Chapter 15
Biosensors, Biofeedback, and Neurofeedback

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ABSTRACT

In this chapter, the authors write about the processes of biofeedback, giving an insight about the sensors that might be used, the overall concept of biofeedback, as well as the evidence regarding the effectiveness of neurofeedback for the treatment of mental disorders.The main goal is to provide those introducing to the biofeedback as a self-regulation technique, used now for more than 50 years, with concise information about the sensors that might be used to detect the most common measured responses, the main types of physiological biofeedback, and the state-of-the-art evidence about neurofeedback as a form of brain training for individuals with the most prevalent mental disorders. Biofeedback and neurofeedback are guided therapies that include a vast and rowing variety of methodologies aimed to return information to the individual, regarding the physiological functions of the organism itself, in order to enable the modification of those otherwise considered unconscious physiological responses, designed to improve the individual's health and wellness.

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SUMMARY

In this chapter we will focus on the processes of biofeedback, giving an insight about the sensors that might be used, the overall concept of biofeedback, as well as the evidence regarding the effectiveness of neurofeedback for the treatment of some mental disorders.

The main goal is to provide an introduction to the biofeedback as a self-regulation technique, used now for more than fifty years, with concise information about the sensors that might be used to detect the most common measured responses, the main types of physiological biofeedback, and the state-of-the-art evidence about neurofeedback as a form of brain training for individuals with the most prevalent mental disorders.

Biofeedback (BF) and neurofeedback (NFB) are guided therapies that include a vast and rowing variety of methodologies aimed to return information to the individual, regarding the physiological functions of the organism itself, in order to enable the modification of those otherwise considered unconscious physiological responses, designed to improve the individual's health and wellness. This can be performed as a straight operant conditioning model relying on the reinforcement of the signals displayed for the individual to change the physiological responses.

In spite of emerging therapeutic and performance approaches and methodologies, in this chapter the authors focus upon the self-control ability to modulate physiological conditions like, for example, muscle tension evidenced by electromyography (EMG), electrodermal activity (EDA), heart rate (HR), heart rate variability (HRV) and bioelectrical brain activity based on electroencephalogram (EEG). These approaches constitute de physiological basis of biofeedback (EMG, EDA, HR and HRV) and neurofeedback (EEG), that can be applied in order to control a wide range of central, peripheral and autonomic nervous system symptomatology. Both BF and NFB modalities are designed in order to improve a healthy condition and reduce abnormal body activity. When that first condition is achieved, a positive visual (videogame or movie control) and/or auditory (on/off) feedback are given, not target if an unwanted second condition is recorded.

To address the effect of BF and NFB in neurodevelopment and mood disorders, throughout this chapter the main clinical EEG-based neurofeedback and biofeedback protocols applied in attention deficit hyperactivity disorder (ADHD), autism spectrum disturbances and in other adult disorders whose anxiety and/or depression symptoms are present (major depression, post-traumatic stress disorder, obsessive-compulsive disorder and insomnia) are covered.

BIOFEEDBACK

Biofeedback is a process whose basic operating principle is the monitorization of a normally automatic physiological function, providing information that may be used to train someone to self-control and improve such function. Traditionally, a biofeedback system is made upon and based in physiological information obtained noninvasively by a sensor attached directly to the body. It is a valuable supplementary treatment and complements rehabilitation protocols to recover healthy functions, mainly related to neuromuscular (Giggins *et al*., 2013; Spencer *et al*., 2021) and psychiatric disorders (Schoenberg and David, 2014; Markiewicz, 2017; Tolin *et al*., 2020).

The ability to modulate physiological conditions like, for example, muscle tension evidenced by electromyography (EMG), electrodermal activity (EDA), heart rate (HR), heart rate variability (HRV)

and bioelectrical brain activity based on electroencephalogram (EEG) constitute de physiological basis of biofeedback (EMG, EDA, HR and HRV) and neurofeedback (EEG), that can be applied to control a wide range of central, peripheral, and autonomic nervous system symptomatology.

In EMG biofeedback myoelectrical signals (Figure 1) coming from surface electrodes over the individual's muscles that detect a change in skeletal muscle activity are converted into visual and auditory signals. In EDA biofeedback (Figure 2) the individuals are presented with visual or auditory signals related to the changes in skin conductance (usually referred as galvanic skin response), altered by the activity of sweat glands controlled by the autonomic nervous system, and detected by surface electrodes usually placed on the individual's fingertips.

Figure 1. EMG signal from surface electrodes during muscle contraction.

