Biological Psychology 161 (2021) 108081

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Review

Closed-loop neurostimulation for affective symptoms and disorders: An overview

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ARTICLE INFO

Keywords:
Closed-loop
NIBS
NTBS
Neurostimulation
Connectivity neurofeedback
Neural stimulation
Affective disorder
Anxiety disorders
Affective symptoms
Therapeutic
Mental illness

ABSTRACT

Affective and anxiety disorders are the most prevalent and incident psychiatric disorders worldwide. Therapeutic approaches to these disorders using non-invasive brain stimulation (NIBS) and analogous techniques have been extensively investigated. In this paper, we discuss the combination of NIBS and neurofeedback in closed-loop setups and its application for affective symptoms and disorders. For this, we first provide a rationale for this combination by presenting some of the main original findings of NIBS, with a primary focus on transcranial magnetic stimulation (TMS), and neurofeedback, including protocols based on electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Then, we provide a scope review of studies combining real-time neurofeedback with NIBS protocols in the so-called closed-loop brain state-dependent neuromodulation (BSDS). Finally, we discuss the concomitant use of TMS and real-time functional near-infrared spectroscopy (fNIRS) as a possible solution to the current limitations of BSDS-based protocols for affective and anxiety disorders.

1. Introduction

Affective and anxiety disorders are the most prevalent and incident psychiatric conditions, being prominent causes of worldwide disease burden (Baxter, Scott, Vos, & Whiteford, 2013; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007; Whiteford et al., 2013). These common mental disorders also exhibit remarkable overlapping regarding the co-occurrence of symptoms and putative neurobiological underpinnings (Gorman, 1996). Recent evidence suggests the existence of common neurocircuitry disruptions across affective and anxiety disorders (Goodkind et al., 2015; McTeague et al., 2017, 2020; Sha, Wager, Mechelli, & He, 2019; Xia et al., 2019). Such circuitry includes parts of the amygdala, hippocampus, thalamus and the dorsal and ventral portions of the lateral prefrontal cortex (dlPFC and vlPFC, respectively), which are recruited during emotional processing (McTeague et al., 2020), and the anterior insula, and the right vlPFC during cognitive control (McTeague et al., 2017). Alongside clinical overlap, this possible common biological pathway opens up a window for neurobiologically informed therapeutic approaches for a variety of disorders classified under the umbrella of affective and anxiety disorders. Of interest, two non-invasive approaches have been extensively explored over the last two decades for different psychiatric disorders: non-invasive brain neurostimulation (NIBS) and neurofeedback.

NIBS consists of a group of techniques that induces changes in local neural excitability and network activity without the need for surgical intervention. The two major techniques for NIBS are the transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS). Both techniques rely on changes of local electromagnetic fields to modulate brain activity (Boes et al., 2018; Wagner, Valero-Cabre, & Pascual-Leone, 2007). The TES technique, which includes approaches like transcranial direct current stimulation (TDCS) and transcranial alternate current stimulation (TACS), applies a weak electrical current

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https://doi.org/10.1016/j.biopsycho.2021.108081
Received 25 October 2020; Received in revised form 12 March 2021; Accepted 15 March 2021
Available online 20 March 2021

directly to the scalp, inducing a subthreshold polarization of cortical neurons (Miniussi, Harris, & Ruzzoli, 2013). The TMS method, uses a coil that conducts an electric current and produces a magnetic field that gives rise to stimulation effects in the area of application and allows different effects depending on the parameters used (Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017). Clinical applications of different NIBS approaches are broad, and we invite curious readers to refer to the recent primer from Brunoni et al. (2019). In this review, we will focus on TMS, which is commonly studied as a treatment of the depressive disorder (DD) (Perera et al., 2016), with recent evidence pointing towards its feasibility for the treatment of anxiety disorders as well (Cirillo et al., 2019).

