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ITACA: An open-source framework for Neurofeedback based on Brain–Computer Interfaces

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ABSTRACT

Background and objective: Neurofeedback (NF) is a paradigm that allows users to self-modulate patterns of brain activity. It is implemented with a closed-loop brain–computer interface (BCI) system that analyzes the user's brain activity in real-time and provides continuous feedback. This paradigm is of great interest due to its potential as a non-pharmacological and non-invasive alternative to treat non-degenerative brain disorders. Nevertheless, currently available NF frameworks have several limitations, such as the lack of a wide variety of real-time analysis metrics or overly simple training scenarios that may negatively affect user performance. To overcome these limitations, this work proposes ITACA: a novel open-source framework for the design, implementation and evaluation of NF training paradigms.

Methods: ITACA is designed to be easy-to-use, flexible and attractive. Specifically, ITACA includes three different gamified training scenarios with a choice of five brain activity metrics as real-time feedback. Among them, novel metrics based on functional connectivity and network theory stand out. It is complemented with five different computerized versions of widespread cognitive assessment tests. To validate the proposed framework, a computational efficiency analysis and an NF training protocol focused on frontal-medial theta modulation were conducted.

Results: Efficiency analysis proved that all implemented metrics allow an optimal feedback update rate for conducting NF sessions. Furthermore, conducted NF protocol yielded results that support the use of ITACA in NF research studies.

Conclusions: ITACA implements a wide variety of features for designing, conducting and evaluating NF studies with the goal of helping researchers expand the current state-of-the-art in NF training.

1. Introduction

Brain–computer interfaces (BCI) establish a direct connection between the user's brain activity and an external device [1]. Among the various methods of acquiring brain activity, the electroencephalogram (EEG) is the most widespread in the field of BCI. This is because EEG is non-invasive, portable, has good temporal resolution and is has lower cost compared to other available methods. BCI systems were originally designed to improve the quality of life of people with severe motor disabilities. However, thanks to the progress made by BCI researchers in recent times, these systems now offer many more applications. Among them, Neurofeedback (NF) training systems stand out for their promising future in the field of neuropsychology. In NF applications, users receive real-time feedback of a certain characteristic of their brain activity (e.g. the power of a certain frequency band) from a closed-loop BCI [2]. This feedback helps users find neurocognitive strategies that allow them to acquire voluntary control over their own brain activity [2]. It has been shown that NF has the potential to induce brain plasticity [2]. Therefore, if a certain neuropsychological disorder has been associated to aberrant brain activity, NF aims to normalize it through a volitional neuromodulation procedure. In this regard,

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it is hypothesized that NF could lead to cognitive and behavioral improvements [2].

In recent years, NF has attracted great interest among the scientific community due to the wide possibilities it offers as a non-pharmacological and non-invasive therapy for the treatment of non-degenerative brain disorders (i.e., those that affect the normal functioning of the neurons) [3] such as ADHD [2,4] or epilepsy [3]. Furthermore, neural rehabilitation for stroke patients using BCI-based NF is attracting significant attention as a complement to traditional motor rehabilitation [5]. The usefulness of NF training to improve cognitive performance in healthy subjects has also been highlighted [6]. Furthermore, it has been proposed as an experimental method to investigate cognition and behavior [6]. However, despite the potential of NF, these systems are less developed compared to other paradigms used in the BCI field. In this regard, it is worth noting that NF presents several singularities that affect its technical and methodological progress. On the one hand, unlike other BCI paradigms based on exogenous stimulus, NF requires the endogenous modulation of neural activity. This means that NF demands a greater number of training sessions than other paradigms [7]. Given the effort involved in repeating similar exercises over several training sessions, user motivation has been highlighted as an important factor that can influence training performance [8]. On the other hand, NF researchers belong predominantly to psychological and clinical fields [7]. However, the development of new BCI applications requires coding and signal processing expertise that may be beyond the reach of these researchers [7,9]. This makes the progress of the NF field conditioned to the technical development of the available NF frameworks.

In this context, there is a need for easy-to-use frameworks with a wide variety of tools to facilitate researchers to design training protocols with flexibility [7]. These frameworks should also include gamified feedback applications, as gamification has been proposed to increase motivation and engagement, as well as to ameliorate the repetitiveness of NF sessions [10]. In this regard, there are several open-source software packages aimed at designing NF applications for research. Nevertheless, these frameworks offer limited options in terms of real-time feedback metrics. For instance, BrainBay [11], Neurofeedback Suite (NFS) [7] and OpenViBE scenarios [12] only implement NF paradigms based on single frequency band power. This implies that researchers must address the task of implementing further features or modifying already provided pipelines to adjust the framework to more complex training protocols. Moreover, the feedback presentation modalities included in these frameworks are, in general, those that have been traditionally used in the past, but which may result overly simple in the current state-of-the-art. In this sense, frameworks as BrainBay [11], NFS [7] or NFBLab [13] implements classical feedback presentations, such as acoustic feedback or simple figures (e.g., a square or a circle) whose shape or color change depending on the training brain activity. These non-gamified training scenarios may not be sufficiently engaging for users who must use the same applications in repeated sessions [8,10]. Finally, it is noteworthy that no NF framework provides a set of cognitive assessment applications. These can be useful tools, as they allow researchers to extract interesting information about brain patterns related to cognition and to assess cognitive changes induced by NF training.

In this paper, we present ITACA (*Interface for Training Against Cognitive Ageing*), a novel NF framework that aims to overcome the limitations identified in currently available NF frameworks. It has been developed in Python and is part of the MEDUSA©, a software ecosystem for the development of BCI systems and neuroscience experiments [9]. ITACA is an open-source framework in active development that promotes open science. The highlights of ITACA are: (1) easy-to-use design with intuitive configuration panels and extensive documentation; (2) wide range of options to flexibly design training protocols, including three different training scenarios, five different cognitive assessment tests, two power-based training metrics and three novel training metrics based on functional connectivity and network theory; and (3) gamified design of the applications to maintain user motivation during their use. The proposed framework has been validated twofold. On the one hand, its computational efficiency has been analyzed. On the other hand, its functionality was evaluated by designing, conducting and evaluating a NF training protocol with 19 healthy users.

2. Methods

2.1. Design

ITACA is a novel framework intended to design, conduct and evaluate NF training studies. It is composed of different apps from MEDUSA© Platform [9]. Specifically, ITACA provides two different types of apps: one NF training app and five cognitive-assessment apps. All of them have the same common architecture (see Fig. 1). On the one hand, a module implemented in Python deals with the acquisition of the biosignal via the lab stream layer (LSL) protocol and its processing and analysis only in the case of the NF app. In addition, it provides the graphical user interface (GUI) for the selection and configuration of the apps. On the other hand, the visual presentation of the apps is implemented in C#, and Unity is used as the graphic engine. The communication between both parts is performed through a multi-client asynchronous TCP/IP-based protocol [9]. These apps are available for free download at www.medusabci.com/market.

