiety [14]–[16], depression [10], [11], [21], addiction [22]–[25], attention deficit [4]–[8], [26]), NF performance was typically compared with other procedures, such as cognitive therapy, mental exercise, and treatment-as-usual [20]. Thus, the behavioral or clinical benefits of NFT may be related to an ensemble of specific and non-specific mechanisms, including psychosocial influences [27], cognitive and attentional/motivational factors [28], test-retest improvement, as well as spontaneous clinical improvement or cognitive development [17], contributing to the ongoing debate about NF efficiency [15], [19].

A key question concerns the neuromodulation associated with NFT, that is, induced by the closed loop between the subject's brain activity and feedback. Addressing this question requires a control condition equating every other aspect of the NF protocol—such as instruction, task, reward. In some NF studies, the control condition was based on linking the feedback to another brain activity than the targeted one [20]. Such control condition may pinpoint the cognitivo-motor changes specifically associated with the targeted brain activity [20]. However, it entails an incongruity between the activity driving the feedback and the task—hence the cognitive efforts—of the subject, with potential, confounding impacts not only on performance, but also on reward and motivation. A sham feedback (sham-FB) condition—where the feedback in the control group is matched on the experimental group feedback— is necessary to allow investigation of the neuromodulation specifically associated with NF. To date, few studies have used such control condition, with mixed results. For instance, Witte et al. did not find evidence for neuromodulation of the sensorimotor rhythm over multiple NFT sessions [29]. Naas et al. [30] used a daily NF protocol targeting upper alpha band over four days and did not reveal any significantly different modulation of the targeted activity between groups over time. In contrast, Beatty [31] showed an increase of the trained alpha activity in the NF group but not in the sham-FB condition during a unique NF session.

Here, we aimed at studying the neuromodulation specifically induced by alpha-based NFT over multiple sessions throughout 12 weeks, by contrasting it to a carefully controlled sham-FB condition in a randomized double-blind study within general population. We used a new compact and wearable EEG-based NF device (Melomind™, myBrain Technologies, Paris, France) [32]. Participants, immersed in a relaxing soundscape delivered by headphones, were engaged in learning to decrease the volume of a sound indicator based on the individual alpha-band EEG activity recorded by two parietal dry electrodes. Alpha-band activity is used in most NF protocols aiming at anxiety reduction, stress-management or well-being [14], [15], [33], [34]. The participants in the sham-FB group received 'yoked' feedback, corresponding to the feedback of randomly-chosen subjects from the NF group at the same stage of learning. Hence, this feedback was similar in every aspect to the one in

the NF group, except that it was not the result of an established closed loop between the subject's alpha-band activity and the auditory stream. In particular, it controlled for reward and performance across both groups [20]. We expected a selective increase of the targeted neural activity across the program only for the NF group. We also examined behavioral outcomes in terms of anxiety level, relaxation, and feeling of control.

Materials and Methods

Participants

Forty-eight healthy volunteers participated in this study (mean age: 33.3 years; age range: 18-60; see Supplementary Table S1 for more details). All declared having normal or corrected-to-normal vision, no hearing problem, no history of neurological or psychiatric disorders, no ongoing psychotropic drug treatment. Participants were randomly and blindly assigned either to the *NF group*—who received real NF—or to the *control group*—who received sham-FB, except for the first few participants who—for the purpose of the sham-FB—were assigned to the *NF group.* The experimenters were also blind to the assignment.

All participants gave written informed consent to participate in the study. All procedures were carried out in accordance with the Declaration of Helsinki. The experimental protocol was identical to the experimental protocol of the clinical study approved by French ethical committee (CPP SUD-OUEST OUTRE-MER I, study nb. 2017-A02786-47), registered on ClinicalTrials.gov (ref. NCT04545359).

EEG recording and preprocessing

Brain activity was recorded by two gold-coated dry electrodes placed on parietal regions (P3 and P4) with the CE marked Melomind™ device (myBrain Technologies, Paris, France; https://www.melomind.com/; Fig. 1). Ground and reference were silver fabric electrodes, placed on the left and right headphones respectively, in mastoid regions.

Fig. 1 **Melomind™ device.** *Left*: The device comprises an audio headset and two posterior branches at the end of which two gold-coated dry electrodes are inserted. *Right*: These electrodes are positioned at P3 and P4 locations (indicated in black) according to the extended 10-20 International System.

EEG signals were amplified and digitized at a sampling rate of 250 Hz, band-pass filtered from 2 Hz to 30 Hz in real-time and sent to the mobile device by embedded electronics in the headset. The headset communicated via Bluetooth with a mobile NF application, which processed EEG data every second to give the user auditory feedback about his/her alpha-band activity (see below). Real-time estimation of signal quality was performed by a dedicated machine learning algorithm [35] to detect noisy segments before computing the feedback.

Experimental protocol

The protocol consisted of 12 NFT sessions, with one session per week (Fig. 2). Each session was composed of 7 exercises of 3 minutes (total: 21 minutes). At the beginning and end of each session, two-minute resting state recording was performed and the participant completed the Spielberger State-Trait Anxiety Inventory (*STAI*, *Y-A* form, in French, [36])—to assess his/her anxiety state level—and a 10-cm visual analog scale (VAS) indicating his/her subjective relaxation level (r*elax-VAS*). Moreover, at the end of each exercise, the participant indicated his/her subjective level of feedback control on a 10-cm VAS (*control-VAS*). Participants completed the protocol in three different locations: at the Center for NeuroImaging Research (CENIR) of the Paris Brain Institute (ICM, Paris, France) (N=20 participants), at their workplace 14 (N=14), or at home (N=14).