On the other hand, in a neurofeedback intervention the patient is a protagonist. For instance, in functional magnetic resonance imaging (fMRI)-based protocols, the participant follows instructed cognitive strategies (e.g., autobiographical mental imagery, cognitive reappraisal, among others) to volitionally control the ongoing neural activity in one or more brain regions while receiving real-time feedback (Arns et al., 2017; Birbaumer, Ramos Murguialday, Weber, & Montoya, 2009; Sitaram et al., 2017; Thibault, MacPherson, Lifshitz, Roth, & Raz, 2018). Examples could include the up- or down-regulation of a specific region of interest (ROI) while imagining emotionally positive or negative memories (Linhartová et al., 2019). The main imaging methods used in neurofeedback protocols are the electroencephalography (EEG) and fMRI. The former commonly target fluctuations on EEG amplitude or frequency, while the latter uses variations in the blood-oxygen-level-dependent signal (BOLD) of one or more ROIs (Sitaram et al., 2017). Although in a more preliminary stage compared to NIBS, neurofeedback trials showed promising outcomes in several affective and anxiety disorders including DD, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), among others (Sitaram et al., 2017; Thibault et al., 2018). Clinical benefits are reported to last for weeks or months after intervention (Rance et al., 2018), while plasticity was observed in both intrinsic functional connectivity (Hampson et al., 2011; Ros et al., 2013; Scheinost et al., 2013) and directed effective connectivity (Zotev et al., 2011; Zotev, Phillips, Young, Drevets, & Bodurka, 2013).

Both neurofeedback and NIBS are feasible methods to modulate local neural activity in the putative substrate of affective symptoms and disorders. Of interest, in NIBS experiments, the effects of the stimulation are dependent on the current brain state (Neuling, Rach, & Herrmann, 2013; Silvanto, Muggleton, Cowey, & Walsh, 2007; Silvanto, Muggleton, & Walsh, 2008). In this context, brain state-dependent stimulation (BSDS) could value from the combination of neurofeedback and NIBS to close the neuromodulatory loop. This study reviews the status of closed-loop BSDS protocols and their potential application as a treatment for affective symptoms and disorders. Given the novelty of closed-loop BSDS protocols for affective disorders, we first provide a brief description of the main achievements of NIBS (with particular attention to TMS) and neurofeedback (with a focus on fMRI and EEG) protocols targeting circuits commonly reported across affective disorders (Goodkind et al., 2015; McTeague et al., 2017, 2020; Sha et al., 2019; Xia et al., 2019). These separate descriptions provide the rationale for the combined approach. Then, we provide an overview of the current achievements of protocols using closed-loop BSDS and discuss the combination of functional near-infrared spectroscopy (fNIRS) and TMS as a possible solution for closed-loop BSDS for affective symptoms and disorders.

2. Results

2.1. Neurostimulation for affective and anxiety disorders: current status

As previously mentioned, NIBS includes TES and TMS. In this review, we will focus on TMS, given its wide use in psychiatry (Huang et al., 2017)) and during BSDS (Bergmann, 2018). Moreover, here we focus on TMS protocols targeting a brain region commonly reported across affective disorders (Goodkind et al., 2015; McTeague et al., 2017, 2020; Sha et al., 2019; Xia et al., 2019). Specifically, the dlPFC reportedly present abnormal activity during emotional processing (McTeague et al., 2020) and has been widely targeted in TMS clinical trials (Broadbent et al., 2011; Noda et al., 2015; Silverstein et al., 2015). Over the last decade, several randomized controlled trials investigated the effectiveness of dlPFC stimulation using repetitive TMS (rTMS) for patients with unipolar or bipolar disorders (for recent systematic reviews, please refer to Mutz, Edgcumbe, Brunoni, and Fu (2018, 2019; Voigt, Carpenter, and Leuchter (2019)). In general, these studies show that participants in the experimental group consistently reduced depressive episodes by applying high-frequency repetitive TMS (HF-rTMS) of the left dlPFC, or low-frequency repetitive TMS (LF-rTMS) over the right dlPFC (Mutz, Edgcumbe, Brunoni, & Fu, 2018). In fact, the treatment for DD was the first approval for rTMS provided by the Food and Drug Administration (FDA) in the United States (Horvath, Mathews, Demitrack, & Pascual-Leone, 2010). Later, rTMS was also cleared for use as a treatment for refractory obsessive-compulsive disorder (OCD), after randomized controlled trials showed higher improvement of OCD symptoms in the TMS group compared to sham stimulation (for recent systematic reviews, please refer to Rapinesi et al. (2019); Trevizol et al. (2016)).

Regarding the group of anxiety disorders, HF-rTMS targeting the right dlPFC shows promising and long-term results, as reportedly fewer anxiety symptoms, in the first time or recurrent cases of generalized anxiety disorder (GAD) (Diefenbach et al., 2016; Dilkov, Hawken, Kaludiev, & Milev, 2017), and improves different symptoms of anxiety and depression by applying LF-rTMS on PTSD (Boggio et al., 2011; Cohen et al., 2004; Nam, Pae, & Chae, 2013; Watts, Landon, Groft, & Young-Xu, 2012). However, long term effects in PTSD are still controversial, with reduced benefits after follow-up (Cirillo et al., 2019).