The NF training app contains multiple options to be configured, allowing to explore different experimental protocols. In this regard, it provides five different metrics for real-time feedback of brain activity characteristics, including power-based metrics, metrics based on functional connectivity and metrics bases on network theory. It also includes three different gamified NF scenarios and multiple options for the temporal distribution of the training blocks during the NF session.

Cognitive assessment apps implement computerized versions of five popular neuropsychological tests. Namely, the provided tests are Dual *N*-back [14], Digit span [15], Corsi block-tapping [16], Stroop test [17] and Go/No-go task [18] (see Fig. 2). These tests are of great relevance, as they are widely applied both in neuropsychological research [14] and in the evaluation of NF training [19]. Among the cognitive functions evaluated are working memory [14–16], selective attention [17], response speed or response inhibition [20]. In addition, they allow to record any type of biosignal during the performance of the tasks. Thus, these apps are useful for analyzing not only cognitive changes derived from NF training, but also physiological responses related to cognitive processes. For instance, user-specific brain activity patterns can be obtained from the EEG, which can be useful for designing individualized NF training protocols.

ITACA's purpose is to provide a versatile and novel NF framework that will help researchers design training protocols that fit their study requirements. In order to achieve it, ITACA has been designed according to the following principles:

- *Easy-to-use:* All ITACA apps are provided with a modern GUI that provides quick and intuitive control over the different configuration options. These configuration panels have been implemented to allow users to design their own experimental protocol without any programming knowledge. In addition, extensive documentation has been prepared with the functionalities and tutorials of each app.
- *Flexibility:* ITACA's NF training app and cognitive assessment apps are highly configurable. This increases the versatility of the framework, which can be used for wide range of experiments.
- *Gamified applications:* Both NF training scenarios and cognitive assessment tests have a gamified and modern aspect. This principle aims to help users stay motivated and engaged along NF study.

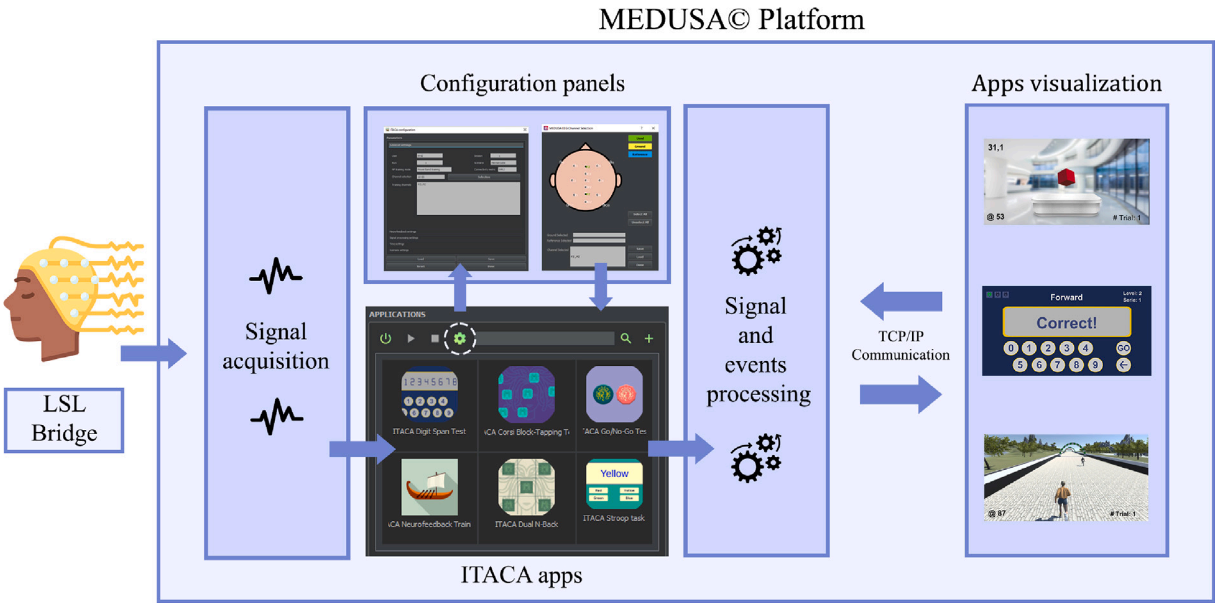

Fig. 1. Schematic overview of ITACA. The framework consists of six apps whose configuration and use is managed from the MEDUSA© Platform.

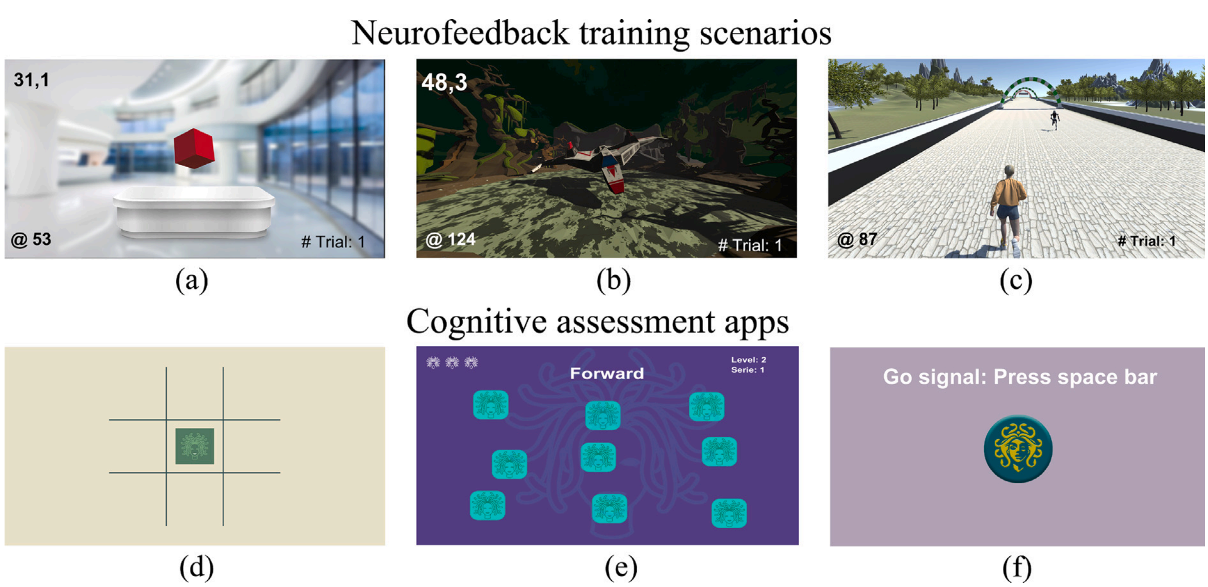

Fig. 2. Snapshots of different ITACA apps. In the top row, the different NF training scenarios: (a) Mental cube, (b) Trapped spaceship and (c) Neuro runner. In the bottom row, three of the five ITACA cognitive assessment apps: (d) Dual *N*-back, (e) Corsi block-tapping test and (f) Go/No-go task.

Two interesting features of ITACA as a consequence of being part of the MEDUSA© Platform [9] are worth mentioning. On the one hand, all configuration panels allow to save and load the settings, ensuring reproducibility of the experiment configuration. On the other hand, the compatibility with different biosignal acquisition devices that LSL protocol is guaranteed.