Fig. 2 **Timeline of the experimental protocol.** Before and after the NFT program, the participants completed three psychometric trait questionnaires, to assess psychological stress (Perceived Stress Scale - PSS) [37], trait anxiety (*STAI-Y-B*) [36], and affectivity (Positive and Negative Affect Schedule - PANAS). NFT was performed over 12 weeks (W1, W2, … W12), with one training session per week (Session 1,… , Session 12). See main text for detailed description of the sessions.

Neurofeedback training procedure

The NF paradigm targeted alpha rhythm centered on the individual alpha frequency (IAF). Before each NFT session, a 30-second calibration phase allowed computing IAF using an optimized, robust estimator dedicated to real-time IAF estimation based on spectral correction and prior IAF estimations [38]. Participants were instructed to close their eyes, be relaxed and try to reduce the auditory feedback volume by their own strategies throughout the exercises (see Supplementary Material for the reported mental strategies). A relaxing landscape background (e.g. forest sounds) was played at a constant, comfortable volume during each exercise. The audio feedback was an electronic chord sound added to this background with a volume intensity derived from EEG signals. More precisely, the individual alpha amplitude was computed in consecutive 1-second epochs as the root mean square (RMS) of EEG activity filtered in IAF±1Hz band (*NF index*); it was normalized to the calibration baseline activity to obtain a 0-1 scale, which was used to modulate the intensity of the feedback sound in the NF group (0: silent feedback; 1: maximal volume). For the participants in the control group, the instruction was identical but they received sham-FB, which was the replayed feedback variations from randomly chosen subjects in the NF group at the same training level (i.e. session).

Data analysis

NF index and learning score

For each participant and each training session, we computed the average value of the NF index (before normalization) for every exercise. Moreover, we built an NF learning score ($\Delta D(t)$)—from the NF index variations across exercises and sessions [39]: we computed the median value (*med*) of the NF index across the 7 exercises of the first session; then, for each session t, we computed $D(t)$, the number of NF index values (1 by second) above or equal to *med*. This corresponded to a cumulated

duration. It was divided by the total duration of the training session (21 minutes) in order to express

D(t) by minute, and transformed into percent change relative to the first session, as follows (Eq. (1)):

$$\Delta D(t) \ = \ \left(\frac{D(t)}{D(t=1)} - 1\right) \times 100 \tag{1}$$

Theta and low beta activities

To study the selectivity of the neuromodulation to the targeted alpha activity, we analyzed the

between-session evolutions of theta (4-7Hz) and low beta (13-18Hz) activities. For each subject, on

each exercise and session, theta activity was computed every second as the RMS of EEG activity

filtered between 4 and 7Hz in 4-second sliding windows, on epochs with high or medium quality (see

[35] for details about signal quality computation). We then averaged these RMS values for each

session. Similar computation was performed between 13 and 18Hz for low beta activity.

Signal quality

As encouraged in [17], the quality of EEG signals was analyzed to test bad EEG data prevalence

between groups and across sessions. For each participant, session, and exercise, the quality of each

1-second EEG epoch on each electrode was determined by a classification-based approach according

to three labels: HIGHq, MEDq, and LOWq (see [35] for more details). A quality index *Q* was then

computed for each electrode, during each exercise, as in Eq. (2):

$$Q = \frac{\#HIGHq \ + \ 0.5 * \#MEDq}{N \ + \ \#LOWq} \tag{2}$$

with: #HIGHq, #MEDq, #LOWq indicating the number of high, median, low quality epochs and N, the

total number of quality labels during the session. Finally, the average value of *Q* was computed

across both electrodes for each exercise.

Behavioral outcomes

The raw scores of the *STAI-Y-A* (between 20 and 80) and *relax-VAS* (between 0 and 10) were computed pre- and post-session. The subjective level of feedback control was measured within- and between-session on the *control-VAS* (between 0 and 10).

Statistical analyses

All statistical analyses were performed using R (v.4.0.2; R Core Team, 2020) and *lme4* package [40]. We used Linear Mixed Models (LMMs) [41], [42], because LMMs allow handling missing data, variability in effect sizes across participants, and unbalanced designs [43]. Available data in this study are detailed in Supplementary Table S2.

For all LMM analyses, the NF group at the first session was set as the level of reference in order to specifically estimate the effects of NFT in this group. A random effect structure with random intercept by participant (subject_id) was fit.

Similarly to [44], we used fixed effects of session, exercise, group, and the 2-way interactions between session and group and between exercise and group to analyze the within- and between-session NFT effects on the NF index (Eq. (3) as coded in R):

Y ~ 1 + session + exercise + group + session:group + exercises:group + 1|subject_id   (3)

Preliminary analyses indicated that the effect of exercises followed a U-curve. Therefore, the exercises were coded as a quadratic term, that is, exercises 1 to 7 were coded as 9, 4, 1, 0, 1, 4, and 9. The sessions were coded as a numeric variable between 0 and 11. Eq. (3) was also used for the analysis of the *control-VAS* scores.

