Optical brain imaging and its application to neurofeedback

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ABSTRACT

Besides passive recording of brain electric or magnetic activity, also non-ionizing electromagnetic or optical radiation can be used for real-time brain imaging. Here, changes in the radiation’s absorption or scattering allow for continuous in vivo assessment of regional neurometabolic and neurovascular activity. Besides magnetic resonance imaging (MRI), over the last years, also functional near-infrared spectroscopy (fNIRS) was successfully established in real-time metabolic brain imaging. In contrast to MRI, fNIRS is portable and can be applied at bedside or in everyday life environments, e.g., to restore communication and movement. Here we provide a comprehensive overview of the history and state-of-the-art of real-time optical brain imaging with a special emphasis on its clinical use towards neurofeedback and brain-computer interface (BCI) applications. Besides pointing to the most critical challenges in clinical use, also novel approaches that combine real-time optical neuroimaging with other recording modalities (e.g. electro- or magnetoencephalography) are described, and their use in the context of neuroergonomics, neuroenhancement or neuroadaptive systems discussed.

1. Introduction

Imaging-based neurofeedback or brain-computer interface (BCI) applications depend on reliable real-time imaging of neural processes reflected by various physiological measures, such as single or multi-unit spike activity, electric or magnetic cortical field potentials, neuroelectric or -magnetic brain oscillations, or cerebral blood flow and oxygenation (Lebedev & Nicolelis, 2017; Soekadar et al., 2008). While some of these measures are recorded passively, i.e., by amplification of signal power originating from the brain itself (e.g., electric or magnetic field potentials and oscillations), others are assessed by directing energy to the brain, e.g., in the form of non-ionizing electromagnetic or optical radiation, and measuring its absorption, scattering, reflection or transmission. Here, due to their biological compatibility and tolerability, use of static magnetic fields, spatial and temporal gradients of magnetic fields, as well as optical radiation, e.g., in the near-infrared spectrum (700–2500 nm), was successfully established in brain imaging over the last years. Being portable and broadly accessible, particularly functional near-infrared spectroscopy (fNIRS) developed into a promising tool in neurofeedback and BCI applications (Naseer & Hong, 2015). Although sharing very similar technical underpinnings, the distinction between neurofeedback and BCI applications mainly derives from their purpose of use: while the term neurofeedback was introduced to denote techniques facilitating self-regulation of brain/neural activity through sensory feedback, e.g., to normalize symptom-related brain activity, BCI is typically used to label technical tools that provide active brain/neural control of external devices, e.g., for restoration of communication or movement (Birbaumer et al., 2014; Nann et al., 2020; Soekadar et al., 2008, 2016; Wolpaw et al., 2002). Beside such active BCIs, also paradigms in which brain/neural activity informs human–machine interaction passively became included under the term BCI (then termed passive BCI or neuroadaptive technology) (Blankertz et al., 2010; Klaproth et al., 2020; Muller et al., 2008; Zander & Jatzev, 2012; Zander & Kothe, 2011), e.g., when adjusting user interfaces in the operational theater to...
the surgeon’s mental state (Arico et al., 2017). As such, most BCI systems feature qualities of neurofeedback, and it was proposed that merging these two different types of application, e.g. in the context of neuro-rehabilitation (Soekadar et al., 2015a), may boost efficacy and adoption of clinical BCIs (Soekadar et al., 2019).

Being noninvasive and wearable, real-time optical brain imaging is a promising modality for both neurofeedback and BCI applications. To appreciate its advantages and recent technical innovations on one side and discuss current challenges and limitations on the other side, we first provide a comprehensive overview of the history and state-of-the-art in optical brain imaging, before highlighting the most recent studies on its application to brain/neural control and neurofeedback.

2. Use of optical radiation to assess brain physiology

When measuring the heating effects of sunlight at different wavelengths, Fredrick William Herschel (1792–1871) discovered that this heating effect increased from the blue to the red part of the optical spectrum and that the thermal effects even further continued beyond the visible spectrum so that he postulated the existence of invisible “calorific rays” (Herschel, 1800). Later, this part of the optical spectrum was termed infrared radiation (spectral wavelength 700–1000 nm).

Based on the discovery that specific elements generate characteristic absorption-lines when exposed to optic radiation (Fraunhofer, 1817), near-infrared light was later used, for instance, in the context of spectrochemical analysis (Abney & Festing, 1881). With the development of very sensitive light detectors (such as photomultiplier tubes or charge-coupled device sensors) and fiber-optic light guides, a whole set of applications in physics, chemistry, and bio-physics emerged that was partially transparent to optical radiation at wavelengths in the (near-) infrared part of the electromagnetic spectrum. Soekadar et al. (2015a) differentiated between two different types of application, e.g. in the context of neurofeedback, and it was proposed that merging these two different types of application, e.g. in the context of neuro-rehabilitation (Soekadar et al., 2015a), may boost efficacy and adoption of clinical BCIs (Soekadar et al., 2019).

Being noninvasive and wearable, real-time optical brain imaging is a promising modality for both neurofeedback and BCI applications. To appreciate its advantages and recent technical innovations on one side and discuss current challenges and limitations on the other side, we first provide a comprehensive overview of the history and state-of-the-art in optical brain imaging, before highlighting the most recent studies on its application to brain/neural control and neurofeedback.

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Oxygenation of hemoglobin alters its absorption characteristics within the near-infrared spectral band between 784 and 894 nm (Hoppe-Seyler, 1864; Stokes, 1864). As biological tissue, including the skull, is partially transparent to optical radiation at wavelengths in the (near-) infrared spectral band between 700 and 1000 nm, near-infrared radiation is particularly attractive to assess, e.g., brain metabolic processes associated with a modification of light absorption and scattering (Jobeis, 1977). Using the Beer-Lambert law (Beer, 1852), the absorbance and concentration in a sample can be related to the attenuation of light with known wavelength and intensity that irradiates this sample. In 1988, Delpy provided a modification of the Beer-Lambert law by taking light scattering into account, e.g. under the condition that it was kept constant and stable. This so-called “modified Beer-Lambert law” permitted the calculation of relative oxygenation levels from the measured near-infrared spectroscopy (NIRS) signal (Delpy et al., 1988) (a technique termed functional NIRS or fNIRS when used for the purpose of assessing metabolic responses linked to a specific function or behavior). Given that attenuation of near-infrared radiation passing through a specific medium relates to the concentration of light-absorbing molecules (chromophores) in the medium, e.g. oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb), changes in molecule concentration can be calculated. This derives from the modified Beer-Lambert law with the following equation:

$$\Delta A(\Delta t, \lambda) = \sum \epsilon_i(\lambda) \Delta c_i \times P(\lambda) d$$

where $\Delta A$ is the measured change in attenuation of light within two consecutive time points $\Delta t$, the index $i$ denotes all investigated chromophores, $\epsilon_i$ is the corresponding extinction coefficient at wavelength $\lambda$, $\Delta c_i$ is the change in concentration, $d$ is the source-detector separation, and $P$ is the differential path length factor that accounts for increased distance traveled by the light due to scattering in the tissue. Provided the scattering/path length $d \times P$ are known, absolute changes in the concentration of a specific chromophore can be calculated. This path length can be estimated using three different approaches: 1. By assessing the phase shift of an intensity-modulated light source, 2. by measuring the direct ‘time of flight’ of short light pulses passing through the substrate, and 3. by measuring absorption at wavelengths that are typical for water molecules assuming constant water concentrations throughout the medium.