2.2. NF training app

2.2.1. Signal processing

The NF training app implements several EEG processing pipelines that have been carefully designed to ensure optimal real-time signal processing and analysis. As for processing stage, the implemented methods are spatial filters, such as common average reference (CAR) and Laplacian filter, and frequency filter, such as Butterworth-type IIR filter. Several configurable options are offered, including the time window used to analyze EEG features or the option to choose between increasing or decreasing the value of the configured feedback metric. The latter is important because there are some brain disorders that have been linked to an abnormal increase in certain brain rhythms [4]. In addition, this app allows easy selection of the EEG channels used to provide the feedback (see Fig. 1). This can be useful when different cognitive functions related to specific regions of the brain are to be trained.

Regarding metrics for real-time analysis of EEG patterns, ITACA NF training app provides five different training modes. On the one hand, it provides two power-based metrics. Namely, the spectral power of a frequency band and the ratio between the spectral powers of two or more frequency bands. These training modes are widely used in NF studies [4,19–21]. Its implementation is based on estimating the power spectral density (*PSD*) using the Welch periodogram. Then, the power in the frequency band of interest (P_f) is calculated as follows:

$$P_f = \frac{f_{samp}}{2N} \sum_{f_l}^{f_u} PSD(f), \tag{1}$$

where f_{samp} is the sampling frequency, f_l and f_u the lower and upper frequency limits of the band of interest, and N the length of the *PSD*. On the other hand, ITACA provides two novel metrics based on functional connectivity and one based on network theory. All of them can be calculated from the adjacency matrix ($\boldsymbol{A}$) given by both the orthogonalized amplitude envelope correlation (AEC), which measures the connectivity as the correlation between the envelopes of two signals [22], and the weighted phase lag index (wPLI), which accounts for the consistency in phase differences between two signals [23]. AEC and wPLI are suitable functional connectivity methods because they have been proved to be less sensitive to noise than other connectivity metrics and robuts against the influence of volume conduction effects. The functional connectivity metrics are global coupling (C_G) and nodes coupling ($\boldsymbol{A}_{i,j}$) [24]. C_G is an index that accounts for the global changes in neural coupling [24] and is calculated as the average of the upper triangular matrix ignoring the elements of the main diagonal:

$$C_G = \frac{1}{N} \sum \mathrm{tri}_u(\boldsymbol{A}_{ij}), \tag{2}$$

where tri_u is the function that gives the elements of the $\boldsymbol{A}$ that are above the main diagonal, and N the number of electrode connections. Nodes coupling metric $\boldsymbol{A}_{ij}$ provides the connectivity values between elements i and j from de adjacency matrix. Regarding the network-based metric, ITACA implements node strength ($S(i)$) [25], which quantifies the degree of connectivity of one electrode with the rest as follows:

$$S(i) = \sum_{j=1, j\neq i}^{N_e} \boldsymbol{A}_{ij}, \tag{3}$$

where N_e is the number of electrodes. $S(i)$ can be interpreted as a measure of centrality, i.e., a measure of the influence that the node exerts over the entire brain network. Functional connectivity and network metrics are currently less widely employed in NF studies, but they have been identified as an interesting line of future research in this field [25]. In this context, ITACA's NF training app provides innovative and useful tools to further develop the NF methodology. Noteworthly, the NF training app also provides a tool to prevent influence of ocular and muscular artifacts on feedback signal. This method is based on the comparison between the statistics of the filtered signal in the frequency bands related to this type of artifacts during NF and the value obtained in a reference period.

2.2.2. Training scenarios

ITACA includes three gamified scenarios with different objectives (see Fig. 2). This allows the design of training protocols of progressive difficulty using more than one scenario. In all of them, any of the five available metrics can be selected for feedback. This feedback is proportional to the change of the metric value over a baseline period. ITACA allows to perform a baseline at the beginning of the execution, or to load a baseline recording. The parameters of each scenario, the duration of the trials, the number of trials and the time between trials can be easily adjusted in the configuration panel. All scenario metrics provide useful information, such as the time remaining to finish the trial, the number of the current trial or the feedback update rate. The latter allows the user to make sure that this real-time feedback rate is adequate to perform the NF session correctly.

The "Mental cube" scenario is intended to serve as the user's first contact with the NF technique. It displays a red cube that the user must raise to the top of the screen (see Fig. 2a). At each feedback refresh, the cube will update its vertical position according to the metric value calculated from the real-time EEG analysis. If this value, after baseline correction, is positive, the cube will go up, otherwise it will go down. This scenario does not require users to achieve large modulations of their brain activity patterns, but aims to help them find a suitable mental strategy to start gaining volitional control over these patterns.

The "Trapped spaceship" scenario is intended to reinforce volitional control of the brain pattern under training. It shows a scene in which a spaceship is sunk in a swamp and must be lifted out of it (see Fig. 2b). Its vertical position is proportional to the percentage change between the training and baseline values of the chosen metric. This scenario makes it possible to design an NF training with an adaptive difficulty by adjusting the maximum change in percentage that the user is expected to achieve. This value will correspond to the maximum height that the spaceship could reach.

The "Neuro runner" scenario also aims to reinforce the self-modulation of the target brain patterns. This scenario shows a foot race against an non-player character (NPC) opponent (see Fig. 2c). The speed of the user's avatar is directly proportional to the percentage increase in the value of the training metric with respect to baseline value. Thus, this scenario not only encourages users to maximize the modulation of their brain patterns, but also requires them to maintain it throughout the race. Opponent's speed can be set to control the difficulty of the scenario. In addition, this scenario has different runner avatars to be selected, both for the player and the NPC opponent.

Detailed documentation is available at https://medusabci.com/market/itaca/. It includes information on the functionalities of the app and a video tutorial showing the set-up of the training scenarios.

2.3. Cognitive assessment apps

The functionalities of each of the five ITACA's cognitive assessment apps are detailed below.

Dual N-back is a continuous performance task and one of the most popular tests used in the evaluation of working memory [14,19,26]. In this test, users are presented with a sequence of stimulus. In our approach, the stimulus is configurable and can be either visual (presented as a square in a 3 × 3 grid), auditory (letters pronounced in Spanish or English) or dual (both stimulus are presented at the same time). Users must indicate when a stimulus matches the stimulus presented N-times before. The ITACA implementation allows to adjust the load factor N, the number of stimulus, or the percentage of target stimulus with respect to the total stimulus. It can be downloaded at (https:/medusabci.com/market/dnbck/).

Digit span test measures the longest list of items that users can repeat in correct order just after it has been presented [15]. As users answer correctly, the length of the sequence presented increases. This memory test is a common measure of phonological working memory [14,26]. The length of the initial sequence, the order in which the user has to respond (forward or backward sequence order), or the number of failures allowed before finishing the test are some of the configurable options of this implementation. This app can be downloaded at (https://medusabci.com/market/dspan/).