For the analysis of NF learning score, theta activity, low beta activity, and the signal quality index, we used the following LMM equation (Eq. (4)):

Y ~ 1 + session + group + session:group + 1|subject_id   (4)

For the behavioral outcomes (*relax-VAS* and *STAI-Y-A*), we used LMMs with session, phase (pre- or post-session), group, and the 2-way interactions between session and group and between phase and group as fixed effects (Eq. (5)):

Y ~ 1 + session + phase + group + session:group + phase:group + 1|subject_id   (5)

For each model, parameter estimates (β) for the effects of interest were obtained by fitting the models on the corresponding dependent variable, using the Restricted Maximum Likelihood (REML) approach. P-values were estimated via t-tests using the Satterthwaite approximation to degrees of freedom with *lmerTest* package [45]. We considered *p < 0.05* as statistically significant. As a complement, we computed analysis of variance (anova) on each LMM to check for main effects when no interaction was found; these are reported in supplementary material.

Results

Neuromodulation induced by NF

The analysis of the NF index showed a statistically significant effect of session. This reflected a significant linear increase of the NF index across sessions in the NF group (slope estimate (β) = 0.04, 95% Confidence Interval (CI) [0.03, 0.06], *p* < .001). We found a significant interaction between group and session (β = -0.08, CI [-0.10, -0.06], *p* < .001), which revealed that the increase of the NF index across sessions was specific to the NF group (Fig. 3a) (see Supplementary Table S3 for details).

The analysis of the NF learning score confirmed this specific NF-based neuromodulation. It showed a significant effect of session (β = 1.08, CI [0.17, 2.00], *p* < .05) and a significant interaction between session and group (β = -1.40, CI [-2.72, -0.09], *p* < .05) (see Supplementary Table S5), reflecting that the NF learning score increased across sessions in the NF group only (Fig. 3b). Additional individual

linear regressions of the NF learning score (see Supplementary Fig. S4 and S5) showed that 76%

(19/25) of the participants from the NF group had a positive regression slope across the 12 sessions,

while the slope was positive for 43.5% (10/23) of the participants from the control group.

In addition, there was a significant effect of exercise on the NF index, reflecting the quadratic

pattern of the NF index across exercises for the NF group (β = 0.03, CI [0.02, 0.05], p < .001). The

non-significant interaction between exercise and group indicated that this effect did not differ

between groups (β = 1.64e-03, CI [-0.02, 0.02], p = 0.88) (Fig. 4).

Fig. 3 **Neuromodulation induced by NFT. a) Evolution of the NF index across sessions, for the NF (in**

red) and the control (in blue) groups. Dotted lines and points represent the values of the NF index

along the 12 sessions, averaged across participants for each group; the shaded areas represent the

standard errors of the means. The solid lines represent the session effect estimated for each group

from the LMM. **b) Evolution of the NF learning score across sessions.** Same legend as in a).

Fig. 4 **Within-sessions modulation of NF index for the NF (in red) and the control (in blue) groups.**
The dotted lines and points represent the values of the NF index along the training exercises,
averaged across sessions and participants for each group. Training exercises are expressed in
minutes (each exercise lasted 3 minutes, with 7 exercises—21 minutes training—in each session).
Shaded areas represent the standard errors of the means. The solid lines represent the exercise
effect estimated for each group from the LMM.

Selectivity of the neuromodulation on alpha activity

To investigate the selectivity of the neuromodulation relative to the targeted alpha activity, we
analyzed EEG activity in two adjacent bands (theta and low beta). For theta activity, there was a
significant effect of session (β = 0.06, CI [0.02, 0.10], p < .01), without any interaction between
group and session (β = -0.04, CI [-0.10, 0.01], p = 0.15). This reflected an increase of theta activity,
which was not specific to the NF group. For low beta activity, no significant effect was observed (see
Supplementary Tables S7, S9 and Supplementary Fig. S6 for details).

Signal quality

The estimate of the slope of the quality index evolution across sessions was significantly negative (β = -2.04e-03, CI [-3.52e-03, -5.55e-04], p < .01), without any interaction between group and session (β = -1.01e-03, CI [-3.14e-03, 1.12e-03], p = 0.35) (see Supplementary Table S11). Thus, there was a slight decrease of signal quality across sessions and it did not differ between groups. See Supplementary Fig. S7.

Behavioral outcomes

Relaxation and anxiety levels

STAI-Y-A – The state anxiety level decreased significantly from pre- to post-session for the NF group (parameter estimate for phase: β = -2.46, CI [-3.45, -1.46], p < .001). This decrease was significantly greater for the control than the NF group as indicated by the interaction between phase and group (β = -2.13, CI [-3.55, -0.71], p < .01) (Fig. 5a). Moreover, there was a significant linear decrease of _STAI-Y-A_ scores across sessions (β = -0.20, CI [-0.34, -0.06], p < .01), which was not different between groups (β for the interaction between session and group = 9.73e-03, CI [-0.20, 0.22], p = 0.93) (Fig. 5b; Supplementary Table S13).

Fig. 5 **Effects of NFT on anxiety level. a) Pre-post (phase) mean effects.** Evolution of the *STAI-Y-A*

scores from pre- to post-NF training sessions, averaged across participants and sessions, for the NF

(in red) and control (in blue) groups. Shaded areas represent standard errors of the means. **b)**

Between-session effect on *STAI-Y-A* scores in each group. For each session, the pre- and post-

session anxiety levels were averaged. Same legend as in Fig. 3a.

relax-VAS – Relaxation, as measured by the *relax-VAS* scores, increased from pre- to post-session for

the NF group (β = 0.85, CI [0.60, 1.09], *p* < .001) and this effect was not significantly different

between groups (β = 0.33, CI [-0.03, 0.68], *p* = 0.07) (Fig. 6a). Moreover, *relax-VAS* scores showed a

significant linear increase across the sessions (β = 0.06, CI [0.03, 0.10], *p* < .001), which did not differ

significantly between groups (β = -0.02, CI [-0.07, 0.03], *p* = 0.45) (Fig. 6b; Supplementary Table

S15).