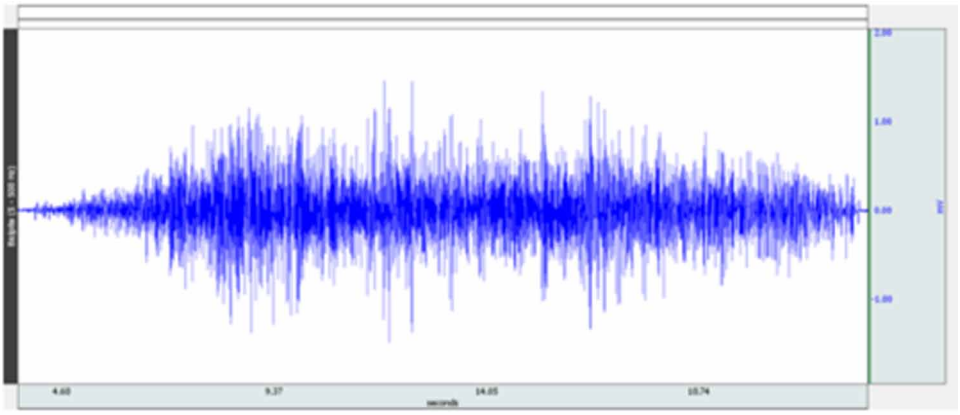
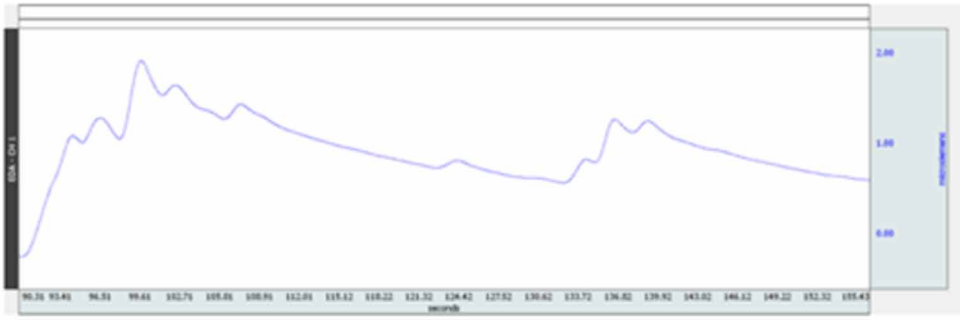


Figure 2. Electrodermal activity of the right fingertips during presentation of stimuli.



In cardiovascular biofeedback different types of responses can be detected as HR and HRV (Figure 3) that can be used to provide real time information about the level of activity of the sympathetic and the parasympathetic divisions of the autonomic nervous system, by using surface electrodes placed in the individual's chest or arms and legs. On the other hand, electrodes placed on the scalp can detect brain

wave patterns (Figure 4) that may be used not only to diagnose disorders as well as in neurofeedback techniques.

Figure 3. ECG signal from lead II in supine position.

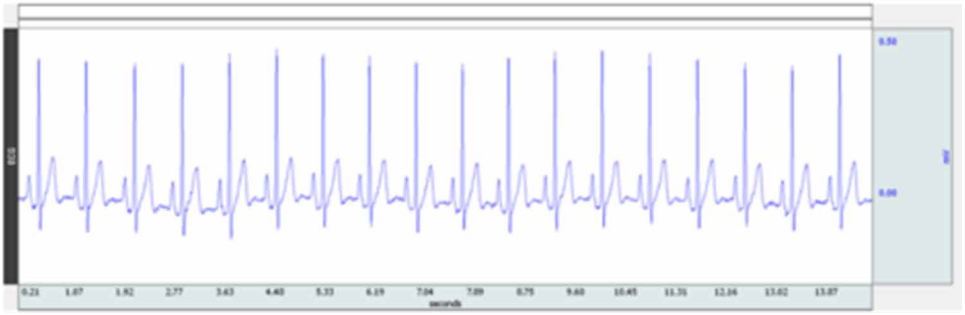
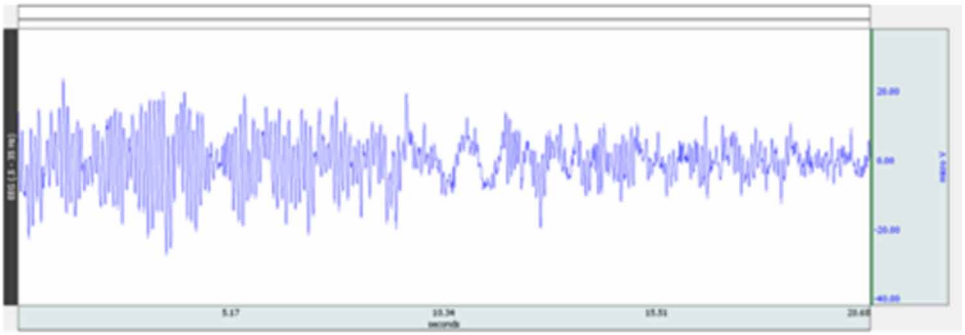


Figure 4. EEG signal from the parietal lobe with the eyes closed followed by open eyes.