There is ample evidence for a close relationship between local neuronal activity and dilatation of nearby blood vessels as well as increase in local blood flow. The spatial and temporal correlation between transient modulations in neural activity and associated hemodynamic responses was termed neurovascular coupling (NVC) (Iadecola, 2017). Building on NVC, there are now three established optical methods to assess modulations of regional neurometabolic and neurovascular activity as surrogate marker for neural activity: 1. intrinsic signal optical imaging, 2. diffuse correlation spectroscopy (DCS) (Durduran & Yodh, 2014) and 3. fNIRS (Scholkmann et al., 2014). While intrinsic signal optical imaging offers high spatial (≈100 μm) and temporal (100 ms) resolution, it requires open-skull or thinned-skull procedures and has only been established in animal research. DCS measures speckle fluctuations of near-infrared diffuse light (i.e., fluctuations in intensity patterns produced by the mutual interference of a set of optical wavefronts) in tissue that are sensitive to the motions of red blood cells. Offering high temporal resolution (up to 100 Hz), a relatively large penetration depth (up to ~1.5 cm) and portability, it is a promising new technique, but has not been established in the neurofeedback or BCI fields yet. Finally, fNIRS is the most established and fastest growing approach in neurofeedback/BCI applications, mainly because of its robustness, portability and commercial accessibility.

All three techniques can evaluate relative changes of oxygen- and deoxy-Hb or cerebral blood flow in superficial cortical layers. It was shown that neural activity resulting in higher oxygen consumption leads to decreased oxy-Hb concentrations (termed “initial dip”) (Bahar et al., 2006), followed by an up-regulation of regional cerebral blood flow (rCBF) within a few hundred milliseconds to seconds. This up-regulation is followed by an increase of total hemoglobin (t-Hb) that, overall, results in a measurable increase in oxy-Hb. As the degree of rCBF increase was shown to exceed the regional cerebral oxygen metabolic rate (rCMRO2) during neural activity (Fox & Raichle, 1986), neural activity can be estimated from the relative increase in oxy-Hb and t-Hb compared to a relative decrease of deoxy-Hb in the venous branch of the cerebral vascular system (Wolf et al., 2002) (Fig. 1).

It should be noted, however, that there is no clear mechanistic understanding yet of how neuronal activity regulates cerebral blood flow and metabolism as measured by, e.g., fNIRS or fMRI (Dvor et al., 2012). According to the “metabolic hypothesis”, neural activity associated with an increase in lactate, adenosine triphosphate/adenosine diphosphate ratio or modulation of some yet unidentified oxygen sensor (Paulson et al., 2010; Raichle & Mintun, 2006), for instance, leads to a metabolic cascade resulting in vasodilatation/constriction. An alternative hypothesis, the “neurogenetic hypothesis”, postulates feed-forward mechanisms in which release of neurotransmitters and neuropeptides influence CBF and metabolism directly. It is conceivable that both mechanisms play a role, and that also glial cells contribute to these mechanisms (Allaman et al., 2011; Iadecola, 2017).

Currently, there are three methods available to infer molecular properties of organic tissue using fNIRS: 1. continuous-wave (CW) spectroscopy, 2. frequency-domain (FD) techniques, and 3. time-domain (TD) (or time-resolved) spectroscopy (Fig. 2). State-of-the-art NIRS systems can comprise up to several hundred channels with temporal resolutions as high as 250 Hz and spatial resolutions of approximately 7–10 mm (Ferrari & Quaresima, 2012).

In CW spectroscopy, a continuous wave of light with either discrete wavelengths (laser diode) or sharply peaked/narrow spectra is used. Typically, continuous-wave NIRS sensitivity is increased by applying amplitude-modulation at low frequencies (in the kHz-range) and using phase-locked detection techniques. While the CW approach can achieve
**Fig. 1.** Assessing brain hemodynamic responses using functional near-infrared spectroscopy (fNIRS). Near-infrared (NIR) light (e.g., at 760 nm and 850 nm) is emitted through the subject’s skull (left panel). Changes in intensity of light absorption and scattering in response to a stimulus are continuously recorded by a NIR light detector. Based on the modified Beer-Lambert Law (mBLL), the measured light intensity can be converted into estimations of cerebral total hemoglobin (HbT) and differentiated into oxygenated and deoxygenated hemoglobin (HbO/HbR) (right panel, t = time, s = seconds, c = concentration).

**Fig. 2.** Most commonly used functional near-infrared spectroscopy (fNIRS) methods to assess molecular properties of organic tissue (modified from Scholkmann et al., 2014). The index i denotes all investigated chromophores, P is the differential path length factor that accounts for increased distance traveled by the light due to scattering in the tissue, and d is the source-detector separation. $\Delta c_i$ is the change in concentration and $e_i(\lambda)$ is the corresponding extinction coefficient at wavelength $\lambda$. $\Delta A$ is the measured change in attenuation of light within two consecutive time points $\Delta t$. $\phi$ is the estimated phase shift between the emitted and detected light waves. Currently, most BCI applications use continuous wave (CW) spectroscopy because it is particularly suitable to continuously assess relative changes in, e.g., oxy- / deoxy-hemoglobin.

High signal-to-noise ratios, a major disadvantage is that CW spectroscopy is unable to quantify light scattering. Thus, light absorption and absolute hemoglobin concentrations can only be estimated based on relative changes, assuming constant scattering, not allowing for resolving contributions of different tissues. Here, to some degree, the use of multiple source-detector distances (M s-d) allows for separating different tissue layers and can substantially improve signal-to-noise ratio (Gagnon et al., 2012; Yuvel et al., 2015).

Frequency-domain techniques also use a continuous wave, but modulate its intensity at high frequencies (100 MHz–1 GHz), using measured phase shifts for estimation of the time of flight. While potentially providing more precise recordings, the advantages of FD techniques over conventional CW techniques have yet to be established (Davies et al., 2017). In time-domain or time-resolved spectroscopy, picosecond light pulses are applied and the photon arrival times are measured directly. Besides determining molecule concentrations from absorption changes, these approaches also provide scattering information and thus enable the separation of different tissue layers. Recently, a first optical BCI was introduced based on such time-resolved fNIRS signal potentially applicable for mental communication in patients with brain injury or stroke (Abdalmalak et al., 2020).