Fig. 6 **Effects of NFT on *relax-VAS* scores. a) Pre-post (phase) mean effects. b) Between-session effect on *relax-VAS* scores in each group.** Same legend as in Fig. 5.

Subjective feeling of control

A significant increase of the feeling of control was observed across sessions for the NF group (β = 0.12, CI [0.10, 0.15], *p* < .001). This increase was more marked in the NF than the control group (β for the interaction between session and group = -0.06, CI [-0.10, -0.02], *p* < .01) (Fig. 7). In addition, similarly to the exercise effect on the NF index, there was a quadratic fit of control feeling over exercises (β = 0.05, CI [0.02, 0.07], *p* < .001) which was not significantly different between groups (β = -0.01, CI [-0.05, 0.02], *p* = 0.47). See Supplementary Table S17 and Fig. S8 for details.

Fig. 7 **Evolution of the between-session effect of feeling of control with NF learning.** See Fig. 3 for legend.

Discussion

We proposed a double-blind randomized study of the neuromodulation induced by alpha-based NFT over 12 weekly sessions using a strictly controlled sham-FB condition as control. NFT was performed with a wearable, dry sensor headset, which delivered intensity-modulated auditory feedback based on EEG signal amplitude in individual alpha frequency band. To avoid non-contingency between produced efforts and the resulting feedback evolution for the control group [20], the control condition consisted in delivering sham-FB—a feedback replayed from randomly chosen users of the NF group at the same training stage. Hence, all participants benefited from the proposed NFT experience, but only those of the NF group experienced a closed-loop between the feedback and their own alpha activity.

NF learning refers to the capacity to self-regulate a targeted activity in the desired direction across training [19]. Here, the NF group was expected to increase individual alpha activity across training sessions, reflecting lasting effects [46]. This was confirmed by the analyses of the NF index and the NF learning score, which both demonstrated a specific session effect in the NF relative to the control group. This finding demonstrates a specific neuromodulation induced by the closed loop between individual alpha activity and FB, which could suggest an Hebbian neuroplasticity associated with NFT [19]. The use of a randomized double-blind protocol together with the strict sham-FB control condition allowed us to control for the many potential confounding factors which may contribute to NFT effects. In particular, it allowed controlling for context, task, reward, and performance, avoiding potential motivational biases in NF versus control conditions [20]. Moreover, we examined if the neuromodulation was selective of the targeted activity, which is rarely studied [47], [48]. As proposed in [39], we analyzed two adjacent frequency bands (theta and low beta). We found an overall increase across sessions for the theta band, not specific to the NF group, and no significant change for the low beta band. This provided evidence for the selectivity of the neuromodulation associated with NFT. To the best of our knowledge, this is the first evidence of selective longitudinal alpha-band neuromodulation (over 12 weeks) in a double-blind randomized study implying healthy participants trained with a wearable dry sensors NF device.

Additionally, we uncovered some interesting aspects of the dynamics of alpha band activity during NF learning, with a U-shape pattern across exercises. Alpha activity is a spontaneous but complex rhythm associated with several cognitive states and processes. Its modulation has been predominantly related to vigilance, attention [49], [50], awake but relaxed state [33], [34], [51]–[56]. Here, the NFT procedure was designed to train participants to increase alpha activity with the ultimate aim to improve their relaxation state. Yet, the alpha activity change across exercises during the sessions seemed to reflect the different cognitive processes involved by the task: Continuous monitoring of the feedback may have required heightened focused attention [57], [58], error detection [59], [60], and working memory processes [61] during the first training minutes, allowing

participants to progressively adapt their cognitive strategy and mental state to the task. This may have resulted in the initial decrease of the alpha activity along the training exercises [58]–[60]. Then, the subjects managed to adjust their cognitive strategy—mainly attentional focus on landscape sounds and attention defocusing—to upregulate their alpha activity. It is important to note that the within-session U-shape pattern of alpha activity was observed in both the NF and control groups. This supports the idea that the sham-FB condition allowed us to rigorously control for the task performed by the subjects. Altogether, the U-shape exercise effect on alpha activity seemed to reflect the combination of multiple cognitive processes in relation with NF learning, while the specific neuromodulation of alpha activity induced by NFT was revealed in the longitudinal effect across the twelve sessions.

We also examined EEG data quality, because it can have a confounding effect on NF learning [17]. EEG quality decreased slightly across sessions in both groups. Thus, it did not seem to contribute to the neuromodulation observed in the NF group.

We investigated the behavioral changes in terms of relaxation and anxiety levels pre- and post-session and across the training program. There was a reduction of anxiety level and an increase of relaxation across sessions, without any group difference. This is likely explained by our study protocol. Thanks to the design of the sham-FB condition, participants in the control group experienced the same immersive, relaxing experience as the NF group. Thus, our behavioral results may be explained by non-specific mechanisms of the NFT, such as the relaxing training context, placebo effect, and repetition-related effect [17]. One may note that anxiety decreased more from pre- to post-session in the control than the NF group. The sham-FB condition may have allowed the subjects from the control group to be rewarded with somewhat less cognitive effort, which may have reduced their state anxiety level, for example related to their performance during the session [62]. Furthermore, the subjects of this study were low to moderately anxious, which might have contributed to the lack of difference between groups. Indeed, Hardt and Kamiya [63], in their alpha-

upregulation NFT study, observed reduction of anxiety level for high but not low anxious subjects. Further investigations with high anxious participants should allow to test if a specific behavioral effect of NF may be highlighted. Overall, our findings showed that NFT induced positive behavioral benefits for all participants but the part due to neuromodulation remained unclear. Indeed, the links between behavioral outcomes and neurophysiology are complex and include several factors [17], such as cognition, attention, motivation [28], training frequency [64], but also the choice of the neuromarker itself [19]. Further investigations should focus on the research of specific biomarkers related to psychophysiological factors, for example using neurophenomenology to study the link between neural activity modulation and participant's inner experience [65].