The surface electromyographic signal resulting from the electrical activity generated by motor units, measured in millivolts (mV), provides information about the level of muscle activity and has been widely used in biofeedback with reports of its use in neuromuscular reeducation back into the 1960s (Schwartz *et al*., 2017). EMG biofeedback have also been used to treat the symptoms and disorders such as headaches and tension myalgias (Rausa *et al*., 2016; Alonazi *et al*., 2021), pelvic floor disorders that include incontinence, and other medical conditions (Kondo *et al*., 2019).

Sweat gland activity is a physiological response under the control of the sympathetic autonomous system that promote the production of sweat, containing electrically conductive salts, that turn the skin more conductive to electricity. Therefore, the application of a very small electric current to the skin, allows us to measure the skin conductance activity (SCA) that may provide information about the change in this electrodermal activity, that historically has been called galvanic skin response (GSR). The higher the activity of sweat glands the higher is the magnitude of the EDA, measured in units of electrical conductance named as microsiemens (microS). Any change in EDA from the baseline levels is called an electrodermal response (EDR) which normally have a magnitude of 0,1 to 1 microS, and that usually

occurs 1 to 3 seconds after the presentation of a stimulus. The use of EDA in biofeedback is concerned with the observation that skin resistance changes with psychological events (Peek, 2017).

Heart rate variability refers to the variability in the duration of consecutive cardiac cycles and allows to evaluate the autonomous nervous system (ANS), by determining the balance between the activity of parasympathetic (PNS) and sympathetic (SNS) nervous systems. HRV is also dependent upon the respiratory cycle, as heart rate increases during inspiration and decreases during expiration, which is the HRV at the frequency of respiration, also known as respiratory sinus arrhythmia (RSA). As during rest the PNS exerts a dominant control over the cardiac pacemaker, HRV is higher than during exertion as the SNS exerts its cardiac chronotropic effects, increasing heart rate, but decreasing HRV. HRV biofeedback increases self-control over autonomic balance and can have a positive impact on various emotional and somatic symptomatology, namely on cardiopulmonary (Giardino *et al*., 2004; Leher et al., 2018) and psychiatric (Zwan *et al*., 2015; Goessl *et al*., 2017; Economides *et al*., 2020; Blase *et al*., 2020) conditions.

The electroencephalographic signal from the scalp can provide information about the background activity of the neurons from the cerebral cortex that is typically characterized by the power of the signal within different frequency bands: delta rhythm (δ), 0-4 Hz; theta rhythm (θ), 4-8 Hz; alpha rhythm (α), 8-12 Hz; beta rhythm (β), 12-30 Hz; and gamma rhythm (γ), usually 30-70 Hz. The modulation of this signal constitutes the basis of neurofeedback, but besides the neural activity, the activity of areas like the anterior cingulate cortex, the insula or the amygdala, key brain areas related with emotional activity and its regulation, have been shown to be successfully regulated through neurofeedback procedures (Johnston *et al*., 2011; Zotev and Bodurka, 2020; Zich *et al*., 2020).

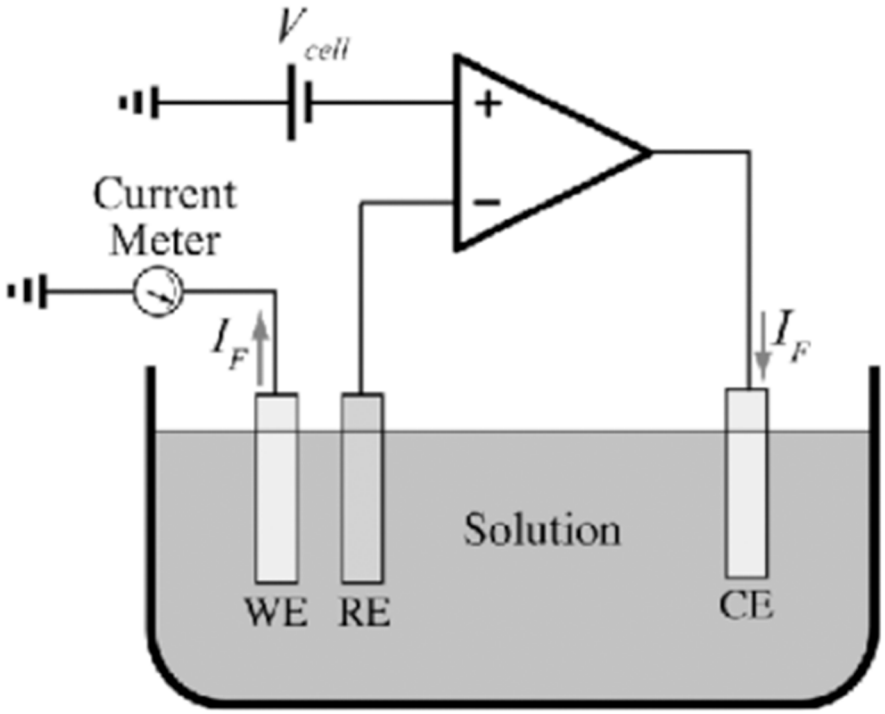
Even though traditional biofeedback is based on physiological information obtained by sensors attached directly to the body, as patients with psychiatric disorders may experience anxiety using sensors attached to their body, new technology has been under development to capture physiological signals with no contact (Oikawa *et al*., 2021) that may, in near future, revolutionize the instruments traditionally used in biofeedback.

