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Abstract

The clinical efficacy of neurofeedback is still a matter of debate. This paper analyzes the factors that should be taken into account in a transdisciplinary approach to evaluate the use of EEG NFB as a therapeutic tool in psychiatry. Neurofeedback is a neurocognitive therapy based on human-computer interaction that enables subjects to train voluntarily and modify functional biomarkers that are related to a defined mental disorder. We investigate three kinds of factors related to this definition of neurofeedback. We focus this article on EEG NFB. The first part of the paper investigates neurophysiological factors underlying the brain mechanisms driving NFB training and learning to modify a functional biomarker voluntarily. Two kinds of neuroplasticity involved in neurofeedback are analyzed: Hebbian neuroplasticity, i.e. long-term modification of neural membrane excitability and/or synaptic potentiation, and homeostatic neuroplasticity, i.e. homeostasis attempts to stabilize network activity. The second part investigates psychophysiological factors related to the targeted biomarker. It is demonstrated that neurofeedback involves clearly defining which kind of relationship between EEG biomarkers and clinical dimensions (symptoms or cognitive processes) is to be targeted. A nomenclature of accurate EEG biomarkers is proposed in the form of a short EEG encyclopedia (EEGcopia). The third part investigates human-computer interaction factors for optimizing NFB training and learning during the closed loop interaction. A model is proposed to summarize the different features that should be controlled to optimize learning. The need for accurate and reliable metrics of training and learning in line with human-computer interaction is also emphasized, including targeted biomarkers and neuroplasticity. All these factors related to neurofeedback show that it can be considered as a fertile ground for innovative research in psychiatry.

Keywords

Neurofeedback; EEG; Neurophysiology; Psychophysiology; Brain Computer Interface; Training; Learning

Outline

Introduction

Neurofeedback (NFB) is a neurocognitive therapy based on human-computer interaction. The objective of NFB is to enable subjects to voluntarily train and modify functional biomarkers that are specific to mental disorders, in order to improve symptoms or cognitive processes. In psychiatry, a biomarker is usually a psychophysiological variable that is objectively measured and evaluated as an indicator of pathogenic processes or therapeutic responses [71]. However, most of the current electroencephalographic (EEG) NFB protocols are not based on the modulation of disorder-specific biomarkers but on the modulation of a few spontaneous *brain rhythms*, mainly defined by the frequency of their oscillation [2, 55, 57]. This strategy is prevalent since spontaneous brain rhythms demonstrate a high signal-to-noise ratio in EEG recordings, and because they can be disrupted in some mental disorders, *e.g.* increased theta and reduced beta power in patients with Attentional Deficit and Hyperactivity Disorder (ADHD) when compared to healthy controls [3]. However, the clinical efficacy of this approach remains a controversial and delicate issue even for well-investigated applications, such as the therapeutic use of EEG NFB in ADHD [14, 54]. Indeed, the effectiveness of neurofeedback is largely debated [22, 56, 79, 80]. In this paper, we propose that several factors related to the concept of biomarker may be responsible for the conflicting results in the EEG NFB literature:

(i) Limited understanding of the brain mechanisms driving NFB learning to modify a functional biomarker voluntarily, *i.e. neurophysiological factors* [22],

(ii) The inconsistent relationship between EEG biomarkers and clinical dimensions (symptoms or cognitive processes), potentially due to the symptom-based classification of psychiatric disorders and the heterogeneity of diagnostic categories, *i.e. psychophysiological factors* [25]

(iii) Superficial knowledge of how best to measure and optimize NFB learning during the closed loop interaction, *i.e. human-computer interaction factors* [36].

This paper investigates these factors (*neurophysiological*, *psychophysiological* and *human-computer interaction*) in a critical review of the existing literature on EEG NFB. The objective is to integrate these interdependent issues into a general NFB framework in order to demonstrate that EEG NFB can be considered as fertile scientific ground for psychiatry and to provide a roadmap for future research in this field.

Neurofeedback and its neurophysiological foundations

From electroencephalographic oscillations to neurofeedback

The EEG may be recorded via non-invasive electrodes placed on the scalp as a result of intracranial fluctuations of electromagnetic field potentials, which are generated by ionic exchanges at cell membranes and synapses during neuronal activity. When neuronal activities occur in a circumscribed region and become temporally synchronized, their local field potentials (LFPs) are then spatially summated, giving rise to large fluctuations of the EEG signal [84]. Hence, changes in EEG oscillation amplitude essentially reflect the degree of synchronization of intracortical neuronal populations. Synchronization is influenced by both the intrinsic excitability of the neuronal population and the synaptic input it receives from other regions. Hence, intra- and inter- electrode EEG measures of amplitude and coherence indicate neuronal excitability within and functional segregation/integration between cortical regions, respectively [17]. Moreover, this dynamic activity can occur simultaneously on different timescales (i.e. frequencies): infraslow (<1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), beta (15–30 Hz), and gamma (>30 Hz). Studies involving patients with mental disorders have reported significant deviations in a host of task-related and resting-state EEG parameters (e.g. amplitude, coherence) compared to healthy controls [13].

Thus, NFB has been developed in these patients mostly to correct notable deviations of cortical oscillations by training subjects to modify their EEG activities. In this perspective, the impact of NFB is thought to be based on the training and subsequent normalization of specific "targeted" neurophysiological signatures to reduce the clinical symptoms related to a given disorder. It has been also postulated that, to achieve therapeutic efficacy with NFB, it is important to demonstrate significant *online* self-regulation of the trained parameter(s) (i.e. during NFB). After which, long-term *offline* changes might be induced through mechanisms of neuroplasticity (i.e. of functionally persistent brain reorganization after termination of NFB training) [74]. Thus, in the simplest scenario, the incremental process of NFB "learning" can be seen as the direct sum of two principal factors:

1) the online component, i.e. the within-session change of the trained signal relative to its resting-state baseline, also called "performance" in the field of Brain Computer Interface - BCI, and

2) the offline component, i.e. the absolute change of the between-session resting-state baseline, which may be related to “skills acquisition”.

Surprisingly however, there is a scarcity of BCI/NFB studies that examine these online and offline criteria in combination. Moreover, a better definition of online/offline metrics would enable a more rigorous assessment of NFB protocols and BCI training [46] together with their impact on brain plasticity [67] (see last section on *human-computer interaction factors*) and the impact of structural and functional brain traits on plasticity [28]. This first section focuses on the basis of neuroplasticity during NFB.