As most neurofeedback and BCI paradigms utilize relative and not absolute changes of brain physiological parameters, up to now mainly CW spectroscopy was established in the neurofeedback/BCI field. FD and TD spectroscopy, however, may offer some complementary advantages that need to be further explored in real-time optical imaging. While CW spectroscopy is already widely available and can be more easily applied in multichannel systems due to its mobility (Ferrari & Quaresima, 2012), FD and TD techniques are potentially more precise due to their penetration depth (Coscia et al., 2019; Gagnon et al., 2012; Yuvel et al., 2015), but also less established and more cost intensive.

The distance between CW fNIRS light sources and detectors is a tradeoff between signal strength (light attenuation and the pathlength of light are exponentially related) and sensitivity to brain tissue (for a larger source-detector separation, more photons ‘see’ the cerebral layer of interest). Injected light has to conform with safety standards and powers usually lie in the range of 5–50 mW. For transcranial assessment of human cortical hemoglobin oxygenation, the light sources and detectors are typically placed at a distance between 2 and 4 cm.

A remaining major challenge in using fNIRS to assess brain physiological activity is the differentiation between neurontemal/vaso-vascular signals and other systemic biological processes. For instance, non-neural activity related to systemic arterial pulse oscillations (~1 Hz), respiration (~0.2 – 0.4 Hz) and low frequency oscillations of other origin (at <~0.1 Hz) (Mayer waves/Traube-Herring waves) modulate the measured oxy-Hb and deoxy-Hb concentrations, and fluctuate both during task and at rest conditions (Toronov et al., 2000). Although a number of strategies were introduced to reduce the impact of these systemic physiological artifacts (Klein & Kranczioch, 2019; von Luhmann et al., 2020), validity of quantitative measures is still limited. Thus, most neurofeedback/BCI applications use a dual-state approach, i.
distinct oxy-Hb concentration increase and deoxy-Hb concentration self-regulation were performed at the beginning of the millennium (Coyle et al., 2004; Sitaram, 2005). It was demonstrated that motor bedside, its superiority over other diagnostic tools remains to efficiently predicting and quantifying local and global injuries for organs like the brain and the lung. They were able to (i) noninvasively form very high fidelity 2D and 3D simulations for accurately and motion artifacts that have yet to be mastered.

### 3. Optical brain imaging and its application to neurofeedback

Given the variety of physiological parameters that can be derived from changes in optical properties of brain tissue (e.g., perturbations in cerebral blood volume, blood flow or metabolic rate of oxygen), several possible clinical NIRS applications were explored over the last years (Mihara & Miyai, 2016; Naseer & Hong, 2015; Wolf et al., 2007). These range from studying the physiological correlates of stroke and cerebrovascular disease to epileptic disorders (e.g., oxygenation response to epileptic activity and focus localization), idiopathic headache syndromes and functional imaging of the diseased brain (e.g., in the context of neurorehabilitation) (Obrig, 2014). fNIRS also showed particular promise as a clinical tool for online brain-monitoring during cardiac surgery (Zheng et al., 2013) or critical care (Moerman NIRS also showed particular promise as a clinical tool for online brain-monitoring during cardiac surgery (Zheng et al., 2013) or critical care (Moerman & De Hert, 2017). It is worth noting that (Kannan and Przekwas, 2011, 2012) have performed very high fidelity 2D and 3D simulations for accurately and efficiently predicting and quantifying local and global injuries for organs like the brain and the lung. They were able to (i) noninvasively “numerically penetrating” the tissues and (ii) reconstruct the optical properties the presence of water, oxygenated, and de-oxygenated blood. These numerical noninvasive measurements are then used to predict the extent and severity of the organ hemorrhage/injury. A major obstacle in establishing NIRS as a routine clinical tool for diagnostics of the diseased brain is the variety of NIRS parameters (such as change in cerebral blood volume, blood flow or oxy-Hb/deoxy-Hb), however, and variability of tasks that are used in clinical studies. This limits comparability and generalizability of findings. Currently, commercial systems provide information on relative change in hemodynamic properties only, but not on absolute change. Also, as NIRS can only assess the optical properties of the superficial cortical layers, deep sulci, as well as all subcortical and infra-tentorial brain regions cannot be studied directly. Moreover, compared to oxy-Hb/deoxy-Hb as measured by fNIRS, signal-to-noise of fMRI BOLD signals was estimated to be up to 2–3 times higher (Cui et al., 2013). While NIRS clearly has the advantage that it can be used at the patient’s bedside, its superiority over other diagnostic tools remains to be proven.

The first studies aiming at establishing NIRS as a modality for brain self-regulation were performed at the beginning of the millennium (Coyle et al., 2004; Sitaram, 2005). It was demonstrated that motor imagery, e.g., the imagination of clenching a ball, is associated with a distinct oxy-Hb concentration increase and deoxy-Hb concentration decrease as measured by contralateral optodes placed over the motor cortex (C3/C4 electrode positions according to the 10/20 EEG system). This metabolic modulation was translated into online visual feedback, e.g., displayed as a growing or shrinking circle on a computer display (Coyle et al., 2004). In a later study, this paradigm was used to establish a binary switch. In this study, two options (e.g., "yes" and "no") were presented to the user who was instructed to perform imagery tasks only when the desired target became highlighted (a control paradigm commonly referred to as “synchronous mode of operation”). The system monitored the sensorimotor cortex activity during both options and compared the response to each. The selection of either state required multiple trials and, after approximately one minute, the classification result was shown on a display. Although performance (defined as information transfer rate, ITR, in bit/sec.) was inferior to many electroencephalographic (EEG) systems, the system could achieve more than 80% correct classifications in healthy participants (Coyle, 2007), a value comparable with other established EEG- or magnetoencephalography (MEG)-based BCIs (Mihara & Miyai, 2016).

Given the tight relatedness of neurofeedback and BCI applications on their technological but also clinical level (Soekadar et al., 2019), the following provides an overview of the most relevant applications that employ real-time optical brain imaging, e.g., for restoration of communication and movement, symptom reduction in neuropsychiatric disorders, or neuroenhancement and neuroergonomics.

#### 3.1. Optical BCIs in restoration of communication

The first clinically meaningful application of a BCI was introduced in the late 1990ies when a patient who suffered from locked-in syndrome (LIS) could select single letters on a screen by self-regulating slow cortical potentials (SCP) recorded by EEG. Applicability and versatility of such BCI systems for restoration of communication were later substantially improved (Blankertz et al., 2011; Blankertz, 2008; Kubler & Kotchoubey, 2007). However, successful application in patients diagnosed with complete locked-in syndrome (CLIS), i.e., the inability to elicit any voluntary muscle contraction, remains a great challenge. While not all reasons for this failure in applicability are entirely clear and remain subject of discussion, e.g., the thought-extinction hypothesis (Kubler & Birbaumer, 2007) predicting that any voluntary cognitive activity, goal-directed thinking or mental imagery would cease once a patient has entered CLIS, an in-depth analysis of data recorded by electrocorticography (ECoG) showed that CLIS can lead to considerable impairment of the circadian system reflected by an increased fragmentation of slow wave sleep (SWS) (Soekadar et al., 2013). This evidenced that use of appropriate tools to monitor attentiveness and alertness during the attempt to establish any form of BCI communication with CLIS patients is critical.