Finally, departing from other studies using sham-FB control groups [20], we asked participants to assess their feeling of control during the training [66]. We found an increase of the feeling of control across sessions in both groups, which suggests that participants of the control group were not aware of the non-contingency between their efforts and the feedback signal and had a qualitatively similar experience as those of the NF group. Moreover, the increase in the feeling of control across sessions was more marked in the NF group. This suggests that the more active nature of FB modulation achieved in the NF group relative to the control group may have resulted in a greater feeling of control, eventually associated with a sense of agency in task performance [66]. Importantly, this result supports the view that the neuromodulation observed in the NF group was due to the subject's gaining control over his/her brain signal, rather than motivational effects [20].

To conclude, our study demonstrated a selective and specific neuromodulation associated with NFT of alpha-band activity with a wearable dry-sensor EEG device. Even if the relationship between the targeted EEG modulation and behavioral outcomes is complex and remains to be fully elucidated, the recent development of such wearable EEG systems is promising to easily perform NF protocols to induce neuromodulation in various applications like Parkinson's disease, epilepsy, sleep, attention or anxiety disorders and better understand underlying mechanisms.

Funding

N.G., L.Y.-C., L.H., and P.F. work on the CENIR MEG-EEG platform and at the Paris Brain Institute, which have received funding from the programs "Investissements d'avenir" ANR-10-IAIHU-06 and ANR-11-INBS-0006. This work was partly supported by an ANR grant in Cognitive and Integrative Neuroscience (project BETAPARK) to N.G.. F.G. was financially supported by myBrain Technologies as a PhD student.

CRediT authorship contribution statement

Fanny Grosselin: Conceptualization, Data curation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration. **Audrey Breton:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing. **Lydia Yahia-Cherif:** Formal analysis, Writing - Review & Editing. **Xi Wang:** Data curation, Formal analysis, Investigation, Writing - Review & Editing. **Giuseppe Spinelli:** Investigation, Writing - Review & Editing. **Laurent Hugueville:** Investigation, Resources, Writing - Review & Editing. **Philippe Fossati:** Conceptualization, Methodology, Writing - Review & Editing. **Yohan Attal:** Conceptualization, Methodology, Writing - Review & Editing, Supervision. **Xavier Navarro-Sune:** Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing, Project administration. **Mario Chavez:** Methodology, Investigation, Writing - Review & Editing. **Nathalie George:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration.

Declaration of competing interest

Acknowledgments

The authors thank myBrain Technologies for the provision of the Melomind[TM] headsets used in this study. The authors thank the Electronic Department of myBrain Technologies, Paris, France, in particular N. Pourchier and M. Bensoussan, for their contribution to the development and improvement of the electronic part of the Melomind[TM] device, as well as S. Zecri for the development of the mobile application used in this study. Finally, the authors thank all the participants for their participation in this study.

Reference

[1]   K. Singer, "The effect of neurofeedback on performance anxiety in dancers," *J. Dance Med. Sci.*, vol. 8, no. 3, pp. 78–81, 2004.

[2]   M. Dupee and P. Werthner, "Managing the Stress Response: The Use of Biofeedback and Neurofeedback with Olympic Athletes," *Biofeedback*, vol. 39, no. 3, pp. 92–94, Nov. 2011, doi: 10.5298/1081-5937-39.3.02.

[3]   M. B. Sterman and L. Friar, "Suppression of seizures in an epileptic following sensorimotor EEG feedback training," *Electroencephalogr. Clin. Neurophysiol.*, vol. 33, no. 1, pp. 89–95, Jul. 1972, doi: 10.1016/0013-4694(72)90028-4.

[4]   J. F. Lubar and M. N. Shouse, "EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report," *Biofeedback Self-Regul.*, vol. 1, no. 3, pp. 293–306, 1976, doi: 10.1007/BF01001170.

[5]   D. J. Fox, D. F. Tharp, and L. C. Fox, "Neurofeedback: An Alternative and Efficacious Treatment for Attention Deficit Hyperactivity Disorder," *Appl. Psychophysiol. Biofeedback*, vol. 30, no. 4, pp. 365–373, Dec. 2005, doi: 10.1007/s10484-005-8422-3.

[6]   M. Arns, S. de Ridder, U. Strehl, M. Breteler, and A. Coenen, "Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis," *Clin. EEG Neurosci.*, vol. 40, no. 3, pp. 180–189, 2009, doi: 10.1177/155005940904000311.

[7]   H. Gevensleben *et al.*, "Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial," *J. Child Psychol. Psychiatry*, vol. 50, no. 7, pp. 780–789, Jul. 2009, doi: 10.1111/j.1469-7610.2008.02033.x.

[8]   N. Lofthouse, K. McBurnett, L. E. Arnold, and E. Hurt, "Biofeedback and neurofeedback treatment for ADHD," *Psychiatr. Ann.*, vol. 41, no. 1, 2011, doi: 10.3928/00485713-20101221-07.