Biosensors

Besides the technologies described above, alternative approaches based on the analysis of disease biomarkers could contribute to the diagnosis and monitoring of a wide variety of disorders. According to the Biomarkers Definitions Working Group (2001), a biomarker is "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (p. 91). This includes abnormalities in DNA (germline or somatic), RNA, proteins, metabolites, and abnormal cellular or tissue processes.

The use of a biochemical sensor, or biosensor, "a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" (Nagel *et al*., 1992, p. 148), for the determination of biomarkers can play an important role in the diagnosis and prognosis of a vast number of diseases/disorders. This is due to several factors, such as their high selectivity, which is a result of the use of a selective biorecognition element on the sensors' transducer surfaces, the possibility of minimally invasive analysis strategies (i.e., analysis of blood, sweat, tears, breath, urine, etc.) using low sample volumes and the possibility of their use in point-of-care scenarios. Therefore, an ever-increasing number of studies regarding biosensor development have been reported over the years.

Figure 5. General concept of an amperometric device.



One of the most widely used type of biosensors are based on electrochemical transduction, employing methods such as voltammetry and amperometry, because they complete the advantages mentioned above with highly sensitive analysis. The electrochemical cell used in these methods is usually composed of 3 electrodes (working- (WE), reference- (RE) and auxiliary/counter electrodes (CE)) that are in contact with the analyte solution. The working electrode has a major importance because the redox reaction of interest, and the corresponding electron transfer, occurs on its surface. This WE is therefore modified with the biological recognition element through a variety of immobilisation procedures (e.g., adsorption, entrapment, cross-linking, covalent and/or affinity binding).

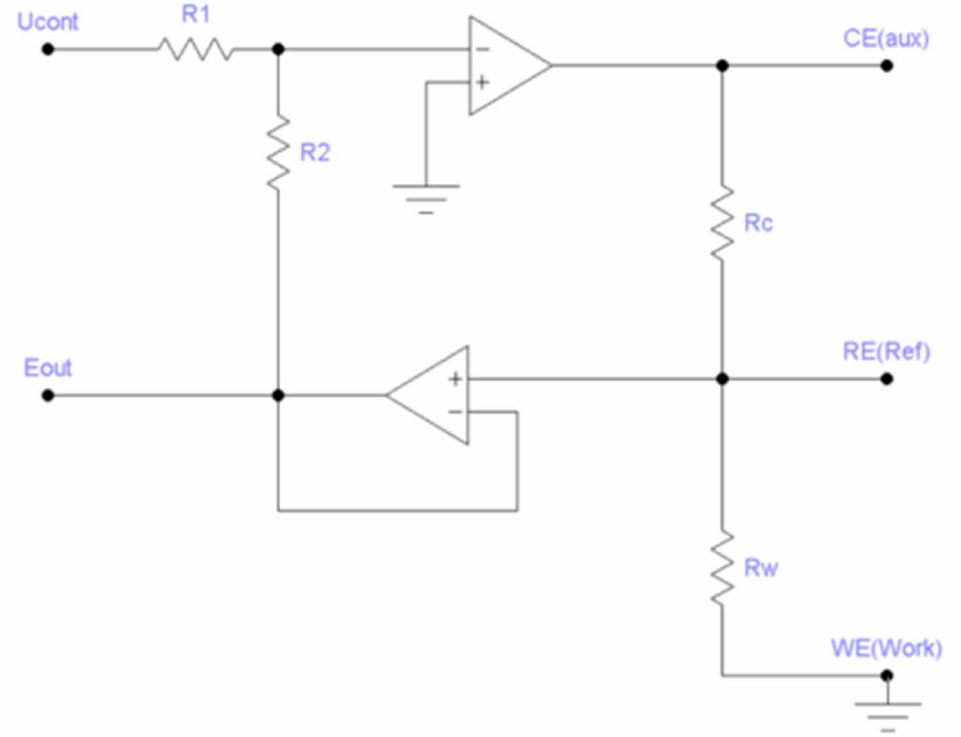
Amperometry

Amperometry is a generic term of a technique that refers to the quantity that is measured, i.e. electrical current. One method to measure current is potentiostatic, whose electrical topology is very similar to a potentiometer since it provides voltage division between three electrical nodes identified by the electrodes themselves: WE, RE and CE (being the *RE* electrode a high impedance input control voltage).