Assuming that instrumentally learned responses and intentional cognitive processes extinguish in complete paralysis (as predicted by the thought extinction hypothesis), alternative approaches based on semantic classical conditioning were introduced and tested (Ruf et al., 2013). Semantic classical conditioning refers to establishing a cortical response to the trueness of a statement (i.e., its semantics) irrespective of the particular constituent words and letters or sounds of the words. For this, an unconditioned stimulus (e.g., an acoustic signal or short electrical pulse) is presented only when a true statement is acoustically

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1 For a more comprehensive overview of NIRS-neurofeedback studies, please see Kohl et al. (2020) as well as https://osf.io/hx5f7/ providing a comprehensive database that includes methodological details of published studies
presented (conditioning and calibration of the classifier). After conditioning, cortical responses are evaluated online (e.g., using linear discriminant analysis) and classification results feedback to the subject at the end of each trial. In a first study involving healthy volunteers, a mean accuracy of 65.4% for classification of “yes” and 68.8% for “no” thinking was found. Offline analysis of the conditioned cortical responses (as measured by area under curve of 2 s-time intervals following acoustic presentation of a true or false statement) revealed significant differences between conditioned “yes” and “no” answers. Successful translation of this approach to LIS patients was later demonstrated in a clinical study that consisted of two weeks of measurements with four sessions per week (De Massari et al., 2013). Although online classification of brain responses was around chance level when averaged across all sessions, use of a non-linear classification algorithm (radial basis function kernel support vector machine) resulted in substantial improvements in classification accuracies. This suggests that, in principle, semantic classical conditioning of brain activity is feasible, but that online single-trial analysis of electric brain activity may not be robust enough to establish reliable communication in CLIS patients. After it was shown that less training is required to learn voluntary control of blood-  

demonstrated regulation of the supplementary motor area (SMA) (Mihara et al., 2013). Recently, (Fujimoto et al., 2017) successfully demonstrated regulation of the supplementary motor area (SMA) without providing any instruction of motor imagery or other mental strategies. Although, mental strategies were not systematically assessed after the training and participants may have engaged in motor imagery, this study underlines the potential of fNIRS-based neurofeedback for modulating brain activity in motor regions. Such neurofeedback may also be used to support motor learning after stroke. In an effort to exploit the advantages of both, (Rieke et al., 2020) introduced a combined, sequential real-time fMRI and fNIRS BCI system aiming at enhancing motor learning after stroke. The patient first underwent three fMRI-neurofeedback sessions receiving feedback of the ipsilesional motor cortex activity while engaging in a wrist extension training. The fMRI sessions allowed for a more precise localization of the signal source informing the channel selection in subsequent fNIRS neurofeedback sessions. During these fNIRS-sessions, the patient additionally received neural-triggered functional electrical stimulation (FES) to assist in wrist movements while the wrist extension training was continued. Besides upper limb movements, also successful regulation of swallowing-related motor regions (within the inferior frontal gyrus) was demonstrated which may prove beneficial to treat dysphagia in the future (Kober et al., 2015, 2018, 2019).

Whereas classification accuracy of motor imagery-related cortical activation ranged between 70% and 90% in healthy subjects (Coyle et al., 2004; Coyle, 2007; Hong et al., 2015; Naseer and Hong, 2013, 2015; Sitaram, 2005), classification accuracies tend to be lower in patient populations (Blokland et al., 2014). More studies are needed to investigate the mechanisms underlying learned self-regulation of metabolic brain activity and how BCI-related functional and structural neuroplasticity relates to specific clinical improvements (Soekadar et al., 2015a; Ushiba & Soekadar, 2016).

3.3. Optical real-time brain imaging in neuropsychiatric disorders

Besides neurorehabilitation, optical real-time brain imaging may also represent a promising tool to improve brain functions and ameliorate symptoms in neuropsychiatric disorders.

E.g., eight sessions of fNIRS-neurofeedback training of prefrontal cortex activation improved inhibitory control in a subclinical sample of highly impulsive adults. This corresponded to higher activation of the left dorsolateral prefrontal cortex (dIPFC) during a Go-NoGo task after the neurofeedback training compared to a control group receiving electromyography (EMG)-biofeedback (Ijubak et al., 2017). Children diagnosed with attention deficit and hyperactivity disorder (ADHD) underwent a similar training protocol. After 12 sessions, study participants showed a trend towards improved inhibitory control, which was accompanied by symptom reduction. However, control groups (EEG- and EMG-biofeedback) also showed marginal symptom reduction and no significant group effect was found. This is in line with data of a small
randomized controlled trial reporting only unspecific improvements of reading abilities in children with ADHD after 15 sessions of neurofeedback (Blume et al., 2020). In patients with social anxiety disorder, 15 sessions of fNIRS neurofeedback training of prefrontal brain regions reduced social threat-related attention bias and improved social and general trait anxiety as well as depressive symptoms (Kimmig et al., 2019). Due to absence of a control group, results are only preliminary, however.

In addition, training protocols have been developed to enhance the effects of a facial-recognition training in autism (Liu et al., 2017), reduce auditory verbal hallucinations and improve cognitive functioning in schizophrenia (Gomes et al., 2018; Storchak et al., 2019) and modulate eating behavior (Percik et al., 2019). To date, mostly single-case studies were reported, however.

Successful classification of neutral and positive affective states was demonstrated (Trambaroli et al., 2018), and it was shown that participants could increase asymmetric activation of the left dIPFC by affective engagement with a virtual agent (Aranyi et al., 2016). These fNIRS-based affective BCIs developed in healthy participants may pave the way for their future application in the treatment of mood disorders such as major depression. Moreover, the effectiveness of fNIRS-neurofeedback training for modulating activation of the orbitofrontal cortex (OFC) was demonstrated in a sham-controlled study involving 60 healthy participants. This brain region was shown to be related to cognitive flexibility and reward processing. Psychiatric disorders characterized by dysregulations in these domains and associated with OFC dysfunction could be targeted with this neurofeedback protocol in future (Li et al., 2019).

3.4. Optical real-time brain imaging for neuroenhancement and neuroergonomics

Next to clinical applications, fNIRS-neurofeedback has been investigated as a tool for cognitive enhancement and improving stress resilience and well-being in healthy people. Aiming to reduce stress in Japanese workers (Kotozaki et al., 2014), combined neurofeedback of the frontal pole with a heart rate variability (HRV) biofeedback training. After four weeks of training in the participants’ home environment, they found improvements in job-related stress measures and lower cortisol responses alongside increases in grey matter volume in brain regions implicated in stress response (hippocampus) and emotion control (orbitofrontal cortex). Unfortunately, the study design did not allow to disentangle the effects of neurofeedback from HRV biofeedback or control for unspecific effects of the training. Lai et al. (2015) investigated the effects of a one-session neurofeedback training of the frontal pole on attentional networks. They reported improved levels of performance as compared with a passive control task (counting), and similar performance as compared to mindfulness meditation. This study provides first evidence that neurofeedback training may have similar effects on attention as mindfulness practices. However, studies employing larger training regimens and follow-up measures are needed to corroborate this finding and to investigate whether neurofeedback is more efficient than meditation as hypothesized by the authors. Also, differences in the involved neural mechanisms need to be investigated.