[9]   A. A. Trevisan, F. Attard, P. Cavallari, N. Caruana, and R. Micallef, "Real-time sonified neurofeedback stimulation for the management and relaxation of patients on the autism spectrum," *Brain Stimul. Basic Transl. Clin. Res. Neuromodulation*, vol. 8, no. 2, p. 354, Mar. 2015, doi: 10.1016/j.brs.2015.01.142.

[10]   D. C. Hammond, "Neurofeedback Treatment of Depression and Anxiety," *J. Adult Dev.*, vol. 12, no. 2–3, pp. 131–137, Aug. 2005, doi: 10.1007/s10804-005-7029-5.

[11]   V. Paquette, M. Beauregard, and D. Beaulieu-Prévost, "Effect of a psychoneurotherapy on brain electromagnetic tomography in individuals with major depressive disorder," *Psychiatry Res. Neuroimaging*, vol. 174, no. 3, pp. 231–239, 2009, doi: 10.1016/j.pscychresns.2009.06.002.

[12]   L. Konicar *et al.*, "Brain self-regulation in criminal psychopaths," *Sci. Rep.*, vol. 5, Mar. 2015, doi: 10.1038/srep09426.

[13]   L. K. Konicar, N. B. Birbaumer, and L. P. Poustka, "Brain self-regulation in criminal psychopaths," *Brain Stimul. Basic Transl. Clin. Res. Neuromodulation*, vol. 10, no. 2, p. 514, Mar. 2017, doi: 10.1016/j.brs.2017.01.501.

[14]   N. C. Moore, "A review of EEG biofeedback treatment of anxiety disorders," *Clin. EEG Neurosci.*, vol. 31, no. 1, pp. 1–6, 2000, doi: 10.1177/155005940003100105.

[15]   D. Hammond, "Neurofeedback with anxiety and affective disorders," *Child Adolesc. Psychiatr. Clin. N. Am.*, vol. 14, no. 1, pp. 105–123, Jan. 2005, doi: 10.1016/j.chc.2004.07.008.

[16]   C. A. Fisher, "Anxiety, depression, and sleep disorders: their relationship and reduction with neurotherapy," University of North Texas, 2010.

[17]   T. Ros *et al.*, "Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist)," *Brain*, vol. 143, no. 6, pp. 1674–1685, Jun. 2020, doi: 10.1093/brain/awaa009.

[18]   A. Zuberer, D. Brandeis, and R. Drechsler, "Are treatment effects of neurofeedback

training in children with ADHD related to the successful regulation of brain activity? A review on the learning of regulation of brain activity and a contribution to the discussion on specificity," *Front. Hum. Neurosci.*, vol. 9, p. 135, 2015, doi: 10.3389/fnhum.2015.00135.

[19] J.-M. Batail *et al.*, "EEG neurofeedback research: A fertile ground for psychiatry?," *L'Encephale*, vol. 45, no. 3, pp. 245–255, Jun. 2019, doi: 10.1016/j.encep.2019.02.001.

[20] B. Sorger, F. Scharnowski, D. E. J. Linden, M. Hampson, and K. D. Young, "Control freaks: Towards optimal selection of control conditions for fMRI neurofeedback studies," *NeuroImage*, vol. 186, pp. 256–265, Feb. 2019, doi: 10.1016/j.neuroimage.2018.11.004.

[21] E. Baehr, J. P. Rosenfeld, and R. Baehr, "The Clinical Use of An Alpha Asymmetry Protocol in the Neurofeedback Treatment of Depression: Two Case Studies," *J. Neurother.*, vol. 2, no. 3, pp. 10–23, Oct. 1997, doi: 10.1300/J184v02n03_02.

[22] E. G. Peniston and P. J. Kulkosky, "α-θ Brainwave Training and β-Endorphin Levels in Alcoholics," *Alcohol. Clin. Exp. Res.*, vol. 13, no. 2, pp. 271–279, 1989, doi: 10.1111/j.1530-0277.1989.tb00325.x.

[23] E. G. Peniston and E. Saxby, "Alpha-theta brainwave neurofeedback training: An effective treatment for male and female alcoholics with depressive symptoms," *J. Clin. Psychol.*, vol. 51, no. 5, 1995, doi: 10.1002/1097-4679(199509)51:5<685::aid-jclp2270510514>3.0.co;2-k.

[24] D. L. Trudeau, "The treatment of addictive disorders by brain wave biofeedback: A review and suggestions for future research," *Clin. EEG Neurosci.*, vol. 31, no. 1, pp. 13–22, 2000, doi: 10.1177/155005940003100107.

[25] T. M. Sokhadze, R. L. Cannon, and D. L. Trudeau, "EEG biofeedback as a treatment for substance use disorders: review, rating of efficacy and recommendations for further research," *J. Neurother.*, vol. 12, no. 1, pp. 5–43, 2008, doi: 10.1007/s10484-007-9047-5.

[26] J. F. Lubar, "Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders," *Biofeedback Self-Regul.*, vol. 16, no. 3, pp. 201–225, 1991, doi: 10.1007/BF01000016.

[27] O. Alkoby, A. Abu-Rmileh, O. Shriki, and D. Todder, "Can We Predict Who Will Respond to Neurofeedback? A Review of the Inefficacy Problem and Existing Predictors for Successful EEG Neurofeedback Learning," *Neuroscience*, vol. 378, pp. 155–164, May 2018, doi: 10.1016/j.neuroscience.2016.12.050.

[28] C. Jeunet, B. N'Kaoua, and F. Lotte, "Advances in user-training for mental-imagery-based BCI control: Psychological and cognitive factors and their neural correlates," *Prog. Brain Res.*, vol. 228, pp. 3–35, 2016, doi: 10.1016/bs.pbr.2016.04.002.