In patients with co-occurring affective and anxiety disorders, results of TMS are comorbidity-specific. For example, the stimulation of the right dlPFC in patients with comorbid panic disorder (PD) and major depressive disorder (MDD) led to significant improvements of PD-related symptoms, but not for MDD (Cirillo et al., 2019; Mantovani, Aly, Dagan, Allart, & Lisanby, 2013). When targeting the dlPFC in both hemispheres (either during simultaneous stimulation, or one after the other) significant decrease in hyperarousal and depressive symptoms in patients with comorbid GAD and MDD, or comorbid PTSD and MDD (Cirillo et al., 2019).

TMS applications go beyond affective and anxiety disorders. For example, decreases in irritability, repetitive behaviors and enhanced autonomic balance in autism spectrum disorder have been reported after LF-TMS over left dlPFC (Oberman et al., 2016). HF-TMS over the left or right dlPFC can lead to reduced depressive symptoms in patients with traumatic brain injury (TBI) (Demirtas-Tatlidede, Vahabzadeh-Hagh, Bernabeu, Tormos, & Pascual-Leone, 2012), as well as to improved memory and verbal performance in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Nardone et al., 2014).

One limitation of this technique is its difficulty to reach deeper areas, which justifies the dlPFC being widely targeted across studies (Broadbent et al., 2011; Noda et al., 2015; Silverstein et al., 2015). However, studies targeting other cortical areas are emerging due to instrumental advances. For example, a study modulating the activity on the medial PFC with HF-TMS decreased anxiety and avoidance behaviors in patients with a specific phobia of heights (acrophobia) (Cirillo et al., 2019; Herrmann et al., 2017). Nevertheless, TMS does not pose an unquestionable superiority as an application technique for affective and anxiety disorders. These protocols still need to be improved, the data is still limited, and state-dependency is a difficult factor to be controlled (Huang et al., 2017). In this context, leading researchers in this field have proposed international guidelines for safe and effective clinical applications of different TMS modalities (McClintock et al., 2018; Perera et al., 2016).

2.2. Neurofeedback for affective and anxiety disorders: current status

In psychiatry, the main objective of neurofeedback is to target abnormal functional structures to reduce or even eliminate mental symptoms (Arns et al., 2017; Kim & Birbaumer, 2014). Common targets for these applications are brain regions, or connections, involved in emotion processing (Johnston, Boehm, Healy, Goebel, & Linden, 2010; Linhartová et al., 2019). Herein, we provide a brief overview or the main achievements of neurofeedback protocols targeting areas involved in emotion processing and consistently reported as involved in several affective disorders, such as the amygdala, and the lateral prefrontal cortex (McTeague et al., 2020).

Given the higher spatial resolution of fMRI-based neurofeedback protocols, different studies target individually those areas that are commonly disturbed in anxiety and affective disorders. The amygdala, for instance, is the most common target for neurofeedback protocols (Barreiros, Almeida, Baía, & Castelo-Branco, 2019). Controlled trials in patients with DD (Young et al., 2014, 2017) and PTSD (Zotev, Phillips et al., 2018) trained to up-regulate the BOLD signal in their left amygdala led to a significant reduction of depressive symptoms in the experimental group compared to controls. Other studies suggest the feasibility of neurofeedback protocols targeting other core subcortical regions for affective and anxiety disorders, such as the ventral striatum (Kirsch, Gruber, Ruf, Kiefer, & Kirsch, 2016), thalamus (Zotev, Misaki, Phillips, Wong, & Bodurka, 2018), and the hippocampus/parahippocampal gyrus (Hohenfeld et al., 2017).

Regarding the cortical surface, the lateral PFC had its ventral (Alegria et al., 2017; Rota et al., 2009) and dorsal (Kohl et al., 2020) portions also explored in recent neurofeedback protocols. Of interest, healthy subjects that learned to self-regulate their right vlPFC showed significantly higher accuracies when identifying emotional prosodic intonations when compared to the control group (Rota et al., 2009). On the other hand, obese subjects that learned to up-regulate their left dlPFC showed decreased preferences to high caloric foods (Kohl et al., 2020).