Corsi block-tapping test is broadly applied to assess spatial working memory [26]. A set of nine blocks are randomly placed on the screen and sequentially illuminated. Users have to mimic the sequence of illuminations. Like in Digit span test, the length of the stimulus sequence is increased until the user repeatedly fails. The ITACA implementation allows to configure the order of user response, the duration of the initial sequence and the number of failures allowed before the end of the test. It can be found at (https://medusabci.com/market/corsi/).

The Go/No-go task is a popular tool for investigating user's sustained attention and response/inhibition control in cognitive neuroscience research [14,18]. In this test, two types of stimulus are presented. Users have to perform an action when a "go" stimulus is presented and do not have to respond in case of a "no-go" stimulus. This app allows to configure parameters such as the number of stimulus, the percentage of no-go stimulus or the duration of each stimulus. It can be downloaded at (https://medusabci.com/market/gonogo/).

Stroop test is based on the Stroop effect, which is the delay in reaction time between congruent and incongruent stimulus [17]. It has been used extensively in selective attention research [17]. This test presents different color names that may or may not match the color in which they are printed. Users are encouraged to respond to the color of the word by pressing the corresponding key. In this implementation it is possible to configure the language of the words (English or Spanish) or the number of stimulus. Stroop test app can be downloaded at (https://medusabci.com/market/stroop/).

2.4. Computational efficiency validation

Computational efficiency is a fundamental aspect of any NF framework, as it is necessary to ensure a feedback update rate that adequately reflects changes in the user's brain activity. In this way, the feedback will help the user to find the optimal neurocognitive strategy to self-modulate the target brain patterns. In order to validate the different real-time analysis metrics implemented in the NF training app, a computational efficiency analysis was performed. For this purpose, different NF sessions were simulated, one for each analysis metric implemented in ITACA. The computation time of the metrics in each feedback update was recorded for 10 min in those sessions. The sessions were carried out using a *g.USBamp* amplifier (*Guger Technologies OG*, Graz, Austria) with 16 active electrodes. To account for the influence of the length of the signal used to calculate the metric in each feedback update, time window of one, two and three seconds were considered. In addition, spatial filtering characteristic of each metric (i.e., CAR for connectivity-based metrics and CAR and Laplacian filtering on power-based metrics) was taken into account during real-time preprocessing. In this way, real conditions of a NF sessions were reproduced. The analysis was performed using a PC with an Intel Core i7-10700F @ 2.90 GHz processor and 32 GB RAM.

2.5. Functionality validation

In order to validate the functionality of ITACA, an NF training protocol was designed and carried out. This protocol was aimed at up-regulating theta (4–8 Hz) activity in the frontal-midline brain region (fm-theta). This brain activity was specifically chosen for two reasons. On one hand, there are previous studies which have proved that it is possible to up-regulate such activity by means of NF [19,21,27,28]. Hence, this enables our protocol to be compared with the results reported in those previous studies. On the other hand, fm-theta is of special interest because it has been related to tasks with high working memory demands [21,27,29]. Working memory is part of the executive functions and it is essential for cognitively demanding daily activities [26]. For this reason, it could be of great interest to study the potential of NF to enhance working memory functions.

2.5.1. Participants

The fm-theta NF training protocol was conducted with 19 healthy people (mean age 25.05 ± 4.18 years), of which 11 were women (mean age 24.36 ± 3.53 years) and 8 men (mean age 26.00 ± 5.04 years). Following the recommendations of *Consensus on Reporting and Experimental Design of Clinical and Cognitive-Behavioral Neurofeedback Studies* (CRED-NF) [30], participants were randomly divided into an experimental training group (TG; 11 subjects), who trained their fm-theta activity, and an active control group (CG; 8 subjects), who received sham feedback. This helps to take into consideration the non-specific effects of the training protocol. All participants gave their informed consent.

2.5.2. EEG data acquisition

For EEG recording, a *g.USBamp* amplifier (*Guger Technologies OG*, Graz, Austria) with 16 active electrodes (F7, F3, Fz, F4, F8, FCz, C3, Cz, C4, CPz, P3, Pz, P4, PO7, POz, PO8), placed in an elastic cap according to the 10–10 standard, was used. Ground electrode was located at AFz channel, whilst the common reference was placed in the right earlobe. The signal was acquired at a sampling rate of 256 Hz.

2.5.3. NF protocol

The protocol consisted of eight sessions spread over two weeks. The first and last sessions were used to assess working memory, while the remaining 6 sessions were used for NF training. Fig. 3 shows a scheme of this experimental protocol.

In the evaluation sessions, users performed three of the five cognitive assessment tests included in ITACA. These were N-back (with $N = 3$ in visual modality), Digit span and Corsi block-tapping tests (both starting with a sequence length of 4 stimulus). The EEG signal was recorded during these evaluation sessions. Following the approach proposed by Enriquez-Geppert et al. [21], an individualized fm-theta definition was calculated for each subject of TG. This was performed by analyzing the EEG recorded during the 3-back test of the pre-training evaluation session. Only fragments of correct responses to the target stimulus were considered. An event-related spectral perturbation (ERSP) analysis was performed to extract the mean theta peak in the Fz channel. Individual fm-theta training band was defined as fm-theta peak ± 1 Hz [21].

The training sessions lasted an average of 1 hour. In these sessions, users performed two minutes of resting-state EEG recording, six runs of NF training and another two minutes of resting-state recording. Each run consisted of five trials of the same NF scenario with a maximum duration of 45 s each. If users reached the trial objective before the end of the trial, it ended. At the beginning of the protocol, users were provided with different examples of mental strategies from the NF literature to gain control over their brain activity (e.g. mental imagery, motor imagery, arithmetic calculations) [30]. The training protocol was designed to have an increasing difficulty. The distribution of NF scenarios throughout the training is shown in Fig. 3. Real-time feedback was extracted from EEG spectral power in the Fz channel. TG users were provided with feedback of their individualized fm-theta activity while CG users were provided with sham feedback from different bands in each session. As proposed in [28], the feedback bands used in the CG users from sessions 1 to 6 were: 16–18 Hz, 14–16 Hz, 18–20 Hz, 20–22 Hz, 12–14 Hz and 22–24 Hz. The artifact rejection tool implemented in ITACA was applied.

2.5.4. Offline EEG data analysis

The pre-processing stage was as follows. During each training run, signals were frequency filtered by applying a bandpass FIR filter between 1 and 40 Hz. Then, CAR was applied to data. Finally, signals were divided into non-overlapping epochs of 5 s duration, and an automatic method was applied to reject noisy epochs. This method excludes epochs whose amplitude was greater than twice the standard deviation of the entire signal.

For the EEG analysis of NF training sessions, the PSD was calculated for each epoch using Welch's method in the Fz channel. A Hamming window of 4.5 s and an overlap of 90% were used. The mean theta power for each training run was extracted for each user. Finally, the value of the runs was averaged, obtaining a single value for each training session. To analyze the effects of NF training, the evolution of fm-theta power over the training sessions was studied. To account for differences between users, the evolution value of fm-theta power in each session was calculated as the change with respect to the value of the first training session. It has been suggested that this procedure is appropriate because it establishes the first contact with the NF as a point of comparison [21].