From electroencephalographic oscillations to neuroplasticity

The dynamic modulation of EEG oscillations using NFB may induce different types of neuroplasticity [67]. Neuroplasticity in general may be defined as a durable (i.e. long-term) change in neural function outlasting the training period itself, underpinned by long-term modification of neural membrane excitability and/or synaptic potentiation. In practice, one may expect long-term plasticity to manifest itself during resting-state EEG recording(s) *outside of* training sessions (i.e. offline), and/or as progressive changes *during* repeated training sessions (i.e. online). Based on the neuroscience literature, there are two main forms of neuroplasticity: the Hebbian type and the homeostatic type.

The underlying mechanism of Hebbian plasticity is *correlation-based*. Hence, NFB-induced Hebbian plasticity may be expected to produce functional changes that occur *in the same direction* as that dictated by the NFB protocol (e.g. long-term alpha increase following alpha-upregulation NFB) [92]. On the other hand, since homeostasis attempts to stabilize network activity within a bounded range, homeostatic plasticity is not correlation-based and may be expected to produce changes in the opposite direction of NFB training (e.g. long-term alpha increase following alpha-downregulation NFB) [40]. Generally, synaptic potentiation brain oscillations are closely linked, given that changes in neuronal coupling directly affect levels of neuronal synchronization, and vice-versa.

Hebbian plasticity and neurofeedback

Historically speaking, pioneering experiments in the 1960s that demonstrated self-regulation of the EEG [39] were followed by reports that NFB training of spindle oscillations during wakefulness may result in their stronger expression during sleep [77]. Recent studies provide convincing data that NFB can be used to induce plastic *increases* of *theta*, *alpha*, *beta*, and

gamma rhythms, as well as their corresponding *decreases* [74]. However, the exact neurophysiological mechanism(s) behind the long-term conditioning of brain rhythms remain unclear.

Given common observations that plasticity manifests in the same direction/frequency targeted by the NFB protocol, Ros and colleagues proposed a mechanism based on associative (i.e. Hebbian) plasticity and encapsulated by the phrase [67]: "synapses that fire together wire together, and synapses that fire apart wire apart". This type of correlation-based plasticity occurs when connectivity is reinforced by temporally-coincident neuronal activation. As explained in the section above, EEG oscillatory amplitude positively covaries with the degree of synchronized neurons/synapses, see **Figure 1.**

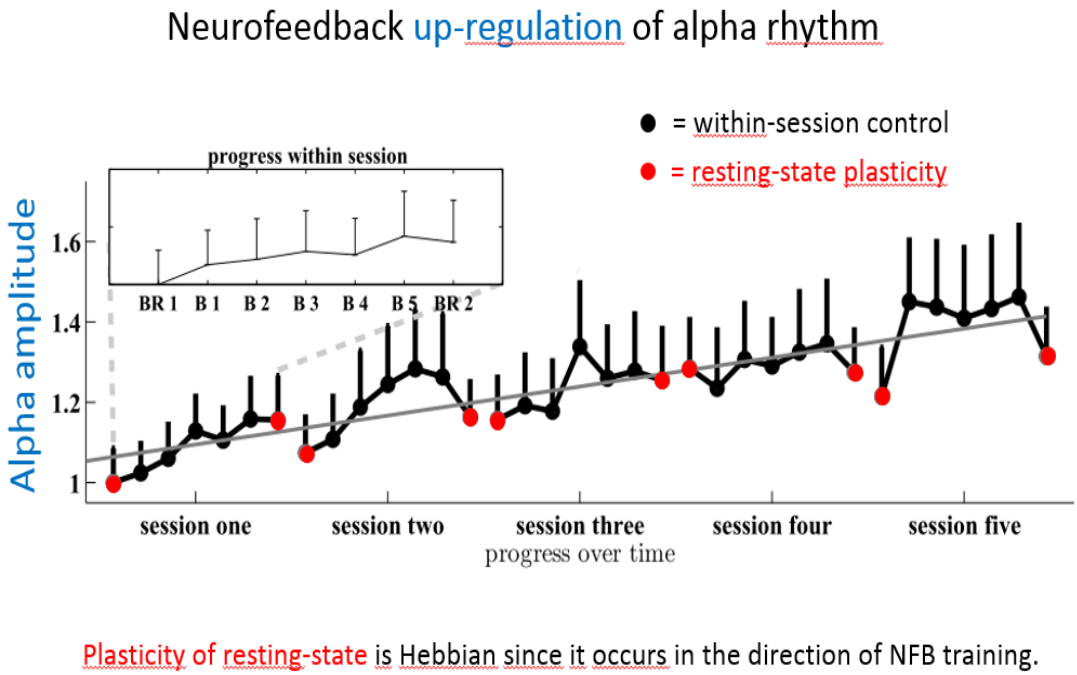

Figure 1: An example of Hebbian-type neuroplasticity mechanism subsuming neurofeedback training with experimental data on alpha rhythm up-regulation (adapted to experimental data from [20]).

Hence, during amplified oscillations, synchronized neural populations involved in generating this oscillatory pattern would, after some time, strengthen the connections between themselves, and further facilitate the oscillation to emerge in the future. Conversely, maintaining a cortical region in a low-amplitude ("desynchronized") state would reduce synaptic correlations and weaken the connections that give rise to synchronization. Encouragingly, recent experimental work provides support for this mechanism outside of

NFB, reporting up-regulation and down-regulation of cortical oscillations using synchronizing and desynchronizing patterns of stimulation, respectively [67, 74].

Homeostatic plasticity and neurofeedback

Animal research has consistently revealed the presence of an additional form of plasticity referred to as 'homeostatic' plasticity, which actively counteracts the Hebbian type so as to prevent its unlimited expression [67]. Otherwise, unchecked Hebbian plasticity would inevitably lead to pathologically high or low neural connectivity, firing or synchronization. Hence, from the point of view of NFB, one would anticipate homeostatic forms of plasticity to produce changes opposite to the direction of training. Early observations within this context were made by Kluetsch and colleagues [40], who reported that following down-training of alpha rhythm, patients with Post Traumatic Stress Disorder (PTSD) displayed a paradoxical increase in alpha rhythm above and beyond its resting-state value. Since PTSD patients are found to exhibit significantly low alpha amplitude at baseline relative to healthy subjects, a recent framework proposed that this might reflect homeostatic regulation of the excitation/ inhibition balance [67, 68].