Recently, (Xu et al., 2020) introduced an fNIRS-neurofeedback training based on frontoparietal connectivity, and demonstrated its feasibility to improve working memory and attention in healthy people. Such an approach may also turn out to be useful in the treatment of neuropsychiatric disorders characterized by deficits in these cognitive domains or to prevent cognitive decline.

Beyond direct feedback and control of brain activity related to various mental or emotional states, including levels of vigilance, attention and mental workload, detecting such states could be used for passive BCIs creating supportive environments in which feedback or task demands are optimally adapted to the mental state of the user (Gerjets et al., 2014; Muller et al., 2008; Zander & Jatzev, 2012). By mitigating the consequences of excessive workload or allowing for strategy changes, safety, performance, effectiveness or motivation in human–machine interaction could be increased. Such neuroergonomic approaches use markers in brain activity to assess covert mental states, such as mental workload, independently of the reported subjective or measured overt performance of a human operator (Parasuraman & Wilson, 2008). Sudden performance declines that follow sustained periods of excessive or too low task demands or engagements could be predicted and avoided, an issue of importance, e.g., in neuro-rehabilitation or psychotherapeutic interventions. In this context, HRV was recently identified as a promising biomarker predicting decline in brain/neural control performance (Nann et al., 2021). Moreover, varying workload conditions have been shown to modulate activation in the dorsolateral and ventrolateral prefrontal cortex as measured by fNIRS (Ayaz et al., 2013; Bruno et al., 2018; Schreppel et al., 2008). Accordingly, frontal oxygen dependent metabolism measured over prefrontal regions using fNIRS could be successfully used for the assessment of expertise development and the assessment of cognitive workload (Ayaz et al., 2013, 2012; Causse et al., 2017).

While recently published studies support the potential of fNIRS-neurofeedback for clinical and non-clinical applications, a recent systematic review concluded that sufficiently powered studies and large randomized controlled trials are still lacking and specificity of the reported effects remains to be demonstrated (Kohl et al., 2020). Also, shortcomings in reporting important information were identified. E.g., online signal processing methods and training success measures were not reported by some of the studies. Moreover, it is noteworthy that some of the above mentioned studies did not use concentrations of HbO or HHb as a feature to calculate the feedback signal but used measures of the optical density of one wavelength (Kotozaki et al., 2014) or the ratio of light intensities of two different wavelengths (Lai et al., 2015; Percik et al., 2019). While these features should, in theory, carry information of HbO concentrations, methodological studies are required to find out if this simplified approach is comparable in terms of signal quality and performance. Future studies will benefit from adopting more rigorous research and reporting practices as encouraged by a recent consensus paper (Ros et al., 2020) and methodological recommendations (Kohl et al., 2020).

3.5. Advancing optical real-time brain imaging towards broader clinical adoption

While optical real-time brain imaging is clearly more suitable for neurofeedback than BCI applications due to its signal features in the seconds range, it was recently suggested that designing paradigms that combine both brain/neural control of an assistive device and instrumental conditioning of brain activity (neurofeedback) may provide decisive advantages to increase the impact of intervention (e.g., fostering generalization of learned skills from the laboratory to real-life scenarios while triggering neuropsychiatric recovery) (Soekadar et al., 2019). Thus, combination of optical brain imaging with other modalities, such as EEG or optically pumped magnetometers (OPM) that exploits shared and complementary information may substantially increase robustness and performance (Fazli et al., 2015, 2012; von Lohmann et al., 2017). By broadening the versatility and reliability of use, such hybrid systems could extend the scope of optical real-time brain imaging towards broader clinical adoption. Numerous studies have investigated feasibility, safety and reliability of such hybrid systems across different brain regions and functional domains (Fazli et al., 2012; Koo et al., 2015; Muller-Putz et al., 2015; Shin et al., 2018) paving the way for various future clinical applications (for an overview of such systems targeting the motor cortex, see table 1).

4. Conclusions and future outlook

Optical real-time brain imaging has demonstrated its clinical
neuro-feedback systems. This is particularly true for applications in neuroenhancement or neuroergonomics that serve other purposes than medical applications aiming at restoration of lost or compromised brain or body function.

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Declaration of Competing Interest

SRS has no competing interests. Avl is Senior Scientist at NRInC LLC, a non-clinical fNIRS research company. MM receives lecture fees from the Shimadzu Corp., and SHK receives payments to consult with Mendi Innovations AB, Stockholm, Sweden.

References

Abdalmalak, A., Milej, D., Yip, L.C.M., Khan, A.R., Diop, M., Owen, A.M., St Lawrence, K., 2020. Assessing time-resolved fNIRS for brain-computer interface applications of mental communication. Front. Neurosci. 14, 105. https://doi.org/10.3389/fnins.2020.00105.

Abney, C., & Festing, L.-C., 1881. On the Influence of the Atomic Grouping in the Molecules of Organic Bodies on Their Absorption in the Infra-Red Region of the Spectrum. Philosophical Transactions of the Royal Society of London, 172, 887-918. http://www.jstor.org/stable/109369.

Allaman, I., Belanger, M., Magistretti, P.J., 2011. Astrocyte-neuron metabolic relationships: for better and for worse. Trends Neurosci. 34 (2), 76-87. https://doi.org/10.1016/j.tins.2010.12.001.

Abanyi, G., Pecu, F., Charles, F., Pelachaud, C., Cavazza, M., 2016. Affective interaction with a virtual character through an fNIRS brain-computer interface. Front. Comput. Neurosci. 10, 70. https://doi.org/10.3389/fncomp.2016.00070.

Arco, P., Berghini, G., Di Frumeri, G., Scalia, A., Colosimo, A., Balbi, L., 2017. Passive BCI in operational environments: insights, recent advances, and future trends. IEEE Trans. Biomed. Eng. 64 (7), 1431–1436. https://doi.org/10.1109/TBME.2017.2694856.

Ayaz, H., Shrewsowki, P.A., Bunce, S., Izzetoglu, K., Willems, B., Onaral, B., 2012. Optical brain monitoring for operator training and mental workload assessment. Neuroimage 59 (1), 36–47. https://doi.org/10.1016/j.neuroimage.2011.06.023.

Ayaz, H., Onaral, B., Izzetoglu, K., Shrewsowki, P.A., McKendrick, R., Parasuraman, R., 2013. Continuous monitoring of brain dynamics with functional near infrared spectroscopy as a tool for neuroergonomics research: empirical examples and a technological development. Front. Hum. Neurosci. 7, 871. https://doi.org/10.3389/fnhum.2013.00871.