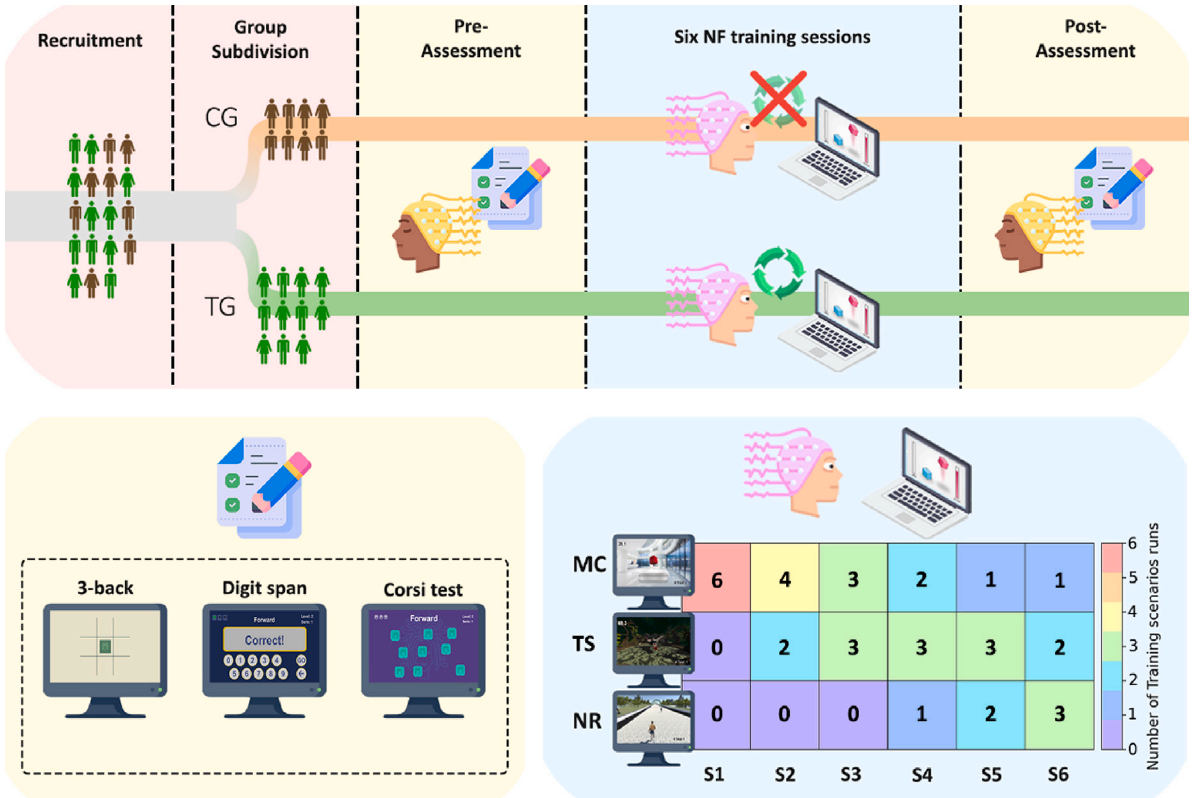

Fig. 3. Scheme of experimental protocol followed in NF training study to validate ITACA (top panel); Cognitive assessment tests used in evaluation sessions (bottom left panel); and heatmap representing NF training scenarios distribution (MC: Mental cube; TS: Trapped spaceship; NR: Neuro runner) along NF sessions (bottom right panel).

2.5.5. Assessment of psychosocial factors

As recommended by CRED-NF [30], psychosocial data were collected from users in both groups. Users rated their motivation and their mental fatigue after completing each training session. All the assessments were carried out using a seven-point Likert-scale.

2.5.6. Analysis of non-responding users

Previous studies on NF reported that certain subgroups of users trained in NF are unable to attain voluntary control over modulation of brain activity [21,31]. The proportion of these users, known as "Non-responders", was estimated to be 25% of the total training participants [21]. In this validation study, due to the fact that the number of TG participants is not large, we screened the results of the TG users and divided the group into non-responders (TG-NR) and responders (TG-R) to NF training. TG-NR were excluded from further analysis. This was done to avoid their excessive influence on the reported results. In this way, it allows us to focus on the validation of ITACA's functionality, which it is in fact the main objective of this work. To determine which participants from TG group were non-responders, a clustering analysis was performed applying K-means clustering. The fm-theta evolution values from sessions 2 to 6 were used as features to classify TG and CG users. A value K = 2 for the analysis was defined since we hypothesized that the modulation values of the fm-theta activity of the non-responders is closer to CG users than to NF responders.

2.5.7. Statistical analysis

NF training effects on fm-theta changes relative to the first training session were analyzed with a two-way mixed ANOVA with the between-subject factor *group* (i.e., TG-R vs. CG) and the within-subject factor *session* (i.e., 2–6). Changes in cognitive test performance between the two evaluation sessions in each group were analyzed using a Wilcoxon signed-rank test. The difference in the change between the two groups was analyzed using a Mann–Whitney U-test. To overcome the problem of false discoveries due to multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR–BH) correction was applied. Finally, motivation and mental fatigue reported by subjects for each training session were analyzed with a two-way mixed ANOVA with the between-subject factor *group* and the within-subject factor *session*.

Table 1
Average computation times and standard deviation of the different metrics implemented in ITACA NF training app. Time window (TW); Spectral power (*SP*); Ratio between spectral powers (*RSP*); Global coupling (C_G); Node strength (*S*); Nodes coupling (C_N).

Metric	Time (ms)		
	TW 1 s	TW 2 s	TW 3 s
SP	27.1 ± 0.8	62.2 ± 0.3	80.2 ± 1.9
RSP	28.8 ± 0.7	64.2 ± 3.2	82.5 ± 2.2
C_G (wPLI)	125.7 ± 5.0	174.0 ± 3.9	205.4 ± 15.9
C_G (AEC)	117.4 ± 7.3	145.1 ± 13.4	174.2 ± 10.9
S (wPLI)	122.2 ± 1.1	174.2 ± 7.7	200.7 ± 15.2
S (AEC)	118.0 ± 7.3	146.7 ± 5.5	167.9 ± 8.7
C_N (wPLI)	127.5 ± 11.1	179.1 ± 1.8	209.4 ± 2.1
C_N (AEC)	121.7 ± 2.4	153.3 ± 9.1	170.6 ± 5.8

3. Results

3.1. Computational analysis

The average computation time and standard deviation values for each metric and each of the time window values are presented in Table 1. Note that the connectivity metrics can be calculated using wPLI and AEC, so their values are shown separately.

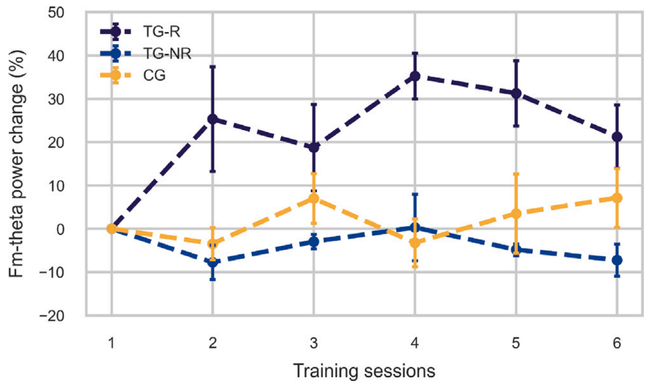

Fig. 4. Evolution of fm-theta power during NF trials relative to first training session. The fm-theta power was averaged for each session and for all users in each group. Bars show the standard error mean. Training group responders (TG-R), training group non-responders (TG-NR) and control group (CG).