Towards new neurophysiological measures of neuroplastic effects of neurofeedback

In addition to EEG-based measures, the neuroplastic effects of NFB have started to be explored using several other techniques, including transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). For example, a single 30-minute session of NFB alpha downregulation has been found to enhance cortical excitability, as measured by a plastic (>20 minute) increase in TMS-induced motor evoked potentials after training [69]. Of note is also the observation of reduced intracortical inhibition, in view of its established association as a cortical state that facilitates plasticity and learning [8]. Elsewhere, fMRI has shown that NFB may induce plastic changes in cortical hubs responsible for cognitive control such as the dorsal anterior cingulate [30], which was associated with improvements in symptoms of ADHD [42] or on-task mind wandering [70]. fMRI studies shown also that NFB training can induce plasticity in patients with mental and brain disorder that may engage other regions and circuits implicated in the physiopathology [61] and that may be correlated with clinical amelioration [91]. Lastly, data from a DTI study make an encouraging case for NFB affecting white matter and grey matter [27].

In closing, this first section has focused on the neurophysiological foundations of EEG NFB, which enable it to be used as a unique therapeutic tool for targeting specific neural activities and inducing neuroplasticity. However, beyond basic up- or down- regulation of brain rhythms, the central challenge of NFB is to target clinically relevant biomarkers that are consistent with the psychophysiological foundations of mental and brain disorders. The following section focuses on this challenge.

Neurofeedback and its psychophysiological foundations

Dimensional approach for neurofeedback in psychiatry

Because the psychiatric nosology has weak biological grounds, on the one hand, and because the link between biomarkers (electrophysiologic biomarkers in particular with EEG or metabolic biomarkers with functional neuroimagery) and cognitive processes remain mostly unraveled, on the other hand, it is impossible to confirm the functional specificity of current NFB EEG biomarkers. In fact, contemporary psychiatry is undergoing a taxonomic crisis that is characterized by the poor diagnostic power of current nosology [15]. Interestingly, in 2010, the National Institute of Mental Health (NIMH) proposed a dimensional approach to circumvent this issue. For Insel et al., the current symptom-based classification probably does not reflect the pathophysiological mechanisms that underlie mental disorders [31]. The aim of the Research Domain Criteria (RDoC) project is to conceptualize mental illnesses as brain disorders with pathophysiological features represented by a reliable and validated continuum from the clinical to the genetic, all defined by tools from neuroscience [31]. Such an approach could be very useful in the field of NFB research applied to mental disorders. By targeting specific biomarkers related to well identified symptoms or cognitive processes, the psychophysiological rationale underlying NFB therapy should be stronger and its efficacy probably greater. Importantly, although the quality of EEG recordings and the design parameters of NFB protocols (e.g. the number of sessions per week) are essential variables to be optimized to foster training, their optimization will never overcome the putative deleterious effects of our current lack of precise knowledge about the underlying brain/mental processes. We advocate here that acknowledging this fundamental limitation is a useful starting point to guide the research and development of future NFB therapies. Furthermore,

this limitation holds whatever the functional modality used to record brain activity (electrophysiology, fMRI, fNIRS, etc.).

As the first step to overcome this limitation, we consider it essential to inventory and refine the existing list of EEG biomarkers and associated cognitive functions. In the following section, we propose an "EEGcopia" to illustrate the need to rely on EEG biomarkers that are strongly linked to symptoms or cognitive processes. We discuss this concept of EEGcopia below and provide a preliminary list that highlights the need to link psychiatric nosology and putative biomarkers with clinical dimensions such as executive function, emotion regulation and reward processing (see **Supplementary material**). The opportunity to construct new therapeutic hypotheses based on other EEG and putatively more specific biomarkers than those used so far in NFB is illustrated in two concrete and very topical fields of NFB/psychiatric research: depression and ADHD.

A proposed EEGcopia for neurofeedback in psychiatry

Most NFB investigations to date have focused on a limited set of EEG frequency ranges (the two most famous being the $\frac{\theta}{/\beta}$ ratio and the Sensory Motor Rhythm - SMR). However, there are several other known correlates of cognitive functions that could be used as potential target biomarkers. Indeed, one can extract numerous biomarkers from EEG signals such as discrete EEG events like event-related potentials (ERP), measures of complexity, or local and long distance neural synchrony, which could have potential NFB applications. The use of these EEG biomarkers for NFB has received little attention until now. We introduce here a brief nomenclature of cognitive functions (see **Supplementary material**), together with their known EEG biomarkers. Dimensional EEG biomarkers of cognitive functions with known neural correlates of sensory processing, executive functions, emotional cognition, memory, embodied cognition and social cognition are presented. This short EEG encyclopedia (EEGcopia) reflects the main theories linking EEG and cognitive dimensions in neurophysiology. A more complete and exhaustive EEGcopia would be of great help to the NFB community.

Among the different biomarkers listed, Event Related Potentials (ERP) for NFB open up new avenues for application. The numerous publications on BCI based on the real-time detection of P300 demonstrate the feasibility of this approach [87]. Recent studies have generalized these results to other ERP components, such as error negativity (ERN) [9] and auditory mismatch negativity (MMN) [7]. However, each ERP has its specific properties, such as

differences in refractoriness [88], which may limit their detection rate for real-time applications and make them usable only for discrete delayed feedback. Another promising candidate is the use of classification algorithms targeting specific dimensions. For instance, arousal detection using the VIGALL algorithm [60] was recently used to investigate brain mechanisms, and it can also be used to design efficient NFB strategies [29].

Linking brain / mental processes and psychiatric disorders

The emblematic research field of depression

Which innovative biomarker could be relevant to treat depression? Recently, Rayner et al. published a comprehensive review of cognition-brain related networks of depression [65]. This neurocognitive hypothesis of depression could be an interesting basis for an applied reflection on the choice of the most relevant target for NFB. Three main networks are involved: autobiographical memory (AMN), affective (AN) and cognitive control networks (CCN) [65]. The former is involved in self-referential cognitive processing and the latter in the ability to perform goal-directed tasks. The authors postulated that AMN is hyperactivated (self-referential cogitation and congruent emotional processing) over the CCN, which is deactivated during a mood depressive episode. This state is also associated with AN overactivation which is linked with deficit of cognitive control network activity and postulated having a key role in dysfunction of mood regulation. This model highlights the central role of cognition (and its neural substrates) in regulating affective symptoms and autobiographical memory in depression [65]. This cognitive dimension could be a promising therapeutic target for NFB instead of more conventional therapeutics. However, the best psychophysiological signal related to this cognitive dimension remains to be determined.