Bahar, S., Soh, M., Zhao, M., Schwartz, T.H., 2006. Intrinsic optical signal imaging of neocortical seizures: the ‘epileptic dip’. Neuroreport 17 (5), 499–503. https://doi.org/10.1097/01.wnr.0000209010.78599.f5.

Beer, A., 1852. Bestimmung der Absorption des rothen Lichts in farbigen Flüssigkeiten. Ann. Phys. 162, 78–88. https://doi.org/10.1007/s10548-013-0282-1.

Birbaumer, N., Ruiz, S., Siratam, R., 2013. Learning regulated brain metabolism. Trends Cogn Sci 17 (6), 295–302. https://doi.org/10.1016/j.tics.2013.04.009.

Birbaumer, N., Gallegos-Ayala, G., Wilgruber, M., Silvoni, S., Soekadar, S.R., 2014. Direct brain control and communication in paralysis. Brain Topogr. 27 (1), 4–11. https://doi.org/10.1007/s10548-013-0282-1.

Blankertz, B., Tomioka, R., Lemm, S., Kawanabe, M., Muller, K.-R., 2008. Optimizing spatial filters for robust EEG single-trial analysis. IEEE Signal Process Mag. 25 (1), 41–56.
NeuroImage: Clinical 30 (2021) 102577

Fu, Y., Xiong, X., Jiang, B., Xu, R., Li, Y., Li, H., 2017. Imagined hand clenching force and speed modulate motor activity and brain are classified by NIRS combined with EEG. IEEE Trans. Neural Syst. Rehabil. Eng. 25 (9), 1641–1652. https://doi.org/10.1109/TNSRE.2016.2627897.

Fujimoto, H., Mihara, M., Hattori, N., Hatakenaka, M., Yagura, H., Kawano, T., Miyai, L., Mochizuki, H., 2017. Neurofeedback-induced facilitation of the supplementary motor area affects postural stability. Neuroinformatics 4 (4), 10.1117/1.NPh.4.4.045003.

Gagnon, L., Cooper, R.J., Yucel, M.A., Perdue, K.L., Greve, D.N., Boas, D.A., 2012. Short separation channel location impacts the performance of short channel regression in NIRS. Neuroimage 59 (3), 2518–2528. https://doi.org/10.1016/j.neuroimage.2011.08.095.

Gallegos-Ayalta, G., Forde, A., Takano, K., Ruff, C.A., Flor, H., Birbaumer, N., 2014. Brain communication in a completely locked patient using bedside near-infrared spectroscopy. Neurology 82 (21), 1930–1932. https://doi.org/10.1212/WNL.0000000000000449.

Gerjets, P., Walter, C., Rosendit, W., Bogdan, M., Zander, T.O., 2014. Cognitive state monitoring and the design of adaptive instruction in digital environments: lessons learned from cognitive workload assessment using a passive brain-computer interface approach. Front. Neurosci. 8, 385. https://doi.org/10.3389/fnins.2014.00385.

Ges, J.S., Ducov, D.V., Gadella, A., Ortiz, B.B., Van Deussen, A.M., Ahlka, H.T., Guimaraes, L.S., Cordeiro, Q., Trevizol, A.P., Lacerda, A., Dias, A.M., 2018. Hemodynamic and photoplethysmography assessment and its integration into an EEG-NIRS-based brain-computer interface. Frontiers in Neuroscience, 12, 455. https://doi.org/10.3389/fnins.2018.00455.

Haug, K.S., Naseer, N., Kim, Y.H., 2015. Classification of prefrontal and motor cortex signals for three-dimensional teleoperated movements. Neurosci. Lett. 587, 87–92. https://doi.org/10.1016/j.neulet.2014.12.029.

Hoschel-Seyfer, F., 1800. Experiments on the refrangibility of the invisible rays of the sun. The Philosophical Magazine, 8(29), 9–15. DOI:10.1080/147864400008562002.

Hong, K.S., Naseer, N., Kim, Y.H., 2015. Classification of prefrontal and motor cortex signals for three-dimensional teleoperated movements. Neurosci. Lett. 587, 87–92. https://doi.org/10.1016/j.neulet.2014.12.029.

Hudak, J., Blume, F., Dresler, T., Haeussinger, F.B., Renner, T.J., Fallgatter, A.J., Gawrilow, C., Ehlis, A.C., 2017. Near-infrared spectroscopy-fMRI brain neurofeedback integrated in virtual reality modulates brain and behavior in highly impulsive adults. Front. Hum. Neurosci. 11, 425. https://doi.org/10.3389/fnhum.2017.00425.

Huppert, T.J., Hoge, R.D., Diamond, S.G., Franceschini, M.A., Boas, D.A., 2006. A temporal comparison of BOLD and fNIRS hemodynamic responses to motor stimuli in adult humans. Neuroimage 29 (2), 368–382. https://doi.org/10.1016/j.neuroimage.2005.08.065.

Iadecola, C., 2017. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron 96 (1), 17–42. https://doi.org/10.1016/j.neuron.2017.07.030.

Johs, F., 1977. Non-invasive, infra-red monitoring of cerebral O2 sufficiency, bloodvolume, HBO2-Hb shifts and bloodflow. Acta Neuro Scand Suppl, 64, 452-453.

Kannan, R., & Przekwas, A., 2011. A computational model and monitor to detect a primary blast lung injury using near-infrared optical tomography [https://doi.org/10.1002/cnm.1406]. International Journal for Numerical Methods in Biomedical Engineering, 27(10), 1309–1324. https://doi.org/10.1002/cnm.1406.

Kannan, R., & Przekwas, A., 2012. A near-infrared spectroscopy computational model for cerebral hemodynamics. Int. J. Numer. Method Biomed. Eng. 28 (11), 1093–1106. https://doi.org/10.1002/cnm.2480.

Khan, R.A., Naseer, N., Quereda, M., Noori, F.M., Naseer, H., Khan, M.U., 2018. NIRS-based neurorehabilitation Interface for gait rehabilitation. J. Neural Eng. Rehabil. 15 (1), 7. https://doi.org/10.1186/s12984-018-0346-2.

Kimmig, A.S., Dresler, T., Hudak, J., Blume, F., Dresler, T., Haeussinger, F.B., Kreifelts, B., 2019. Feasibility of NIRS-based neurofeedback training in clinical and non-clinical conditions. Neuroimage 106, 593. https://doi.org/10.1016/j.neuroimage.2019.07.059.

Klopproth, O. W., Halbritter, M., Krol, I. L., Vermaelen, C., Zander, T. O., & Rumschink, N. M., 2020. NeuroAdaptive Cognitive Model for Dealing With Uncertainty in Tracing Pilots’ Cognitive State. Topics in Cognitive Science, 12(3), 1012-1029. DOI:10.1111/tops.12515.

Klein, F., Kranzioch, C., 2019. Signal processing in NIRS: a case for the removal of dynamic activity for single-channel recordings. Front. Hum. Neurosci. 13, 331. https://doi.org/10.3389/fnhum.2019.00331.