3.2. Functionality validation results

3.2.1. Exclusion of non-responders

The K-means clustering analysis yielded that three users from TG were assigned to the cluster of CG users. Thus, their fm-theta modulation values throughout training were more similar to CG users than TG users who responded to NF training. Therefore, they were identified as non-responders participants to the training protocol (TG-NR) and were excluded from further analysis. Hereafter, only the results of TG-R and CG users were analyzed.

3.2.2. Evolution of fm-theta power over sessions

The change in percent in fm-theta power relative to the first training sessions is shown in Fig. 4. TG-NR values have also been included in this graph, showing that TG-NR curve is more similar to the CG curve than to the TG-R curve. Visually, it can be seen that NF training led to a greater increase in fm-theta modulation in the TG-R than the changes observed in the CG users. These results are confirmed by a significant main effect of *group* in the ANOVA test (F(1,14) = 11.438, $p < 0.01$). No other effects were found significant.

3.2.3. Analysis of motivation and mental fatigue

Fig. 5 depicts the evolution of users self-report on motivation and mental fatigue across training sessions using a seven-point Likert scale. In general, the motivation rating of users in both groups was high throughout the training protocol. The TG-R users motivation was similar throughout the training sessions, whereas CG users motivation decreased moderately in the last two sessions. The two-way mixed ANOVA test reported no significant effect of *group* or *session* main factors. The mental fatigue reported by the users after completing each training sessions showed a similar trend in the different groups. The values decreased slightly from the first to the fourth session. Afterwards, mental fatigue increased. ANOVA test revealed a significant main effect of *session* factor (F(5,70) = 3.022, $p < 0.05$). No further effects were found.

3.2.4. Cognitive assessment performance change

Regarding N-back test performance, Fig. 6a shows that CG accuracy in target stimulus responses at pre-training evaluation were higher than TG-R accuracy. However, TG-R improved their performance in the post-training assessment, outperforming CG results on average. Significant improvement in the performance of 3-back was found ($p < 0.05$) in the TG-R users. This was not observed in the CG results ($p > 0.1$). In addition, there was observed a significant difference ($p < 0.05$) between TG-R and CG in the change in pre- vs. post-training 3-back scores.

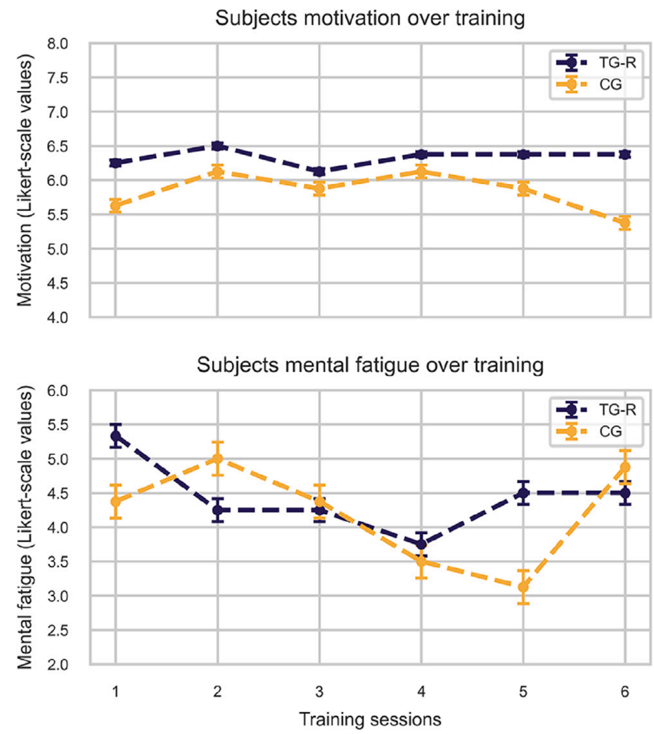

Fig. 5. Motivation ratings after the six training sessions (top panel). Mental fatigue values after the six training sessions (bottom panel).

With regard to the Digit Span test results, as can be seen in Fig. 6b, the scores of both groups increased in the final evaluation session. However, neither the TG-R nor the CG showed significant improvements. In turn, no significant difference between the changes in TG-R and CG in Digit span scores was found.

Lastly, as for Corsi block-tapping performance, CG scores were higher than TG-R scores at first evaluation (see Fig. 6c). Nevertheless, only TG-R participants improved their scores in the post-training assessment. In terms of statistical analyses, no significant changes were found, neither in the within-group nor between-group analyses.

4. Discussion

ITACA includes a set of features that are intended to provide an useful, versatile and easy-to-use framework for conducting novel NF studies. In the following paragraphs, the strengths of ITACA, and the novelties that it brings to the NF field will be discussed in depth. Afterward, these features are compared with existing frameworks. Finally, the results of the validation studies are assessed.

4.1. ITACA's strengths

One key feature of ITACA is its flexibility. The development of our framework is based on the fact that most researchers in the NF field are more specialized in the clinical and psychological aspects rather than in computer science and real-time signal processing [7]. For that reason, ITACA implements several highly-configurable elements that allow designing different training protocols without the need for programming new components. Three elements of ITACA are worth emphasizing in this respect: the metrics for online EEG analysis, the cognitive assessment apps and the NF training scenarios.

The variety of real-time EEG analysis metrics offered by ITACA is also one of the main novelties of our framework. ITACA includes the most commonly used metrics in NF studies (i.e., spectral power-based analysis). More interestingly, it also includes two training modes

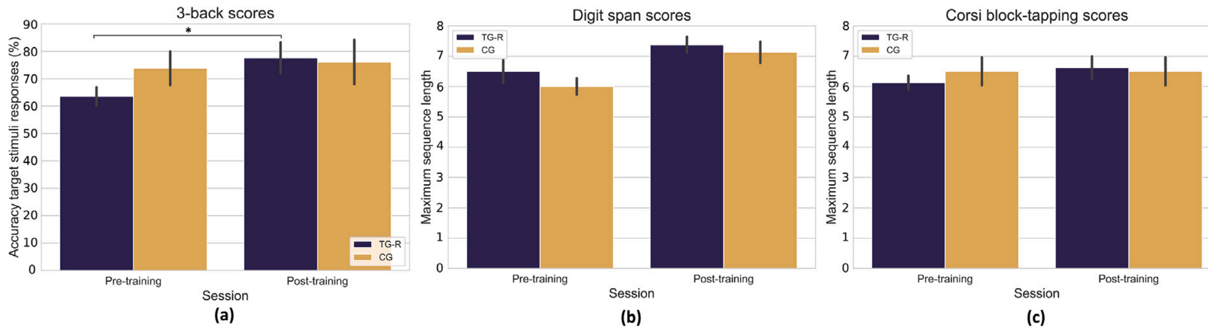

Fig. 6. Results and standard error means from cognitive assessment evaluations (pre- and post-training). Significant within-group increases relative to pre-training evaluation are marked with an asterisk ($p < 0.05$). (a) Accuracy of responses to target stimulus in 3-back tests; (b) maximum digit sequence length achieved in Digit span tests; and (c) maximum stimulus sequence length achieved in Corsi block-tapping tests.