Most of the literature on EEG-NFB has focused on alpha asymmetry but with controversial results concerning its efficacy. In fact, EEG-NFB protocols on depression enhance cognitive functioning [20] but have failed to have any effect on emotional and mood features (for review; see Arns et al., 2017 [2]). As alpha asymmetry protocol is identified as a promising EEG-biomarker for depression [12], one recent open label trial proposed to work on another psychophysiological signal such as beta power band and alpha/theta training [11]. This latter has shown that combined NFB on EEG-biomarkers of cognitions could be critical in depression. Mehler and colleagues has questioned the specificity of EEG NFB from emotion-regulating areas and its efficacy on depressive symptoms. Interestingly, fMRI-NFB has been described as an effective treatment for depression by targeting limbic areas involved in

emotional processing [43]. Through a single-blind trial, they have highlighted that experiencing self-regulation may probably be therapeutic, irrespective of brain areas targeted (emotional or higher visual area) [53]. Elsewhere, Young and colleagues has exhibited that amygdala fMRI NFB upregulation in a task of autobiographical memory is linked with decreased of anxiety and increase of happiness ratings [90]. They have confirmed this result in a randomized control trial in which residualized amygdala activity is a mediator of the relationship between residualized positive specific autobiographical memory recall and residualized MADRS score at follow-up [89].

Taken together, these data highlight that both cognitive and emotional/limbic areas might be relevant for therapeutic NFB-protocols in depression. But to date, there is a lack of data on the effect of EEG NFB working on both sides of depression, emotion and its cognitive regulation. Based on the cognitive dimension of depression [65], it can be hypothesized that the ultimate NFB should disengage the emotional cognitive processes of AMN, strengthen cognitive processes oriented to external stimuli (CCN), and strengthen working memory. Therefore, NFB targeting both AMN and CCN should fit this issue well. Some recent work on NFB has proposed to combine EEG and fMRI in order to provide a more specific self-regulation of these targets [50, 62]. These studies suggest that bimodal/simultaneous EEG and fMRI NFB could be more specific and more engaging than EEG-NFB alone. Zotev et al. have demonstrated its feasibility and potential in depression [93, 94]. This perspective seems to be of great interest for targeting complex psychophysiological processes involved in mental disorders such as depression.

The emblematic research field of ADHD and P300-based training

Which innovative biomarker could be relevant to treat ADHD? The effectiveness of classical EEG NFB, targeting the $\frac{\theta}{/\beta}$ ratio and the Sensory Motor Rhythm – SMR, in ADHD remain debated [5, 10, 16, 75, 81, 82]. Four meta-analyses studies analysed the therapeutic usefulness of EEG NFB in ADHD [4, 14, 54, 76]. The results of these meta-analyses depend of the choice of studies included, in particular if a criteria concerning the training during the neurofeedback protocol was added to include a study in the meta-analysis. Moreover, it should be noted that the classical EEG biomarker chosen in ADHD is probably not the most valid concerning the physiopathology of the disoder. Thus, P300 based training has been recently proposed.

The P300 is a large positive complex that reaches its peak at approximately 300 milliseconds after stimulus onset and is composed of two subcomponents, a frontal P3a reflecting attentional capture by some external stimulation, followed by a parietal P3b elicited by the voluntary orientation of attention [64]. The amplitude of the P300 grows with the amount of attentional resources engaged in processing the external event [37]. Although this biomarker has never been used for NFB, it is very much used online for controlling BCI applications such as the P300 speller [51]. With this interface, items are selected on screen based on the orientation of spatial attention. Interestingly, the same principle can be used in engaging EEG-controlled video games [49]. Such games offer a motivating training environment, may include strategic components (e.g. “Connect Four”) and rely on clear instructions about the requested mental effort to be produced in order to control the game and possibly win (e.g. focus spatial attention and avoid being distracted). Interestingly, the P300 is known to be altered in children with ADHD [38]. It is also a marker of treatment efficacy as P300 amplitude has been shown to return to normal levels in patients who respond positively to methylphenidate [72]. This has led to an ongoing clinical trial to evaluate the usefulness of P300-based training in children with ADHD [21]. If successful, this trial will support the extension of this kind of training to other pathological states associated with impairment in selective attention.

This second section has focused on the psychophysiological foundations of NFB applied to mental disorder and has demonstrated how it should be related to a better definition of biomarker in order to target neural activities specific to symptoms or cognitive processes. However, even if the chosen biomarker is strictly related to symptoms or cognitive processes, it should also be verified that it is effectively modified during the NFB sessions. Moreover, it should be studied the impact of control beliefs [86], i.e., participants’ beliefs that their efforts to learn would result in a positive outcome, and self-efficacy [6], which can be defined as participants’ beliefs in their own abilities to manage future events, on the NFB training. Surprisingly, this domain on which the following section focuses remains a major challenge for NFB, and the field of BCI is of great interest to enhance knowledge on optimized training and learning for NFB in psychiatry [22].

NF and BCIs are traditionally underlain by different methods. In NF, the target neurophysiological pattern (location, frequency) is usually defined in advance. Users are asked to figure out by themselves how to self-regulate this pattern. In BCI however, a machine learning approach is most of the time employed. Such an approach consists in using

signal processing algorithms in order to determine the location and frequency of the target neurophysiological pattern that enables the best discrimination between different states (e.g., motor-imagery task vs. rest). In case of a BCI involving left vs. right-hand motor imagery tasks, these EEG patterns would theoretically correspond to modulations of sensorimotor rhythms. However, when a pure machine learning approach is used (i.e., without any a priori on the location/frequency of the pattern), as is mostly the case in BCIs, other EEG patterns could be selected.

Neurofeedback and its human-computer interaction foundations

A human computer interaction model for neurofeedback

To globally improve NFB efficacy in patients, it is necessary to understand and then reduce its variability. To this end, Sitaram et al. (2016) and Gaume et al. (2016) have reviewed the neurophysiological [74] and neuropsychological [25] mechanisms underlying NFB training procedures. In addition, Enriquez-Geppert et al. (2017) have proposed a tutorial explaining how to design rigorous NFB training protocols [19]. While Sitaram et al. (2016) and Gaume et al. (2016) adopted a standpoint purely centered on "human learning" (*i.e.* centered on the psychological and neurophysiological mechanisms that enable patients to learn how to self-regulate specific neural substrates), Enriquez-Geppert et al. (2017) focused on "machine learning" (*i.e.* centered on the technological factors, especially signal processing and machine learning, potentially impacting performance). These papers offer insightful elements to understand and reduce the variability of clinical NFB efficacy.