Kober, S.E., Wood, G., Kurzmann, J., Friedrich, E.V., Stangl, M., Wippel, T., Valjamme, A., Neuper, C., 2014. Near-infrared spectroscopy based neurofeedback training increases specific motor imagery related cortical activation compared to sham feedback. Biol. Psychol. 95, 21–30. https://doi.org/10.1016/j.biopsycho.2013.10.007.

Kober, S.E., Motsch, M., 2014. A Neuroadaptive Cognitive Model for Dealing With Uncertainty in Tracing Pilots’ Cognitive State. Topics in Cognitive Science, 12(3), 1012-1029. DOI:10.1111/tops.12515.

Krause, A., Ruprecht, B., Sibomana, I., Muller, J., 2020. Development of reading abilities in children with ADHD following fNIRS-based reading training: a randomized controlled trial. Front. Hum. Neurosci. 14, 42. https://doi.org/10.3389/fnhum.2020.00425.

Krause, A., Ruprecht, B., Sibomana, I., Muller, J., 2020. Development of reading abilities in children with ADHD following fNIRS-based reading training: a randomized controlled trial. Front. Hum. Neurosci. 14, 42. https://doi.org/10.3389/fnhum.2020.00425.
Nann, M., Cordella, F., Trigili, E., Lauretti, C., Bravi, M., Miccinilli, S., Catalan, J., Muller-Putz, G., Leeb, R., Tangermann, M., Hohne, J., Kubler, A., Cincotti, F., Mattia, D., Mihara, M., Miyai, I., 2016. Review of functional near-infrared spectroscopy in
Mihara, M., Miyai, I., Hattori, N., Hatakenaka, M., Yagura, H., Kawano, T., Li, R., Potter, T., Huang, W., Zhang, Y., 2017. Enhancing performance of a Hybrid EEG-
Lebedev, M.A., Nicolelis, M.A., 2017. Brain-machine interfaces: from basic science to
Lai, C., MacNeil, B., Frewen, P., 2015. A comparison of the attentional effects of single-
Kubler, A., Birbaumer, N., 2008. Brain-computer interfaces and communication in
Kohl, S.H., Mehler, D.M.A., Luhrs, M., Thibault, R.T., Konrad, K., Sorger, B., 2020. The
S.R. Soekadar et al.
neulet.2013.08.021.
brain-computer interface. Neurosci Lett, 553, 84-89. DOI:10.1016/j.
potential of functional near-infrared spectroscopy-based neurofeedback-a systematic review and recommendations for best practice. Front. Neurosci. 14, 594. https://doi.org/10.3389/fnins.2020.00584.
Koo, B., Lee, H.G., Nam, Y., Kang, H., Koh, C.S., Shin, H.C., Choi, S., 2015. A hybrid NIRS-EEG system for self-paced brain computer interface with online motor imaging. J. Neurosci. Methods 244, 26–32. https://doi.org/10.1016/j.jneumeth.2014.04.016.
Kotaniz, Y., Takeuchi, H., Sekiguchi, A., Yamamoto, Y., Shinada, T., Araki, T., Takahashi, K., Taki, Y., Ogino, T., Iiguchi, M., Kawaharada, R., 2014. Biofeedback-based training for stress management in daily hassles: an intervention study. Brain Behav. Sci. 44 (1), 566–579. https://doi.org/10.1016/j.brbs.2013.08.001.
Kubler, A., Birkbauer, M., Rosch, T., Enriquez-Geppert, S., Zotev, V., Young, K. D., Wood, G., Whitfield-Gabrieli, S., 2019. Online classification of brain states using real-time near-infrared spectroscopy and functional MRI for control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. J. Neurosci. 39, 1019–1109. https://doi.org/10.1523/JNEUROSCI.1098-18.2018.
Kumar, A., Zhang, X., Dong, Y., Bian, G., Whithiff-Schriefler, S., Wang, F., Vuillenmeur, P., Vialate, F., Van De Ville, D., Toddler, D., Surmiel, T., Sulzer, J. S., Strehl, U., Stemmer, M. B., Stein, J. N., Surmiel, S., Robert, S. R., Birbaumer, S., Kerner, S., Shin, J., Kwon, J., Im, C.H., 2018. A ternary hybrid EEG-NIRS brain-computer interface for neurofeedback training to regulate attention in children with autism: methodology and initial data. Neuroinformatics 17 (3), 259–270. https://doi.org/10.1007/s12021-018-9317-3.
Kim, J., Song, Y., Cho, W., Suh, J., Han, K., Chung, G., Kim, J., 2015. Use of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 617, 119–122. https://doi.org/10.1016/j.neulet.2015.09.050.
Kim, S., Wang, H., Kwon, J., Lee, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Adaptive near infrared spectroscopy-based brain-computer interface for control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. J. Neurosci. 39, 968–978. https://doi.org/10.1523/JNEUROSCI.2354-18.2018.
Kim, S., Kwon, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Jeong, J., Shim, J., Park, J., Kim, J., 2020. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 687, 1098–1102. https://doi.org/10.1016/j.neulet.2020.10.007.
Kim, S., Park, J., Lee, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Kim, S., Park, J., Nam, J., Hwang, B., Kang, J., Kim, J., 2019. Development of a hybrid EEG-NIRS system for self-paced brain-computer interface: a feasibility study. Neurosci. Lett. 678, 1–6. https://doi.org/10.1016/j.neulet.2019.03.004.
Soekadar, S., Birbaumer, N., Cohen, L.G., 2011a. Brain-computer interfaces in the rehabilitation of stroke and neurotrauma. In: Kansaku, K., Cohen, L.G. (Eds.), Systems Neuroscience and Rehabilitation. Springer, pp. 3-18.

Soekadar, S.R., Born, J., Birbaumer, N., Bensch, M., Halder, S., Murguialday, A.R., Gharabaghi, A., Nijboer, F., Schloof, B., Martens, S., 2013. Fragmentation of slow wave sleep after onset of complete locked-in state. J. Clin. Sleep Med. 9 (9), 951-953. https://doi.org/10.5664/jocm.3002.

Soekadar, S.R., Birbaumer, N., Slutzky, M.W., Cohen, L.G., 2015a. Brain-machine interfaces in neurorehabilitation of stroke. Neurobiol. Dis. 83, 172–179. https://doi.org/10.1016/j.nbd.2014.11.025.

Soekadar, S. R., Haagen, K., Birbaumer, N., 2018. Functional Stokes, G. G., 1864. Ueber das lange Spectrum des elektrischen Lichts [https://doi.org/10.1002/andp.18641991105]. Annalen der Physik, 199(11), 472-489. DOI: 10.1002/andp.18641991105.