[29] M. Witte, S. E. Kober, M. Ninaus, C. Neuper, and G. Wood, "Control beliefs can predict the ability to up-regulate sensorimotor rhythm during neurofeedback training," *Front. Hum. Neurosci.*, vol. 7, p. 478, 2013, doi: 10.3389/fnhum.2013.00478.

[30] A. Naas, J. Rodrigues, J.-P. Knirsch, and A. Sonderegger, "Neurofeedback training with a low-priced EEG device leads to faster alpha enhancement but shows no effect on cognitive performance: A single-blind, sham-feedback study," *PloS One*, vol. 14, no. 9, p. e0211668, Sep. 2019, doi: 10.1371/journal.pone.0211668.

[31] J. Beatty, "Effects of initial alpha wave abundance and operant training procedures on occipital alpha and beta wave activity," *Psychon. Sci.*, vol. 23, no. 3, pp. 197–199, Sep. 1971, doi: 10.3758/BF03336074.

[32] G. Spinelli *et al.*, "Validation of melomind™ signal quality: a proof of concept resting-state and ERPs study," *bioRxiv*, p. 2020.02.28.969808, Mar. 2020, doi: 10.1101/2020.02.28.969808. *[Unpublished results]*

[33] K. M. Rice, E. B. Blanchard, and M. Purcell, "Biofeedback treatments of generalized anxiety disorder: preliminary results," *Biofeedback Self-Regul.*, vol. 18, no. 2, pp. 93–105, Jun. 1993, doi: 10.1007/BF01848110.

[34] J. S. Sandhu, M. Paul, and H. Agnihotri, "Biofeedback approach in the treatment of generalized anxiety disorder," *Iran. J. Psychiatry*, vol. 2, no. 3, pp. 90–95, 2007.

[35] F. Grosselin *et al.*, "Quality Assessment of Single-Channel EEG for Wearable Devices," *Sensors*, vol. 19, no. 3, p. 601, Jan. 2019, doi: 10.3390/s19030601.

[36] C. D. Spielberger, "Manual for the State-Trait Anxiety Inventory STAI (form Y)('self-evaluation questionnaire')," *Palo Alto CA Consult. Psychol. Press*, 1983, [Online]. Available: https://ubir.buffalo.edu/xmlui/handle/10477/1873.

[37] S. Cohen, T. Kamarck, and R. Mermelstein, "Perceived stress scale," *Meas. Stress Guide Health Soc. Sci.*, 1994, [Online]. Available: http://mindgarden.com/documents/PerceivedStressScale.pdf.

[38] F. Grosselin, Y. Attal, and M. Chavez, "A Robust Method for the Individual Alpha Frequency Detection in EEG:," in *Proceedings of the 6th International Congress on Neurotechnology, Electronics and Informatics*, Seville, Spain, 2018, pp. 35–40, doi: 10.5220/0006895700350040.

[39] S. Enriquez-Geppert, R. J. Huster, and C. S. Herrmann, "EEG-Neurofeedback as a Tool to Modulate Cognition and Behavior: A Review Tutorial," *Front. Hum. Neurosci.*, vol. 11, Feb. 2017, doi: 10.3389/fnhum.2017.00051.

[40] D. Bates, M. Mächler, B. Bolker, and S. Walker, "Fitting Linear Mixed-Effects Models Using lme4," *J. Stat. Softw.*, vol. 67, no. 1, pp. 1–48, Oct. 2015, doi: 10.18637/jss.v067.i01.

[41] G. Verbeke and G. Molenberghs, *Linear Mixed Models for Longitudinal Data*. New York, 2010.

[42] J. W. R. Twisk, *Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide*, 2nd ed. Cambridge: Cambridge University Press, 2013.

[43] R. Frömer, M. Maier, and R. Abdel Rahman, "Group-Level EEG-Processing Pipeline for Flexible Single Trial-Based Analyses Including Linear Mixed Models," *Front. Neurosci.*, vol. 12, Feb. 2018, doi: 10.3389/fnins.2018.00048.

[44] T. W. P. Janssen *et al.*, "Learning curves of theta/beta neurofeedback in children with ADHD," *Eur. Child Adolesc. Psychiatry*, vol. 26, no. 5, pp. 573–582, 2017, doi: 10.1007/s00787-016-0920-8.

[45] A. Kuznetsova, P. B. Brockhoff, and R. H. B. Christensen, "lmerTest Package: Tests in Linear Mixed Effects Models," *J. Stat. Softw.*, vol. 82, no. 1, pp. 1–26, Dec. 2017, doi: 10.18637/jss.v082.i13.

[46] L. Mayaud *et al.*, "Alpha-phase synchrony EEG training for multi-resistant chronic low back pain patients: an open-label pilot study," *Eur. Spine J.*, Jun. 2019, doi: 10.1007/s00586-019-06051-9.

[47] S. Enriquez-Geppert, R. J. Huster, R. Scharfenort, Z. N. Mokom, J. Zimmermann, and C. S. Herrmann, "Modulation of frontal-midline theta by neurofeedback," *Biol. Psychol.*, vol. 95, pp. 59–69, Jan. 2014, doi: 10.1016/j.biopsycho.2013.02.019.

[48] M. G. Pimenta, C. van Run, J. W. de Fockert, and J. H. Gruzelier, "Neurofeedback of SMR and Beta1 Frequencies: An Investigation of Learning Indices and Frequency-Specific Effects," *Neuroscience*, vol. 378, pp. 211–224, 15 2018, doi: 10.1016/j.neuroscience.2017.07.056.