based on functional connectivity and one based on network theory. It is noteworthy that these novel training modes can be performed using either phase-based functional connectivity analysis (wPLI) or amplitude-based functional connectivity analysis (AEC). Therefore, the number of training modes based on connectivity and network theory offered by our framework amounts to six. Since orthogonalized AEC and wPLI are functional connectivity metrics robust to the influence of volume conduction effect [22,23], their use ensures a reliable feedback during training. Although the use of the novel metrics included by ITACA to provide feedback in NF training is less widespread than power-based ones, there are some studies that have proposed it as an interesting feature for NF training, showing promising results [25,32]. In contrast to local activation metrics, which reflects local neural synchronization, functional connectivity metrics provide a more global insight of the brain synchronization [25,33]. Besides, network theory metrics, such as node strength, provide interesting information about the importance of each node in the brain network and how they relate to their neighbors [25,33]. In this regard, ITACA provides cutting-edge tools to further expand the state-of-the-art of NF research, offering the possibility to design new NF training protocols that match current trends in neuroscience research.

With regard to cognitive assessment apps, ITACA provides a comprehensive battery of computerized cognitive assessment tests of great utility both in NF studies and in neurocognition research. The wide range of cognitive functions they cover makes them suitable for use in NF studies that aim to alleviate the impact of various disorders such as ADHD [2], age-related cognitive decline [14] or major depressive disorder [34], or focus on enhancing the cognitive performance of healthy users [19]. In addition to the cognitive performance metrics it is possible to obtain from the applications, each of them can be used in conjunction with EEG and other biosignals recording equipments. This allows a detailed study of dynamic brain activity, as well as other physiological measurements associated with specific cognitive events. This practice is extremely useful in NF studies because, unlike other BCI paradigms such P300-based BCI, NF training requires a training hypothesis [7]. In this sense, it is necessary to gather information about specific brain patterns associated with cognitive functions in order to determine the brain activity to be trained. Thus, the cognitive assessment apps provided by ITACA are not only useful for evaluating NF outcomes, but also for designing the experimental protocol of an NF study.

ITACA offers three NF training scenarios, each with a different gamified design and neuromodulation objective. Voluntarily controlling certain patterns of brain activity has been shown to be a difficult process that requires a great deal of effort over the course of several NF sessions [3]. In this context, the availability of different NF training scenarios makes it possible to combine them with a twofold objective. On the one hand, it allows to design training protocols of progressive difficulty that, at first, allows the user to slightly control his neural activity and, subsequently, to optimize this process. Therefore, this combination of training scenarios could help to improve the control of target brain patterns by setting a difficulty adapted to the degree of control of the user. On the other hand, it avoids the excessive repetition of the same environment, which can negatively affect the user's motivation and performance in NF training [8]. Along the same lines, the gamification of scenarios seeks to increase user engagement while reducing the feeling of repetitiveness of NF sessions [10]. For this reason, the three different NF training scenarios included in the ITACA NF training app could be of great help in improving user performance and motivation in NF training studies.

Another important aspect of our framework is its easy-to-use design. All of our applications have GUIs that allow a quick and easy configuration. However, this design does not limit the versatility of the framework. In this sense, users of ITACA apps can design a variety of different experimental protocols in a simple and straightforward way without having to worry about the more technicall details related to real-time signal processing. It is worth noting that each of the applications allows the configuration settings to be saved and loaded. This makes it possible to share with other researchers the configuration used in a given experimental protocol [9]. In addition, extensive documentation on the features and tutorials for each application are provided. This is intended to make the process of learning to use the applications as easy as possible.

4.2. Comparison with other NF frameworks

ITACA provides a feature-rich framework that overcome the limitations found in available NF frameworks. Therefore, it is worthwhile to compare these features between ITACA and existing NF alternatives. This comparison is summarized in Table 2.

Regarding the availability of user-friendly GUIs for setting up and running NF training sessions, only NFBLab [13] and NFS [7] have a similar GUI in terms of design and ease of use. OpenViBE [12] and BrainBay [11] are frameworks that implement several examples of processing pipelines for NF application as configurable block diagrams. Although the provided pipelines are simple, these frameworks come with a number of tools for combining and designing personalized pipelines. This allows a great customization. However, given the simplicity of the examples provided, it is necessary to make in-depth changes to the pipelines to make them fit the actual needs of an NF study. Considering the block connection based design, this process may be too complicated for users unfamiliar with this type of environment.

Different training scenarios could increase user's motivation. However, this is generally not a widespread practice in the NF field. It could be due to the fact that some of the software used only provides one training scenario. This is the case for NFBLab [13] and NFS [7]. In turn, OpenVIBE [12] and BrainBay [11] implement more than one training scenario. Nevertheless, it should be noted that the scenarios provided are examples of what can be implemented with these frameworks. For this reason, as we mentioned before, these scenarios are limited in

Table 2
Comparison between different NF frameworks. Variety of training scenarios: if more than one NF training scenario is implemented; Power-based feedback: if feedback can be obtained from power spectral analysis; Connectivity-based feedback: if feedback can be obtained from functional connectivity analysis; Network-based feedback: if feedback can be obtained from metrics derived from network theory.

Platform	Easy-to-use GUI	Variety of training scenarios	Gamified training scenarios	Power-based feedback	Connectivity-based feedback	Network-based feedback	Cognitive assessment
NFS [7]	✓			✓			
BrainBay [11]		✓		✓			
OpenViBE [12]		✓	✓	✓			
NFBLab [13]	✓			✓	✓		
ITACA	✓	✓	✓	✓	✓	✓	✓

terms of configuration options and may require significant changes to suit the needs of a particular NF study. Therefore, only ITACA provides a wide variety of ready-to-use NF training scenarios. Focusing on the design of the training scenarios included in these frameworks, they tend to be more simplistic and monotonous. For instance, NFS [7] offers a two-dimensional square whose color changes according to the user's brain activity. Brainbay [11] includes different scenarios in which simple elements, such as a histogram, a wave or a sound, change when the user's brain activity is above a threshold. NFBLab [13] training scenario shows a circle with random boundary shape. The user has to smooth it increasing the target brain activity. Only OpenViBE [12] offers a gamified training scenario among the examples it provides. We believe that the simple design of the training scenarios offered by the majority of NF frameworks could negatively affect the motivation or even the performance of the users [8,10].