Soekadar, S. R., Witkowski, M., Mellinger, J., Ramos, A., Birbaumer, N., & Cohen, L. G., 2011b. ERD-based online brain-machine interfaces (BMI) in the context of neurorehabilitation: optimizing BMI learning and performance. IEEE Trans Neural Syst Rehabil Eng, 19(5), 542-549. DOI:10.1109/TNSRE.2011.2166809.

Soekadar, S.R., Witkowski, M., Birbaumer, N., Cohen, L.G., 2015b. Enhancing hebbian learning to control brain oscillatory activity. Cereb. Cortex 25 (9), 2409-2415. https://doi.org/10.1093/cercor/bhu043.

Soekadar, S.R., Witkowski, M., Gómez, C., Opisio, E., Medina, J., Cortese, M., Cempi, M., Carrozza, M.C., Cohen, L.G., Birbaumer, N., Vitelli, N., 2016. Hybrid EEG/EGD-based brain/neural hand exoskeleton restores fully independent daily living activities after quadriplegia [10.1126/scirobotics.aag3296]. Sci. Robotics 1 (1), eaag3296. http://robotics.thesciencemag.org/content/1/1/eaag3296.abstract.

Soekadar, S. R., Nann, M., Crea, S., Trigili, E., Gómez, C., Opisio, E., Cohen, L. G., Birbaumer, N., & Vitelli, N., 2019. Restoration of Finger and Arm Movements Using Hybrid Brain/Neural Assistive Technology in Everyday Life Environments. In N. M. K. Christoph Guger, Brendan Z. Allison (Ed.), Brain-Computer Interface Research, A State-of-the-Art Summary 7 (pp. 53-61). Springer International Publishing.

Stokes, G., 1864. Ueber das lange Spectrum des elektrischen Lichts [https://doi.org/10.1002/andp.18641991105]. Annalen der Physik, 199(11), 472-489. DOI: 10.1002/andp.18641991105.

Storchak, H., Hudak, J., Haussinger, F.B., Rosenbaum, D., Fallgatter, A.J., Ehls, A.C., 2019. Reducing auditory verbal hallucinations by means of fNIRS neurofeedback - a case study with a paranoid schizophrenic patient. Schizophr. Res. 204, 401–403. https://doi.org/10.1016/j.schres.2018.09.018.

Tanino, K., Miura, H., Matsuda, N., & Taki, H., 2015. The Analysis of the Brain State Measuring by NIRS-based BMI in Answering yes-no Questions. Procedia Computer Science, 60, 1233-1239. DOI:10.1016/j.procs.2015.08.189.

Toronov, K., Franceschini, M.A., Fiilaci, M., Fantini, S., Wolf, M., Michalos, A., Gratton, E., 2000. Near-infrared study of fluctuations in cerebral hemodynamics during rest and motor stimulation: temporal analysis and spatial mapping. Med. Phys. 27 (4), 801-813. https://doi.org/10.1118/1.598945.

Trambaioli, L.R., Biazoli Jr., C.E., Cravo, A.M., Falk, T.H., Sato, J.R., 2018. Functional near-infrared spectroscopy-based affective neurofeedback: feedback effect, litterary phenomena, and whole-connectivity profiles. Neurophotonics 5 (3). https://doi.org/10.1117/1.NPh.5.3.035009.

Ushiba, J., Soekadar, S.R., 2016. Brain-machine interfaces for rehabilitation of poststroke hemiplegia. Prog. Brain Res. 228, 163–183. https://doi.org/10.1016/bs.pbr.2016.04.020.

von Lüllmann, A., Herrf, C., Heger, D., Schultz, T., 2015. Toward a wireless open source instrument: functional near-infrared spectroscopy in mobile neuroergonomics and BCI applications. Front. Hum. Neurosci. 9, 617. https://doi.org/10.3389/fnhum.2015.00617.

von Lüllmann, A., Ortega-Martinez, A., Boas, D.A., Yuce, M.A., 2020. Using the general linear model to improve performance in fNIRS single trial analysis and classification: a perspective. Front. Hum. Neurosci. 14, 30. https://doi.org/10.3389/fnhum.2020.00303.

von Lüllmann, A., Wabnitz, H., Sander, T., & Muller, K. R., 2017. MBBA: A Mobile, Modular, Multimodal Biostignal Acquisition Architecture for Miniaturized EEG-NIRS-Based Hybrid BCI and Monitoring. IEEE Trans Biomed Eng, 64(6), 1199-1210. DOI: 10.1109/TBME.2016.2594127.

Wang, J., Hu, X., Hu, Z., Sun, Z., Laureys, S., Di, H., 2020. The misdiagnosis of prolonged disorders of consciousness by a clinical consensus compared with repeated coma-recovery scale-revised assessment. BMC Neurol. 20 (1), 343. https://doi.org/10.1186/s12883-020-01924-9.

Wolf, M., Wolf, U., Toronov, V., Michalos, A., Paunesku, L.A., Choi, J.H., Gratton, E., 2002. Different time evolution of oxyhemoglobin and deoxyhemoglobin concentration changes in the visual and motor cortices during functional stimulation: a near-infrared spectroscopy study. Neuroimage 16 (3 Pt 1), 704–712.

Wolf, M., Ferrari, M., Quaresima, V., 2007. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. J. Biomed. Opt. 12 (6) https://doi.org/10.1117/1.2804899.

Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G., Vaughan, T.M., 2002. Brain-computer interfaces for communication and control. Clin. Neurophysiol. 113 (6), 767-791. https://doi.org/10.1016/s1388-2457(02)00057-3.

Wolf, M., Wang, L.V., 2014. Photoacoustic brain imaging: from microscopic to macroscopic scales. Neurophotonics 1, 011003. https://doi.org/10.1117/1. NPh.1.1.011003.

Yin, X., Xu, B., Jiang, C., Fu, Y., Wang, Z., Li, H., Shi, G., 2015. A hybrid BCI based on EEG and fNIRS signals improves the performance of decoding motor imagery of both force and speed of hand clutching. J. Neural Eng. 12 (3) https://doi.org/10.1088/1741-2560/12/3/036004.

Yuce, M.A., Selj, J., Aasted, C.M., Petkov, M.P., Becerra, L., Borsook, D., Boas, D.A., 2015. Short separation regression improves statistical significance and better localizes the hemodynamic response obtained by near-infrared spectroscopy for tasks with differing autonomic responses. Neurophotonics 2 (3) https://doi.org/10.1117/1.NPh.2.3.035005.

Zander, T.O., Katzev, S., 2012. Context-aware brain-computer interfaces: exploring the information space of user, technical system and environment. J. Neural Eng. 9 (1) https://doi.org/10.1088/1741-2550/9/1/016005.

Zander, T.O., Kothe, C., 2011. Towards passive brain-computer interfaces technology to human-machine systems in general. Front. Neurosci. 5 (2) https://doi.org/10.3389/fnins.2011.003505.

Zhang, F., Shieh, S., Lee, M.K., Ono, M., Zheng, Y., Hogue, C.W., 2013. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesth. Analg. 116 (3), 663–676. https://doi.org/10.1213/ANE.0b013e318277a255.