When studying user training in NFB and BCI, it is indeed essential to consider the impact that both machine and user learning can have, and how they interact with each other. In the EEG-based NFB/BCI context, machine learning usually aims at learning from examples of EEG data the user-specific EEG patterns corresponding to the target to self-regulate [44]. For instance, machine learning can be used to identify the spectral and spatial components of a user EEG signals that vary with different attention level (e.g., for ADHD NFB). Most BCI and most fMRI-NFB use machine learning techniques, while most EEG-NFB do not [35, 74]. When machine learning is used, the success of the NFB/BCI training thus depends in part on the machine learning algorithms used. On the other hand, user learning is involved in both NFB and BCI, in particular in Mental Imagery BCI [32]. User learning refers to the user

learning to self-regulate increasingly better the target neurophysiological pattern by learning from the feedback she receives during NFB/BCI training. The success of the NFB/BCI training thus also depends on the quality of the user learning, which in turns depends on the feedback and training tasks used. If machine learning is used, both machine learning and user learning interact: the machine learns to recognize the EEG patterns of the user, while the user learns to produce EEG patterns that will be recognized by the machine. This is a form of co-adaption or co-learning between the machine and the user [83]. Unfortunately, while this co-learning is very common in BCI and NFB, how it works and how its impacts NFB/BCI training is still mostly unknown. An open challenge is thus to understand and model this co-learning, in order to design BCI/NFB training with feedbacks and machine learning algorithms whose interaction will favor an effective self-regulation and clinical outcome [47].

Thus, as illustrated in **Figure 2**, uni-centered approaches are not sufficient to reach a deep understanding of the NFB training process. "A human-computer interaction/human-factor standpoint", like the one proposed by Alkoby et al. (2017) [1] and Jeunet et al. (2017&2018) [34, 35], is also needed to understand how, depending on their profile (i.e., psychological, cognitive and neurophysiological states and traits), patients interact with the training protocol and what the consequences of this interaction on learning and on clinical efficacy are. In fact, we have proposed a model combining factors that influence learning in Brain Computer Interface (BCI) and NFB (NF) [34]. The model is based substantially on the BCI literature and more specifically on Mental-Imagery-based BCIs (MI-BCIs) [33, 36]. MI-BCIs are neurotechnologies that enable a user to control an application through the completion of mental-imagery tasks such as imagining movements, *i.e.*, motor-imagery, that are associated with a specific modulation of the user's brain activity. Therefore, as is the case in NFB applications, MI-BCI users have to learn to modulate a target neurophysiological substrate. Consequently, the literature on BCI is of interest to better understand the factors influencing learning in NFB.

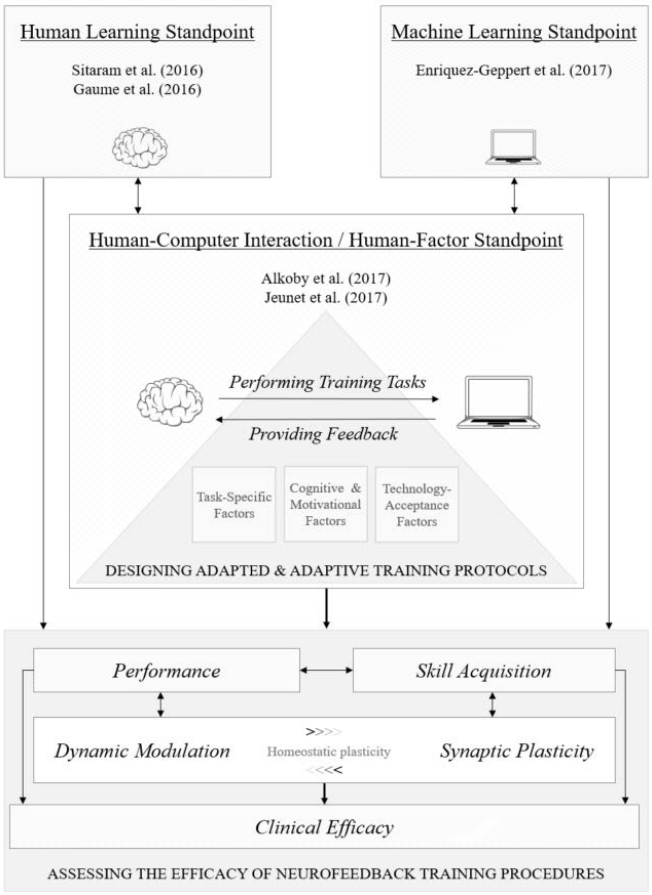

Figure 2: Schematic representation of proposed approach. While some studies contribute to improving the efficacy of neurofeedback procedures by adopting either purely "human-learning" or "machine learning" standpoints, we posit that a "human-computer interaction / human-factor" approach would enable deeper understanding of the processes subsuming neurofeedback-related performance and skill acquisition, and thus improve its clinical efficacy. This would provide insights into how users' traits and states impact the efficacy of neurofeedback, notably through three types of factors, and allow training tasks and feedback to be adapted in order to better grasp the interaction and improve the efficacy of neurofeedback. For an extensive description of the factors involved in the model, see [54, 55]. Moreover, we believe that neuroplasticity indicators are important intermediate variables to be considered between NFB training/learning and clinical efficacy. We distinguish two kinds of neuroplasticity indicators: dynamic modulation indicators and synaptic plasticity (also called Hebbian plasticity) indicators. For an extensive discussion on neuroplasticity and neurofeedback, see [17, 19].