In terms of real-time EEG analysis metrics, all of the current NF frameworks include the possibility of calculating the feedback using spectral power based analysis. However, the availability of analysis parameters based on functional connectivity and network theory is more limited. In this sense, only NFBLab [13] includes the option to use a metric based on functional connectivity to obtain the real-time feedback. However, the implemented metric is the coherence, which has been pointed out to be sensitive to the volume conduction effect [23]. Therefore, the use of this metric for feedback is less recommended than more robust metrics such as orthogonalized AEC [22] or wPLI [23]. On the other hand, OpenViBE [12] includes among its analysis functions some coherence-based metrics. However, this framework does not provide as an example any already designed NF training pipeline that includes such metrics. Accordingly, this must be addressed by researchers, which can be challenging in terms of optimal real-time signal processing for researchers with limited signal processing knowledge. Therefore, in view of the comparison, we can state that ITACA has the widest offer of NF training modes.

To the best of our knowledge, none of the existing NF frameworks include computerized assessment tests. Given the importance of these tests in both the design and evaluation of NF training protocols, their use is necessary in almost all NF training studies. Therefore, ITACA is the only NF framework that provides all the necessary tools to accomplish all stages of an NF study without the need for additional software.

4.3. Efficiency analysis discussion

The study of computational efficiency of real-time analysis metrics implemented in ITACA NF training app indicated that all these metrics fit the recommended latency values [6]. That is, no metric exceeds a latency of 350 ms [6]. This is the case even for functional connectivity and network theory metrics, whose computation is more complex than that of metrics based on spectral power. Therefore, these results support the suitability of ITACA real-time analysis metrics for providing optimal feedback in an NF training session. In addition, the user can track his own computation times with the display included in the training scenarios of the NF training application. In this way, the user can easily evaluate on their own device a paramount factor of NF training, such as the rate of feedback updates.

4.4. Functionality validation discussion

4.4.1. Change in fm-theta power

The analysis of the evolution of fm-theta power over the NF training sessions showed a remarkable increase only in the TG-R participants. The influence of NF training conducted was confirmed by the significant main effect of *group* in the ANOVA test. Noteworthy, the fm-theta increment values obtained in our validation study were higher than those reported in previous studies which carried out a fm-theta up-regulating protocol [19,28]. On average, the maximum increase in these studies was 8–14% with respect to the activity of the first session, whereas in our study it increased by 26% in average, reaching a maximum increase value of 35% in the fourth session. In contrast to our experimental protocol, these studies did not follow a training of progressive difficulty. The use of a single NF training scenario with a fixed difficulty from the beginning could limit the evolution of the subjects during training (e.g., excessively high neuromodulation objectives in the first sessions may negatively influence the motivation of the subjects or the development of optimal training strategies). Therefore, our results have proven the efficacy of ITACA NF training scenarios to improve target brain activity. Furthermore, they also point out that the use of different NF training scenarios could be beneficial in improving the performance of training subjects.

4.4.2. Motivation and mental fatigue

It was observed that the motivation reported by users from both groups remained high during all sessions. Nevertheless, TG-R values were higher than CG values even from the first training session. This could be explained by the fact that these reports were made after the end of each session and part of the TG-R participants achieved some degree of volitional control over fm-theta modulation in their first training session. On the other hand, it is worth noting that these motivation values (both TG-R and CG) were higher than those reported in a previous study which followed a similar seven-point Likert-scale [21]. As mentioned, a common practice among NF studies is to employ a single training scenario with a fixed level of difficulty throughout the protocol [20,21,27]. Therefore, this greater motivation reported by users in our study may be due to the fact that the introduction of different training scenarios kept the subjects engaged and committed to improve throughout the training. With regard to mental fatigue, the significant effect of the *session* factor obtained in the ANOVA test indicates a similar change over sessions in mental fatigue reported by TG-R and CG subjects. It is suggested that the decrease in fatigue ratings from sessions 2 to 4 could be related to a greater mental effort made by users in the first sessions to find an optimal neurocognitive strategy that allowed them to reach voluntary control over feedback. On the other hand, the increase observed in the last two sessions could be due to the increased use of "Neuro runner", which is the most cognitively demanding of the three scenarios.

4.4.3. Change in cognitive test performance

Of the three cognitive assessment tests performed, only the 3-back test showed a significant improvement in the TG-R scores with respect to the pre-training evaluation. The *N*-back task is a commonly used measure of central executive function, which is considered the most important element in Baddeley's model of working memory [26]. Several studies have shown an association between executive functioning and the frontal lobes [21,29]. On the other hand, two of the systems dependent on the central executive are the phonological loop and the visuospatial sketchpad [26]. The phonological loop is responsible for processing phonological information and has been suggested to be located in the left tempoparietal cortex [26]. Meanwhile, the visuospatial sketchpad processes visual and spatial information and is distributed in different lobes of the right hemisphere [26]. Considering this, it is suggested that the significant improvement observed for the TG-R only in the 3-back test could be due to the specificity of the NF training performed. In this regard, only the N-back task is spatially related to the trained brain activity, while the Digit span and Corsi block-tapping tests assess the phonological loop system and the visual sketchpad, respectively. To corroborate this hypothesis, further studies with a larger study population and a higher density of EEG channels would be desirable.

4.5. Limitations and future work

Despite the wide variety of options included in ITACA and the promising results obtained in its validation studies, we acknowledge that there are some limitations that need to be addressed. Firstly, our framework has potential for future enhancements, including the incorporation of additional metrics for feedback calculation to increase its versatility, and expanding ITACA's usability with other brain activity recording methods like magnetoencephalography or functional magnetic resonance imaging. To further improve the framework, a forum entry (https://forum.medusabci.com/d/6-itaca-issues) has been facilitated for people to share their suggestions. This, together with the fact that the code of our applications is open access, makes it possible to develop this framework in a collaborative way by the scientific community. Secondly, there are several promising features that are not yet included in ITACA, such as training scenarios with virtual reality or a multiplayer option. These features could contribute to improve the user experience during training [10], as well as their results [8], so it would be interesting to include them in future ITACA updates. Finally, we acknowledge that the population used in our validation study may be limited. This is a common problem among NF studies, as it requires users to perform a considerable number of training sessions to get their brain activity under control. Indeed, the framework has only been tested in a group of healthy young people. ITACA functionalities need to be further tested in other NF studies focused on cognitive enhancement in healthy individuals, but also need to be tested in NF studies aimed at improving cognitive functions in individuals suffering from brain disorders.

5. Conclusion

This paper presents ITACA, a novel open-source framework for NF training based on BCI systems. ITACA aims to the limitations found in the current NF frameworks. In this regard, it presents easy-to-use and highly configurable apps that allow the design, implementation and evaluation of NF training studies without prior knowledge of computer science. Of note, it provides a wide range of analysis metrics for real-time feedback, including power-based, functional connectivity and network theory metrics. All this, together with its three gamified NF scenarios and five computerized neurocognitive tests, makes ITACA one of the most feature-rich NF frameworks currently available. Its efficiency was assessed in a computational time analysis, while its functionalities were tested in a NF training protocol with 19 healthy users. The results of these validation studies support the suitability of ITACA in NF studies to further expand the state-of-the-art of NF research.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Roberto Hornero** reports financial support was provided by Spain Ministry of Science and Innovation.

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