The device's general concept is schematically like the one depicted in Figure 5 (Ahmadi & Jullien, 2008).

A brief look at the circuit identifies a servo loop injecting current I_F at the CE and sampling reference voltage at the RE.

Figure 6. Example of a potentiostat circuit.



As the input impedance of the servo OpAmp is very high, at both inverting (-) and non-inverting (+) inputs, it is a reasonable rational to suppose I_F circulates to the WE.

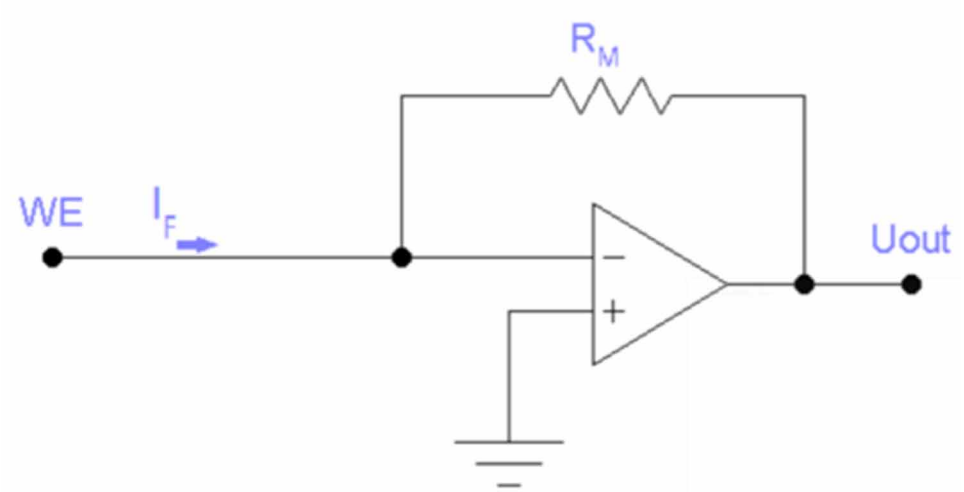
Although the behaviour of amperometric sensors is determined by the WE's specifications, (mainly where, typically, chemical redox reaction takes place), some more insight on how electrical measurements arise could be useful. Indeed, the other two electrodes (RE and CE) also intervene in the measurement.

Generally, amperometric devices use a constant voltage in some convenient neighbourhood of the WE, defining a geometry where electrical field (electrical potential gradient, which is a vectorial quantity) is constant in magnitude. This conception guarantees for WE area chemical reactions reproducibility purposes, as follows: such voltage is usually provided by a conveniently shaped good conductive sheet of material (typically metal like gold or platinum but also conducting carbon) whose conducting properties materialize an iso-potential or equipotential surface and it is connected to a very high input voltage-sampling-control-current loop (OpAmp in Figure 5), the **RE**. Such an electrode, although there is no significant current, either injected or absorbed, forces the shapes of the expected iso-potential surfaces to inherit the same shape parallelly to the WE. This desired spatial homogeneity voltage promotes, in principle, an equally desired reaction rate homogeneity at the WE, minimizing the WE's neighbourhood electrical field (or potential gradient) differences.

In this way, at the WE the current should be, in the neighbourhood of the ground voltage, proportional to the analyte concentration and be well distributed on the entire WE area.

Such voltage definition implies the design of power supplies with good feedback control loops and suitable instrumentation (i.e. voltmeters and ammeters equivalents) in order to assess current measurements.

Figure 7. Detail of the WE current measurement.



At WE electrode surface layer, ion adsorption can, however, impose supplementary caution in the applied voltage and subsequent current measurement.

Some of the exemplar circuits used in a potentiostat are like the one depicted in the Figure 6 (Hernández *et al*., 2003).

As can be seen, the circuit establishes the RE potential with the aid of the CE excitation while current is measured at the WE. Current measurements imply the use of resistances that are dimensioned to allow a very small to ground (reference *zero* potential) voltage difference. Also, the CE should remain chemically absent (while any oxidation-reduction process at the WE imply an opposite reduction-oxidation process at the CE). CE material choices could include platinum or gold for its relative inertness. In the schematics, Rc and Rw are the electrical equivalent solution resistances and so they are naturally implemented as soon as electrodes are introduced in the solution.