However, emotion regulation is a complex cognitive process and requires multiple brain areas to be engaged simultaneously (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Ruiz et al., 2013). Thus, a prominent approach is to target the self-regulating of multiple ROIs at once. For example, the up-regulation of brain areas responsive to positive valence, including the vlPFC, dlPFC, insula and medial temporal lobe was proven possible in healthy subjects (Johnston et al., 2011) and patients with MDD (Linden et al., 2012; Mehler et al., 2018). With this approach, patients showed significant improvement of depressive symptoms after a few sessions, with improvements persisting at follow-up (Linden et al., 2012; Mehler et al., 2018).

EEG-based protocols have lower spatial resolution compared to those fMRI-based. However, protocols can explore different brain rhythms that are relevant across major psychiatric disorders. The most common approach, when working with affective and anxiety symptoms and disorders, is to self-regulate the frontal asymmetry in the alpha band (Choi et al., 2011; Mennella, Patron, & Palomba, 2017; Wang et al., 2019). Experiments using this approach in healthy subjects show reduced incidence of anxiety scores, but no effect in mood (Mennella et al., 2017; Peeters, Ronner, Bodar, van Os, & Lousberg, 2014). In patients with DD, otherwise, significant effects were reported in both depressive and anxiety symptoms compared to control conditions (Choi et al., 2011; Wang et al., 2019). Another target for EEG-based protocols is the alpha self-regulation over the parietal cortex, with DD patients showing improved cognitive performance after up-regulation training (Escolano et al., 2014), and PTSD patients showing reduced anxiety after down-regulation (Escolano et al., 2014; Kluetsch et al., 2014). Of interest, down-regulation of alpha frequencies on the parietal cortex led to increased functional connectivity between nodes of the salience network in healthy subjects (Ros et al., 2013) and PTSD patients (Kluetsch et al., 2014).

Lastly, a recent approach that is receiving increased attention is the use of multimodal protocols merging EEG and fMRI data during self-regulation (Mano et al., 2017; Zotev, Phillips, Yuan, Misaki, & Bodurka, 2014). Indeed, comparative studies show that regional activation during neurofeedback is higher when using multimodal approaches when compared to unimodal protocols (Perronnet et al., 2017). Multimodal setups show that depressive patients undergoing the amygdala down-regulation protocol showed a temporal correlation between the amygdala activation and the frontal EEG asymmetry (Zotev et al., 2016). Also, functional connectivity changes related to neurofeedback in PTSD patients are consistent across both modalities (Zotev, Phillips et al., 2018).

Although promising, results from neurofeedback studies are still inconclusive and have not yet achieved sufficient evidence of efficacy for clinical application in affective and anxiety disorders (Arns et al., 2017; Thibault et al., 2018). Specifically, the heterogeneity of protocols and lack of randomized-controlled studies makes the generalization of results unclear. Thus, there are a series of current efforts regarding experimental design (Paret et al., 2019), control conditions (Sorger, Scharnowski, Linden, Hampson, & Young, 2019), signal processing standards (Heunis et al., 2020), and reporting practices (Ros et al., 2020).

2.3. Closed-loop brain state-dependent stimulation

Neurofeedback and brain computer interfaces (BCI) are, by definition, based on the real-time evaluation of the activity level of local neuron populations (Sitaram et al., 2017). In most cases, the feedback modality does not provide a direct stimulation to the same ROI. However, if the feedback provides a direct stimulation to the ROI, or areas functionally related with the ROIs, this can close the brain-feedback-brain loop and positively affect the control over the local neural activity. For instance, motor imagery experiments using EEG target the central electrodes, covering sensorimotor representations in the brain (Pfurtscheller & Neuper, 1997, 2001; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). In BCI experiments combining motor imagery with proprioceptive feedback from an exoskeleton, participants presented superior neurofeedback control than groups not receiving this feedback modality (Gomez-Rodriguez et al., 2011; Ramos-Murguialday et al., 2012). However, in this case, the loop is indirectly closed since the feedback is not delivered directly to a brain region.