The model in **Figure 2** includes three categories of factors: task-specific, cognitive/motivational and technology-acceptance related factors. As this model focuses on

MI-BCIs, the task-specific factors refer to spatial abilities, *i.e.*, the ability to produce, transform and manipulate mental images. It is likely that in other kinds of BCI or NFB paradigms, different task-specific factors related to the targeted neurophysiological will have to be identified. The other two families of factors are more generic and do not depend upon the BCI/NFB paradigm used. They include, on the one hand, factors related to cognitive and motivational traits and states, and on the other hand, factors related to patients' acceptance of the technology, *i.e.*, the way they perceive the technology and consequently the way they will interact with it, *e.g.*, to what extent they feel in control as well as their anxiety or confidence. The model suggests that the learning process during BCI or NFB training procedures is influenced by patients' traits and states, which in turn are modulated by the perception of the technology. By considering these factors, one could design training protocols and feedback adapted to the profile of each patient and adaptive to the evolution of their states and skills as they evolve during the course of BCI or NF. Both the training tasks and the feedback can be adapted (*i.e.*, specific to the patient's profile - traits and states - estimated at the beginning of training) and adaptive (*i.e.*, modified dynamically during training to fit the evolving state of the patient) in order to optimize the learning process. The first subsection is dedicated to a review of the literature on how to design efficient adapted and adaptive training tasks and feedback. Then, to evaluate the efficacy of NFB training procedures, relevant metrics of performance, skills acquisition and clinical efficacy are needed. However, to date such relevant metrics have received little attention. Thus, the second subsection describes some metrics dedicated to assessing users' performance and skills and then discusses the relationship between these metrics and the clinical efficacy of NFB procedures.

BCI principles to adapt training tasks and feedback in neurofeedback

Based on an analysis of the literature, the following paragraphs present insights on how a training protocol may be adapted. The protocol comprises two main parts: training tasks and feedback. Indeed, during BCI/NFB training, the patient performs different training tasks according to the instructions provided by the system or experimenter, so as to self-regulate their EEG. They are then provided with feedback from the machine to inform them about the quality of their EEG self-regulation (see **Figure 2**). Thus, training tasks are neurocognitive exercises that the patient will perform, such as trying different mental strategies or trying to self-regulate the targeted EEG feature with various levels of difficulty, *e.g.*, thresholds to

reach. The feedback is the information provided by the machine to represent real-time variations in the EEG feature and/or to guide the patient in the training task, *e.g.*, towards a modification of their strategy. For instance, feedback can be a visual gauge or an audio sound of which the size or amplitude varies according to the EEG feature value. The following sections first present various training tasks that have been explored for BCI training, and then present different types of feedback that have been used for the same purpose. They also describe which of these tasks and feedback types are adapted and adaptive according to the users' traits and states, or how they could be made so.

Towards adapted and adaptive BCI/Neurofeedback training tasks

This subsection analyzes a training task that can be adapted and adaptive in order to optimize the learning process. The type of the task and its difficulty can be adapted [59]. The type of the task comprises the psychophysiological parameter that the user is asked to modulate. This modulation can be used to control various applications. For instance, with motor imagery, the different exercise types would be the possible mental commands; *e.g.*, motor imagery of hands, feet or tongue. The instructions serve to guide the user in knowing which exact mental command he is supposed to perform in real time (trial-by-trial). The type of the task can be adapted or adaptive. So far in the literature, adapted types do not seem to have been explored. However, adaptive BCI/NFB task types have been explored. For instance, the machine could automatically identify which psychophysiological parameter works best for the users to assist them to more easily manipulate the system. For instance, machine learning (Bandit algorithm) has been used to select the MI task type within runs (among hands, feet and tongue) in order to identify as quickly as possible for which one the user has the best performance [24]. The same could apply for NFB tasks, where the user is asked to regulate different EEG patterns from the initial ones if he is unable to regulate or produce them.

The difficulty of the task may be defined by the amount of mental resources that the patient needs to engage in it in order to complete it successfully. This is related to the skills of the user at EEG self-regulation. Ideally, to ensure efficient learning, the task difficulty should match the user's skills in order to be neither too easy - which would be boring - nor too difficult - which would be frustrating. The difficulty of the task can be adapted or adaptive, *i.e.*, increased or decreased according to the user's profile and the speed at which he acquires skills. Traditionally, adapted and adaptive task difficulty has been set by using a threshold initially adapted to the user's physiology and regularly updated between sessions. It has not yet been adapted to the user's cognitive profile, which thus remains to be explored.

Additionally, recent research is now exploring other ways to dynamically adapt the difficulty instead of changing the threshold between sessions. For instance, in McFarland et al. (2010) motor-imagery task difficulty was increased from 1D, then to 2D, and finally to 3D cursor control within sessions [52]. Another way to increase user performance and motivation is to adapt the perceived task difficulty by providing a feedback which does not comply with the real performance of the user but is positively biased or is adaptively biased [58]. Finally, the difficulty in an experimental context can differ from an ecological one, so virtual reality coupled with NF/BCI could be useful to train the subject in a more realistic environment [45]. Indeed, in these types of protocol, the level of the environmental distractors and therefore difficulty can be controlled, *e.g.*, by increasing the speed of instructions or adding distracting, real-life, environmental noise.

Adaptive difficulty can be further explored by educational theories. Indeed, instructional design theories and flow theory show that to promote progress and intrinsic motivation, a task should be engaging, often ludic and adapted to the user's skills [48, 58]. This suggests that NFB training tasks could also follow educational theories to foster learning and intrinsic motivation. Moreover, the cognitive strategy of the user, which refers to the way the user tries to modulate the psychophysiological parameter used in the exercise, could be influenced by the instructions as well as by various feedback.

Towards adapted and adaptive feedback for BCI/Neurofeedback

This subsection analyzed the feedback that can be adapted and adaptive in order to optimize the learning process. Feedback is an indication provided to users that allows them to learn to modulate their brain activity. However, providing feedback that is appropriate and informative is a great challenge [48]. A substantial number of studies on BCI have focused on feedback modality, content and social features.

Concerning the feedback modality, the effects of adapted and adaptive classic visual feedback, auditory feedback, tactile feedback or even multiple sensory modalities feedback have been studied. Such feedback can improve control display mapping to further enhance the sense of agency which influences the technology acceptance factor presented in **Figure 2**. Adapting the modality of the feedback also makes it possible to take general cognitive principles into account, e.g. the presentation of information on different modalities enables a faster response, related to the "redundant signal effect", but it also makes it possible to adapt to the sensorial impairments of patients [41]. Moreover, virtual reality can be used to improve training by providing motivating and immersive feedback [45].

Concerning the content of feedback, some task-specific elements have been studied. For example, a key element for controlling BCI is for users to understand how their brain activity is modified when performing a task. Such representation of their brain activity can be provided by new visualization tools, e.g., TEEGI [23]. These can show users an engaging visualization of their own brain activity in real time to help them to understand which EEG patterns should be produced.