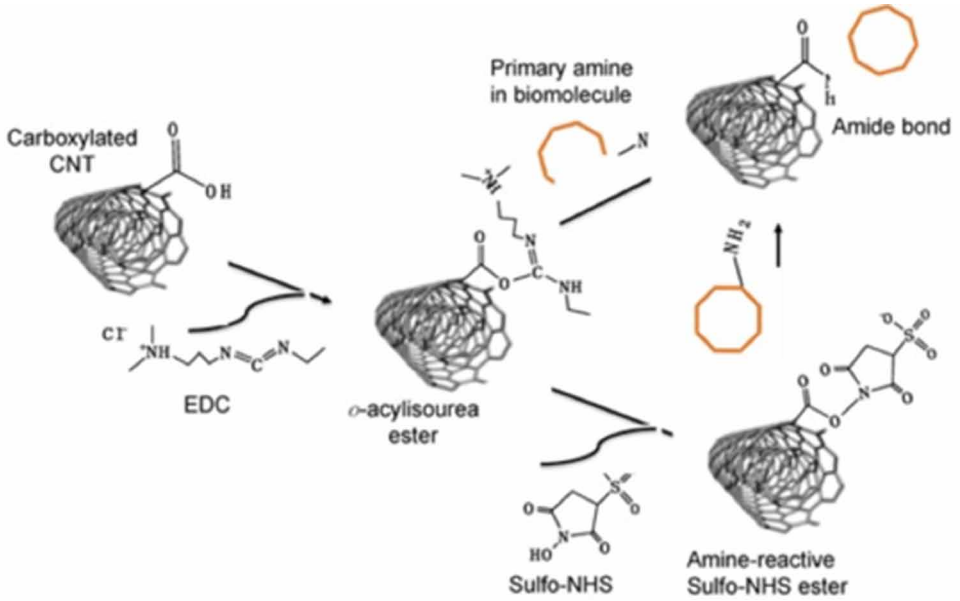
As a last step, WE currents can be enormously magnified by an equivalent transimpedance amplifier whose main task is the current to voltage transfer function $U_{out} = -I_F \cdot R_M$. It is this voltage, rather than the WE current, that is recorded and processed to assess WE biochemical redox phenomena (Figure 7) (Ahmadi & Jullien, 2008).

Biosensors for Neurological Disorders

Measurement of neurotransmitter concentrations can be used for the identification of several neurological disorders such as Parkinson's disease, Alzheimer's disease, post-traumatic stress disorder, epilepsy, schizophrenia, etc.

Glutamate is one of the biomarkers used for the diagnosis and evaluation of neurological disorders because its dysregulation is associated with several neuropathological conditions. A high level of glutamate in the blood and other biological fluids can indicate ischemic stroke, epilepsy, or other neurological disorders. Therefore, many biosensors for the analysis of glutamate have been developed, some of which are highlighted below.

Figure 8. Schematic representation of the reaction scheme for EDC and EDC-NHS based covalent immobilization of biomolecules on carbon nanotubes (Zhou et al., 2019).