[49] M.-P. Deiber *et al.*, "Linking alpha oscillations, attention and inhibitory control in adult ADHD with EEG neurofeedback," *NeuroImage Clin.*, vol. 25, p. 102145, Jan. 2020, doi: 10.1016/j.nicl.2019.102145.

[50] W. Klimesch, "Alpha-band oscillations, attention, and controlled access to stored information," *Trends Cogn. Sci.*, vol. 16, no. 12, 2012, doi: 10.1016/j.tics.2012.10.007.

[51] H. Berger, "Über das Elektrenkephalogramm des Menschen," *Arch. Für Psychiatr. Nervenkrankh.*, vol. 87, no. 1, pp. 527–570, Dec. 1929, doi: 10.1007/BF01797193.

[52] E. D. Adrian and B. H. C. Matthews, "The Berger Rhythm: Potential Changes From The Occipital Lobes In Man," *Brain*, vol. 57, no. 4, pp. 355–385, Dec. 1934, doi: 10.1093/brain/57.4.355.

[53] M. W. DiFrancesco, S. K. Holland, and J. P. Szaflarski, "Simultaneous EEG/Functional Magnetic Resonance Imaging at 4 Tesla: Correlates of Brain Activity to Spontaneous Alpha Rhythm During Relaxation," *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.*, vol. 25, no. 5, pp. 255–264, Oct. 2008, doi:

10.1097/WNP.0b013e3181879d56.

[54] A. S. Gorev, A. V. Kovaleva, E. N. Panova, and A. K. Gorbacheva, "Organization of the cortical bioelectric activity at different stages of a relaxation session," *Hum. Physiol.*, vol. 38, no. 5, pp. 463–469, Sep. 2012, doi: 10.1134/S0362119712050076.

[55] A. S. Gorev, A. V. Kovaleva, E. N. Panova, and A. K. Gorbacheva, "Dynamics of spatial synchronization of EEG parameters during relaxation and their relationship with regulation of heart rate," *Hum. Physiol.*, vol. 40, no. 5, pp. 504–512, Sep. 2014, doi: 10.1134/S0362119714050053.

[56] M. Mikicin and M. Kowalczyk, "Audio-Visual and Autogenic Relaxation Alter Amplitude of Alpha EEG Band, Causing Improvements in Mental Work Performance in Athletes," *Appl. Psychophysiol. Biofeedback*, vol. 40, no. 3, pp. 219–227, Sep. 2015, doi: 10.1007/s10484-015-9290-0.

[57] J. J. Foxe and A. C. Snyder, "The Role of Alpha-Band Brain Oscillations as a Sensory Suppression Mechanism during Selective Attention," *Front. Psychol.*, vol. 2, 2011, doi: 10.3389/fpsyg.2011.00154.

[58] M. Bauer, S. Kennett, and J. Driver, "Attentional selection of location and modality in vision and touch modulates low-frequency activity in associated sensory cortices," *J. Neurophysiol.*, vol. 107, no. 9, pp. 2342–2351, May 2012, doi: 10.1152/jn.00973.2011.

[59] J. Carp and R. J. Compton, "Alpha power is influenced by performance errors," *Psychophysiology*, vol. 46, no. 2, pp. 336–343, Mar. 2009, doi: 10.1111/j.1469-8986.2008.00773.x.

[60] J. van Driel, K. R. Ridderinkhof, and M. X. Cohen, "Not All Errors Are Alike: Theta and Alpha EEG Dynamics Relate to Differences in Error-Processing Dynamics," *J. Neurosci.*, vol. 32, no. 47, pp. 16795–16806, Nov. 2012, doi: 10.1523/JNEUROSCI.0802-12.2012.

[61] E. Başar and B. Güntekin, "A short review of alpha activity in cognitive processes and in cognitive impairment," *Int. J. Psychophysiol.*, vol. 86, no. 1, pp. 25–38, Oct. 2012, doi: 10.1016/j.ijpsycho.2012.07.001.

[62] M. Alino, "A Critical View of Neurofeedback Experimental Designs: Sham and Control as Necessary Conditions," *Int. J. Neurol. Neurother.*, vol. 3, no. 1, Feb. 2016, doi: 10.23937/2378-3001/3/1/1041.

[63] J. V. Hardt and J. Kamiya, "Anxiety change through electroencephalographic alpha feedback seen only in high anxiety subjects," *Science*, vol. 201, no. 4350, pp. 79–81, Jul. 1978, doi: 10.1126/science.663641.

[64] A. Bussalb *et al.*, "Clinical and Experimental Factors Influencing the Efficacy of Neurofeedback in ADHD: A Meta-Analysis," *Front. Psychiatry*, vol. 10, Feb. 2019, doi: 10.3389/fpsyt.2019.00035.

[65] A. Lutz, H. A. Slagter, J. D. Dunne, and R. J. Davidson, "Attention regulation and monitoring in meditation," *Trends Cogn. Sci.*, vol. 12, no. 4, pp. 163–169, Apr. 2008, doi: 10.1016/j.tics.2008.01.005.

[66] A. Gaume, A. Vialatte, A. Mora-Sánchez, C. Ramdani, and F. B. Vialatte, "A psychoengineering paradigm for the neurocognitive mechanisms of biofeedback and neurofeedback," *Neurosci. Biobehav. Rev.*, vol. 68, pp. 891–910, Sep. 2016, doi: 10.1016/j.neubiorev.2016.06.012.