On the other hand, the effects of NIBS are knowingly dependent on current neural state during stimulation (Neuling et al., 2013; Silvanto et al., 2007, 2008). Studies evaluating this effect show that NIBS achieves its peak effects when targeting a less active local neural population (Neuling et al., 2013; Silvanto et al., 2007). With this in mind, some researchers recently proposed the concept of closed-loop BSDS, in which the local neural activity is monitored in real-time to control a NIBS mechanism (Bergmann, 2018; Micoulaud Franchi, Fond, & Dumas, 2013; Sergeeva, Henrich-Noack, Bola, & Sabel, 2014). Current challenges to properly implementing BSDS include the identification of state markers sensitive enough to control, or to be stimulated by NIBS. These markers can comprise the same, or different brain regions, but must provide fast and reliable information about the brain-feedback-brain loop to continue offering efficient parameters of action (Karabanov, Thielscher, & Siebner, 2016).

Although being a recent concept, some proof-of-concept studies bring exciting results suggesting the feasibility of this approach. For instance, most studies using this concept aim the combination of EEG motor imagery event-related desynchronization with TMS of the motor cortex and haptic feedback. The first proof-of-concept study showed increased excitability of the stimulated motor cortex in one healthy subject and one patient with stroke-related hand paresis (Gharabaghi et al., 2014). Later, controlled experiments demonstrated that healthy subjects undergoing motor imagery-based BSDS presented increased

corticospinal excitability compared to the control conditions (Kraus et al., 2016). The combination of multiple stimulation techniques in a BSDS setup showed similar results, with increased corticospinal excitability following TMS and peripheral electrical stimulation in healthy subjects (Royter & Gharabaghi, 2016).

As explained, most studies combine EEG and some stimulation technique. Indeed, EEG is the most efficient approach to monitor brain activity, considering its high temporal resolution and the possibility of dynamic control of the provided stimulus (Bergmann, 2018). Since the emergence of this series of techniques, joint use of TMS-EEG presented high stimulus-related interference given the electromagnetic nature of both techniques (Walter, Murguialday, Rosenstiel, Birbaumer, & Bogdan, 2012). However, with the availability of 24-bit high dynamic range analogue-to-digital converters, the artefact produced by the TMS stimulus can be simply captured by the amplifier, enabling an optimized artifactual removing (Zrenner, Belardinelli, Müller-Dahlhaus, & Ziemann, 2016). On the other hand, magnetoencephalography (MEG) or fMRI-based combinations also present electromagnetic interactions with the stimulation technique, in addition to low mobility and possible claustrophobic effects (Bergmann, 2018).

Illustrating the feasibility and interest of combining TMS and EEG for basic neuroscientific investigations, Madsen et al. (2019) studied the effect of mu phase on corticospinal excitability. Contrary to a large number of similar investigations, this article did not find any effect of mu phase or mu potency on motor evoked potentials (MEPs). It is important to emphasize, besides closed-loop montages, that other methods based on phase dependence in different types of NIBS could be used for similar purposes. Though we focus on BSDS, traditional post-hoc analysis of the oscillatory phase (Kundu, Johnson, & Postle, 2014) and combining transcranial alternating current stimulation (tACS) with TMS to control the phase in which stimulation occurs are alternative approaches to BSDS protocols (see Raco, Bauer, Tharsan, and Gharabaghi (2016) for detailed information).

Given these promising results, potential applications for closed-loop BSDS include the modulation of putative circuits underlying affective disorders (Bergmann, 2018). Although such applications are currently under discussion and evaluation using deep-brain stimulation (DBS) methods (Price et al., 2020; Widge, Malone, & Dougherty, 2018), such approach using non-invasive technologies still needs further investigation.

2.4. *Functional near-infrared spectroscopy as a potential solution for closed-loop setups*

During the last decade, there is an emerging interest in using functional near-infrared spectroscopy (fNIRS) for BCI (Naseer & Hong, 2015) and neurofeedback protocols (Ehlis et al., 2018; Kohl et al., 2020). This methodology uses light emitters and receptors in the near-infrared range over the scalp (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006; Strangman, Boas, & Sutton, 2002; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993). The light in this color range has different absorption levels in oxygenated and deoxygenated hemoglobin particles, providing information about the oxygen concentration in superficial cortical layers (Hoshi, 2003; Villringer et al., 1993). Hemoglobin variations registered by fNIRS are strongly correlated with the fMRI BOLD signal (Cui, Bray, Bryant, Glover, & Reiss, 2011; Huppert et al., 2006; Strangman et al., 2002), although limited to superficial cortical gyri (Hoshi, 2003; Strangman et al., 2002; Villringer et al., 1993). Its low susceptibility to muscular and environmental noises allows for the use in experiments in naturalistic environments (Balardin et al., 2017; Pinti et al., 2018).