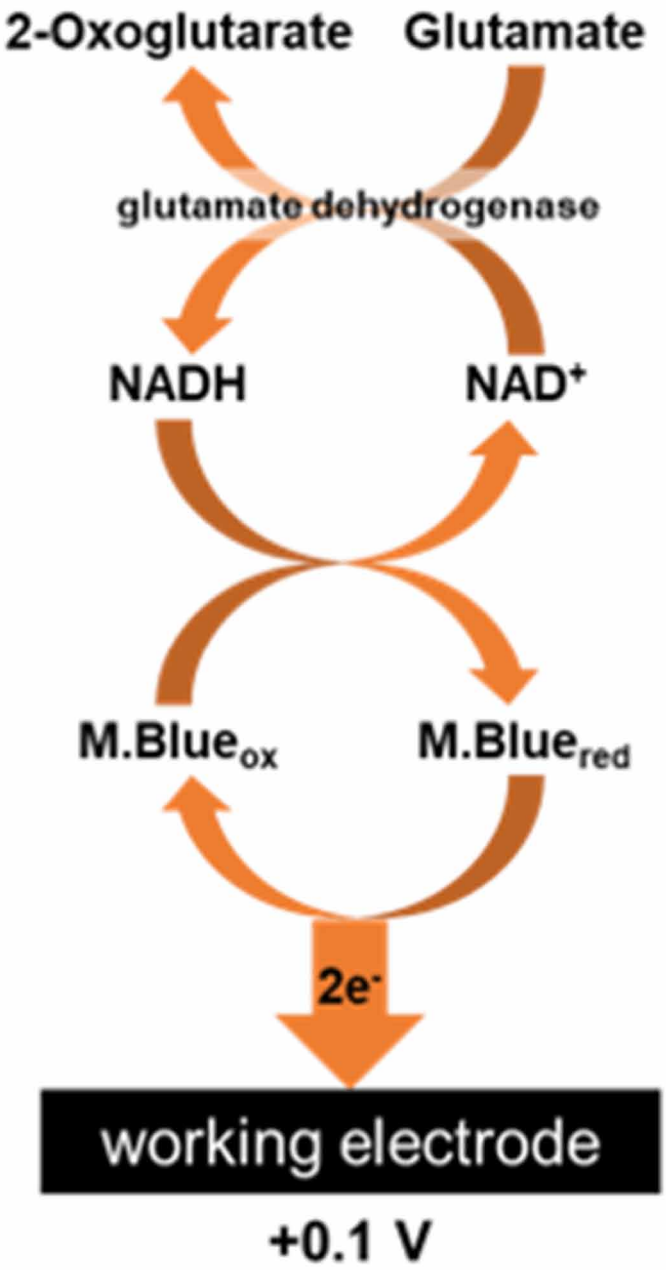


Batra and Pundir (2013) developed an amperometric biosensor for the determination of glutamate in human sera using the enzyme glutamate oxidase as the biological recognition element and a gold electrode transducer that was modified with multiwalled carbon nanotubes (MWCNTs), gold nanoparticles, and a chitosan composite film. The enzyme was covalently immobilized on the MWCNTs using N-ethyl-N′-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) (Figure 8), providing a stable sensing platform. L-glutamate oxidase catalyzes the oxidative deamination of L-glutamate, in the presence of water and oxygen, to form 2-oxoglutarate, ammonia and hydrogen peroxide. In this work the quantification of glutamate was based on the fast (2 s) amperometric measurement (+0.135 V vs. Ag/AgCl) of the hydrogen peroxide formed in the enzymatic reaction. The authors reported a linear concentration range between 5 and 500 μM and a limit of detection of 1.6 μM.

In another approach, glutamate was also quantified in serum samples (Mruga *et al.*, 2021). The authors likewise used glutamate oxidase and measured hydrogen peroxide by amperometry (+0.6 V vs. Ag/AgCl, response time: 5-20s), but employed a platinum disk working electrode and immobilized the enzyme by using bovine serum albumin and gluteraldehyde. In this work the authors constructed the working electrode by soldering a platinum wire in a glass capillary. A fusible Wood's alloy was used to connect the platinum wire to an internal conductor, which was then linked to a contact pad to be able to connect the electrode to the potentiostat. In this case a linear concentration range between 5 and 600 μM and a limit of detection 3 μM were achieved.

Hughes et al. (2015) used another enzyme, glutamate dehydrogenase, for the construction of a reagentless amperometric biosensor for the analysis of glutamate in food and human serum samples. The transducer for the construction of this biosensor was a screen-printed carbon electrode modified with Meldola's Blue, which greatly reduces the over-potential for the oxidation of NADH (see below). Chitosan and multiwalled carbon nanotubes (MWCNTs) were used to encapsulate the enzyme and the

Figure 9. Schematic representation of the reactions that occurred at the amperometric glutamate biosensor's surface developed by Hughes et al. (2015).



co-factor nicotinamide adenine dinucleotide (NAD^+). The working principle of this biosensor was based on the oxidation of glutamate forming 2-oxoglutarate in the presence of the enzyme and NAD^+. NADH is also formed during the enzymatic reaction and subsequently reduces Meldola's Blue which was then electrochemically oxidized (+0.1 V vs. Ag/AgCl, response time: 20-30 s) at the electrode's surface to produce the analytical signal (Figure 9).

In this study a linear concentration range between 7.5 and 105 μM and a limit of detection 3 μM were achieved.

Non-Invasive Sensors

Non-invasive methods would be a sensational upgrade of the techniques for the evaluation of neurological disorders. One example is breath analysis for the detection of epilepsy crisis in early stage (van Dartel *et al*., 2020), which was based on the presence of volatile organic compounds in exhaled breath. Although the developed method was able to differentiate between epilepsy patients and control subjects, the number of false positives and false negatives was rather high, so additional research is still needed. Nevertheless, the proposed method is a promising concept because it is non-invasive and does not need the same amount of apparatus as amperometric-based devices.