Lastly, concerning social features, some original studies have provided adapted and adaptive emotional support as well as a social presence to compensate for the lack of interaction during BCI/NFB sessions by using a learning companion, see **Figure 3** [63]. Each of the companion interventions was composed of an animation of its face and a spoken sentence. The feedback provided took the performances and progression of the user into account. It focused on the subject's effort and strategy and on reinforcing good performances and progress. Results showed a beneficial impact on the user's experience and might also indicate a differential effect on users that is yet to be verified. These results are encouraging and require further investigation.

Figure 3: Brain Computer Interface training during which PEANUT (on the left) provides user with social presence and emotional support adapted to his performance and progression [64].

A key objective for future research should be to focus on making feedback more informative by better understanding learning processes and improving measures of performances of BCI. Moreover, a challenge arises from enriching the feedback without overloading users with more information than they can process given their capacities. Assessing cognitive abilities such as attention and providing related adaptive feedback would provide interesting insights into this issue. Overall, BCI/NFB would benefit from studies combining several of these factors and assessing the interactions between them. The goal is to provide feedback that is both adapted and adaptive to training tasks, users' profiles, and their social and physical environment, a criterion often forgotten but which should be given more consideration by doing more ecological experiments, *e.g*. by using virtual reality.

Redefining the assessment of BCI/Neurofeedback training efficacy

The assessment of NFB training efficacy is essential to better understand the clinical efficacy of such therapeutics. Indeed, most studies that investigated the clinical efficacy of NFB did not evaluate or even report the efficacy of training [95]. Thus, it cannot be concluded whether patients gained control over their brain activity during the NFB training procedure or not. However, as learning is the most immediate result of NFB training according to the principle of NFB, it seems essential to measure the learning that takes place across sessions. As Rémond & Rémond stressed: "*Doubting the effectiveness of a biofeedback treatment on a physiological variable when this treatment is carried out without previously testing the modification of this variable, is the equivalent of doubting the effectiveness of a drug to cure a disease when the drug has not been absorbed by the patient*" [66].

The principles behind NFB is that self-regulation of a target neurophysiological pattern underlying a cognitive function should lead to clinical benefits linked to that cognitive function. Thus, a positive clinical outcome requires that the user learned to self-regulate the target pattern. Unfortunately, as mentioned before, many NFB publications do not report any metric of user learning [22]. There is also no clear consensus on what these metrics should be. It is thus necessary to identify relevant metrics of performance reflecting user learning of self-regulation. Some metrics of this sort have been recently proposed for BCI for instance [46]. Then, we will need to study how these metrics are related to the clinical outcome. Ideally, we need metrics that would enable us to compare how different feedback approaches or machine learning impact user learning, as well as to predict clinical outcome. This would enable us to

screen participants that are likely to benefit from neurofeedback as well as to identify the best NFB/BCI training methods.

Thus, the following subsections first present how to assess NFB and BCI user learning by distinguishing: (i) how well users can self-regulate their EEG activity at a given time, which represents their current "performance", and (ii) how well they acquire new skills across sessions to improve this EEG self-regulation, which represents their EEG self-regulation "skill". The following subsection describes the issues involved in redefining such metrics in order to both (i) improve the design of adapted and adaptive training tasks and feedback in NF, and (ii) better link such metrics to neurophysiological and neuroplasticity indicators.

Towards new performance and skill metrics in BCI/Neurofeedback

Performance is typically assessed by using success rates as metrics , *i.e.*, how often a) users' NFB features successfully crossed the threshold, or b) users' mental tasks are successfully recognized by the BCI. In both cases, a threshold is used: generally, a univariate one for classical NFB analysis in mental disorders (*i.e.*, a single value to be crossed by the unidimensional feature value) [2], usually defined manually, or a multivariate one for BCI, the EEG classifier typically used being a multidimensional threshold on all the features used by the BCI to recognize each mental task. While success rates are typically used in NFB/BCI, it can be argued that they are a poor performance metric of user learning. Indeed, success rates are discrete and depend on the data used to determine the threshold/classifier, whereas users' skills at EEG self-regulation are continuous and threshold/classifier-independent. This means that an improvement in EEG self-regulation might not translate into an improvement in success rates, e.g. if the threshold is too high. This also means that if the threshold or classifier is calibrated on data of poor quality, this will result in poor feedback and in a poor measure of performance based on them. To date, only a few studies have evaluated the relevance of performance metrics in BCI/NFB during a session. Recently, new metrics were proposed to study BCI user training that provide a continuous and threshold-free measure of how stable and distinct EEG patterns for each mental task are [46]. Comparisons showed that such metrics could reveal fast learning of EEG self-regulation in several BCI subjects whereas success rates sometimes did not. NFB success rates very likely have the same limitation and should thus be reconsidered when assessing NFB interventions. In any case, research into more specific and learning-related metrics of performance is needed.

Skill metrics are computed to quantify learning across sessions. They are typically based on relevant performance metrics estimated on each session/run. They estimate whether these

performance metrics increase over time and sessions, which would indicate learning. An example of such a metric could be the difference between performances obtained during the previous sessions and those obtained during the first ones, or the slope of the regression line passing by the performances across sessions (the steeper the regression line, assuming increasing performances, the faster the learning). Nonetheless, so far there is no gold standard in skill metrics and the ones currently used suffer from several limitations. For instance, the metrics mentioned above are very sensitive to outliers, and a single failed session (*e.g.*, due to a failing sensor or a tired patient) or an overly good one (due, *e.g.*, to chance) may lead to an inadequate corresponding skill metric. Skill metrics also depend typically on the threshold used in the performance metrics. If the threshold changes across sessions, which is typically the case in NF as in BCI if the classifiers are adaptive or recalibrated regularly, then performances are not comparable between sessions and the resulting skill metric may be meaningless. Finally, performance metrics also depend on rest/baseline EEG, such baseline values typically changing at each session. As such, the performance metrics used to compute skill metrics may not be comparable with each other. Overall, there is thus a need for new relevant skill metrics that are stable, meaningful and robust to outliers, as well as for investigation into their impact on clinical efficacy.