Of interest for psychiatric applications, fNIRS provides a valuable tool to study affective processing and emotion regulation, especially when covering the PFC (Bendall, Eachus, & Thompson, 2016; Doi, Nishitani, & Shinohara, 2013). Recent studies have shown, for example, the feasibility of using fNIRS recordings from the PFC to decode affection induced by pictures (Hosseini et al., 2011; Trambaiolli, Biazoli, Cravo, & Sato, 2018), videos (Bandara, Velipasalar, Bratt, & Hirshfield, 2018; Hu et al., 2019), and autobiographical affective imagery (Tai & Chau, 2009; Trambaiolli, Biazoli, Cravo, Sato et al., 2018). With this in mind, Trambaiolli and colleagues trained healthy subjects to control a decoding-based neurofeedback protocol recalling positive autobiographical memories (Trambaiolli, Biazoli, Cravo, Falk, & Sato, 2018). This protocol evaluated different patterns of oxy- and deoxyhemoglobin in different areas of the prefrontal and occipital cortex.

Using a region-specific protocol, Aranyi and colleagues showed that healthy participants can self-regulate the asymmetry of oxyhemoglobin concentrations in the dlPFC (Aranyi, Pecune, Charles, Pelachaud, & Cavazza, 2016). Other experiments targeting the oxyhemoglobin self-regulation in the bilateral dlPFC are reported in children with attention deficit hyperactivity disorder (ADHD) (Kimmig et al., 2019; Marx et al., 2015), adults with high impulsivity (Hudak et al., 2017) or social anxiety disorder (Kimmig et al., 2019). These studies showed that, compared to control conditions, fNIRS-based neurofeedback training leads to significant symptom improvement compared to baseline (Kimmig et al., 2019; Marx et al., 2015), improved performance in attention tasks (Hudak et al., 2017), and reduced response to threat stimuli (Kimmig et al., 2019).

fNIRS is also widely explored in multimodal experiments combined with EEG (Chiarelli, Zappasodi, Di Pompeo, & Merla, 2017) since there is no electromagnetic-optical interference (Chiarelli et al., 2017; Curtin et al., 2019; McKendrick, Parasuraman, & Ayaz, 2015; Talukdar, Frost, & Diamond, 2015). This technology can also be expanded for BSDS protocols, allowing the combination of fNIRS with TES or TMS methods for the same reason (Curtin et al., 2019; McKendrick et al., 2015).

As previously described, a potential application of fNIRS-based BSDS would include the identification of self-regulatory patterns and the NIBS in the same brain region. As listed in the previous sections, the dlPFC emerges as a potential candidate for this approach, since it's widely explored in TMS studies, as well as in fNIRS-based neurofeedback protocols. Indeed, the similar spatial resolution of these techniques set the stage for this co-localized application.

On the other hand, given the exquisitely interconnected nature of the human brain, previous studies show that the self-regulation of one brain region leads to excitability changes in a different region (Zotev et al., 2013). Thus, a second possibility would be the use of fNIRS registration and NIBS occurring at different components of the same network. For example, among the aforementioned common areas across affective and anxiety disorders (McTeague et al., 2017, 2020), the registration could occur over the vlPFC, with the stimulation occurring in the dlPFC. Another option could be the use of decoding-based approaches, with the real-time evaluation of different nodes of the affective processing network (Lindquist et al., 2012; Lindquist, Satpute, Wager, Weber, & Barrett, 2015), and the stimulation of the dlPFC.

3. Final considerations

Here we reviewed the main recent advances on NIBS and neurofeedback protocols targeting areas commonly affected in affective and anxiety disorders. We also discuss how these approaches can be combined in closed-loop BSDS protocols, given the recent advances of proof-of-concept experiments targeting motor regions. In particular, we provided a discussion on how the association of TMS and fNIRS-based neurofeedback protocols can be combined to avoid interferences across modalities. We highlight that this discussion is still conceptual, and future studies should be performed to validate this concept. However, given the existing tools and the need for modern approaches in psychiatry, we believe in the viability of this approach in the short term.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported in part by the "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES) - Brazil - Finance Code 001. AFB is supported by a level II scholarship from "Conselho Nacional de Desenvolvimento Científico e Tecnológico" (CNPq) - Brazil (314149/2018-0).

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