Towards optimizing clinical efficacy based on new metrics and neuroplastic approaches

We need to improve our knowledge about the relevant performance and skill metrics in order to optimize the clinical efficacy of NFB. Indeed, such metrics are essential for designing adapted and adaptive training tasks and feedback in NFB. At present, the task and the feedback are adapted by NFB practitioners before and during the training procedure. An important step for NFB practitioners is determining a threshold and the kind of feedback [73, 78, 85]. Adjusting a threshold and a given occupation time determines the number of positive reinforcements. Traditionally, the threshold may be set automatically or manually. When the threshold is determined automatically, it is continuously updated in order to provide patients with a positive reinforcement for a given percentage of occupation time below or above the threshold. The threshold is continuously estimated according to the signal recorded just before. However, the limitation is that the patient is rewarded only for changing his/her brain signal based on the previous averaged time period and not from the starting point, which drastically reduces the chance of learning across NFB sessions [73]. When the threshold is set manually by the professional, it is based on a baseline recorded before the NFB session. If the

number of positive reinforcements is too high or too low during the session, the threshold can be adjusted [73]. However, there is a risk of inconsistency between different NFB practitioners, as each one will adapt the task according to their own clinical experience. Moreover, different practitioners will typically take the profile of each patient into account (*i.e.*, psychological, cognitive and neurophysiological states and traits) subjectively according to their global feeling and not according to evidence and objective features. Moreover, the clinician may not be able to evaluate a state or a trait evolution that would be crucial to adapt the training task. Strehl (2014) stressed that "*the therapist will need to know the laws of learning as well as how to apply NFB training in order to be a competent partner*". However, the limitation of this standpoint is that these skills currently rely on clinical experience [26] rather than on scientific knowledge related to NFB learning processes [73, 85, 95]. Thus, the remaining challenge for assessing the efficacy of NFB therapies is to develop rigorous standards that ensure the consistency (*a.k.a.*, fidelity - Gevensleben et al., 2012) of NFB training protocols in order to optimize the potential positive effects of NFB on learning. However, no "optimal" NFB training procedure has yet been defined, and one research challenge is to design and evaluate optimal NFB training based on relevant performance and skill metrics.

The second challenge is to improve understanding about how these metrics and neuroplasticity indicators are linked in order to grasp the underlying neurophysiological mechanisms that explain EEG self-regulation and skills acquisition. If this relationship could be established, it would go a long way to validating such metrics. Indeed, as shown in **Figure 2**, performance and skills metrics should be understood not only in terms of the training BCI/NFB task but also with regard to indicators of neuroplasticity specific to the trained neural substrate [74]. Furthermore, this relationship could be considered as an important intermediate variable between NFB training/learning and clinical efficacy. As described in the first section of this paper, there are two kinds of indicators: dynamic modulation indicators based on EEG oscillation and Hebbian-type neuroplasticity indicators [67]. Thus, as EEG-based BCI/NFB tasks generally tend to modify EEG oscillations, performance metrics need to be related to dynamic modulation indicators. Maintaining the brain in a persistent oscillatory pattern improves the brain circuit so that it can produce the same pattern with a higher probability in the future [67]. Thus, as BCI/NFB trains the brain to maintain certain oscillatory patterns, skills metrics need to be related to Hebbian neuroplasticity. See **Figure 2**. Very few studies dedicated to the clinical efficacy of NFB have investigated such

neurophysiological indicators. Thus, in NFB, the neurophysiological relationship between dynamic modulation and deserves further attention [18, 92].

In conclusion, the human-computer interaction foundations of NFB demonstrates that training and learning are central to designing rigorous NFB protocols. Such protocols should be designed so that the induction of neuroplasticity is optimized *i.e.* it produces a lasting change after the training session. The relationship between NFB training performance, skills metrics and neuroplasticity induction is very exciting new ground that must now be explored in order to find new means of optimizing the clinical effect of NFB in the long term.

Conclusion

This paper investigated the neurophysiological, psychophysiological and human computer interaction foundations of neurofeedback. A transdisciplinary approach is now needed to evaluate rigorously the use of EEG NFB as a therapeutic tool in psychiatry. **Figure 4**. Notwithstanding the debate on the efficacy of NFB for treating mental disorders, this field of research remains fertile ground for innovative research in psychiatry. Neurophysiology, psychophysiology and human-computer interaction approaches of NFB pave the way for innovative research on two levels: for fundamental research attempting to define the mechanisms subsuming NFB training; and for clinical research aiming to establish better designed EEG NFB protocols, control/active groups and clinical criteria that define efficacy in terms of targeted biomarkers.

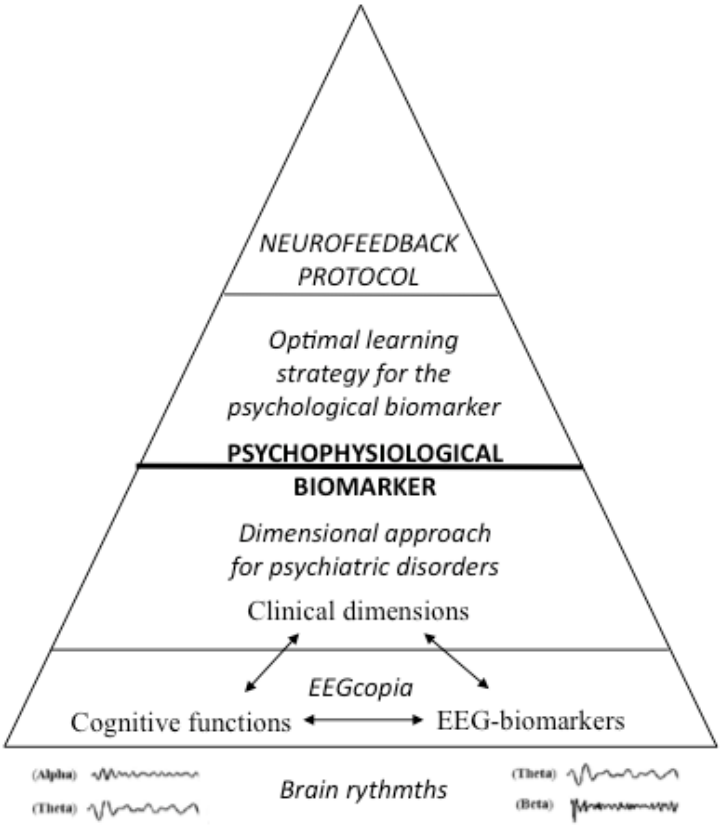

Figure 4: The quest to optimize neurofeedback protocol according to a transdisciplinary approach taking into account the neurophysiological, psychophysiological and human computer interaction bases of neurofeedback.

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Conflict of interest

None to declare concerning this paper.

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