NEUROFEEDBACK

The history of neurofeedback goes back to the beginning of the 20th century with the studies of Pavlov's conditioned reflexes in dogs. Later, between 1930 and 1940, feedback was transposed to living beings through self-regulation mechanisms, by Norbert Wiener and Petr Anokhin. But it is between 1960 and 1980, in the United States of America, that the true evolution of the technique and transposition for human beings takes place, with Joe Kamiya demonstrating, in 1962, that a person could control his alpha activity through feedback and with Roy John, during the 80's to develop different EEG-biofeedback protocols (Kropotov, 2009).

Neurofeedback (NFB) is thus part of neurotherapies, being a technique that, based on the subject's electroencephalographic activity, attempts to self-regulate using a modality of auditory and visual feedback, aiming at the alteration of a given parameter of brain activity in a conscious and voluntary way (Kropotov, 2009). In some cases, combined biofeedback skin conductance, electromyography and hear-rate variability are accessed to improve autonomic nervous system benefits.

In a global approach, clinical data, psychological tests assessment and qEEG analysis contribute to elaborate the patient protocol. Commonly, two brain frequencies are modulated. One example is SMR/Theta protocol applied in bipolar C3-C4 montage in scalp areas, in which first frequency (SMR) tends to be rewarded, and second frequency (Theta) tend to be blocked. NFB protocols allow us to train amplitude, coherence, Z-scores and power of certain brain rhythms.

It is estimated that 30% to 50% of people benefit from biofeedback and neurofeedback therapy. When good outcomes are reported, 20 to 50 sessions, twice a week are applied. Reduced number of sessions, lack of motivation or misunderstanding of the purpose of the intervention (commonly in very young children or in older population) are limiting factors to the success of the therapies (Kadosh and Staunton, 2019).

In Children population, both attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ADSs), exhibit poor ability in behavioral control and in lower academic outcomes are achieved.

ASDs are characterized by early onset of impairments in social interaction and communication and the development of uncommon stereotyped behaviors, loss of face contact, poor attention, impulsivity, aggression, self-injury and, sometimes, hypersensitivities to sensory stimulation (Austin, 2008). Abnormal function in brain regions and networks associated with social cognition and action perception (Pelphrey and Carter, 2008) are linked with human mirror neurons (Hamilton 2013). Increased firing in

inferior frontal gyrus and inferior parietal lobule during execution action's observation have been linked to potential mechanism of perceiver's sensorimotor (SMR) rhythm (Rizzolatti and Craighero, 2004; Pineda, 2005; Depretto *et al.*, 2006; Oberman *et al.*, 2008). Based on these mechanisms, NFB training protocols involving right and/or left sensorimotor cortex have been successfully applied. Positive behavior improvement was obtained after right (C4) SMR band reward and theta or beta band amplitude inhibition during a videogame or a DVD movie (Datko *et al.*, 2018). Imitation a simple finger-lifting action during NFB training was also applied (Iacoboni, 1999). Other neurophysiological changes in ASDs showed high delta and theta activity in frontal and central areas and a Betha/Theta protocol in Fz-Cz areas can be applied. Also, high beta activity was observed in 25% of cases. Because children with ASD show deficits in autonomic states, a model of neurovisceral integration, which proposes heart rate variability and skin conductance, BFB have been suggested in combination with NFB protocols (Friedrich *et al.*, 2014).

A complex ADHD etiology involving common and rare genetic variabilities, dopamine (Levy, 1991), norepinephrine (Del Campo *et al*., 2011), GABA (Edden *et al*., 2013) and serotonin (Quist and Kennedy, 2001) changes as well as several environmental risk factors including those associated to neuroinflammation (Reus *et al*., 2015; Hassan *et al*., 2016) has been linked to hyperactivity as well as impaired attention. These can induce electrophysiological changes in several cortical and subcortical areas, namely prefrontal cortex and its connection to striatal, cerebellar and parietal regions (Arnsten and Rubia, 2012), basal ganglia (Chen *et al*., 2018) and substantia nigra (Krauel *et al*., 2010; Romanos *et al.*, 2010) explaining the lack in behavior control and disability in attention skills. Also, children with poor disability in motor planning and in concentration/attention seems to have an EEG market of slower fontal and central brain activity, reason why, in majority of cases, SMR, Betha/Tetha or even Betha/Delta protocols in frontal Fz-Cz (Schönenberg *et al.*, 2021) or monopolar F3, F4, Fz alpha power improvement (Hanslmayer *et al*., 2005) can be applied. Regarding with motor control, SMR 12-15 Hz activity reinforcement seems to be a very effective training applied in ADHD (Lubar and Shouse, 1976; Leins *et al.*, 2007; Arns *et al*., 2014; Cortese *et al*., 2016) and also in human epilepsy (Syerman and Friar, 1972), given SMR activity, performed by thalamocortical pathways, occurring if both attention and relaxation muscle are present. In order to improve the results, some therapists use EMG biofeedback in face, arms or legs muscles.

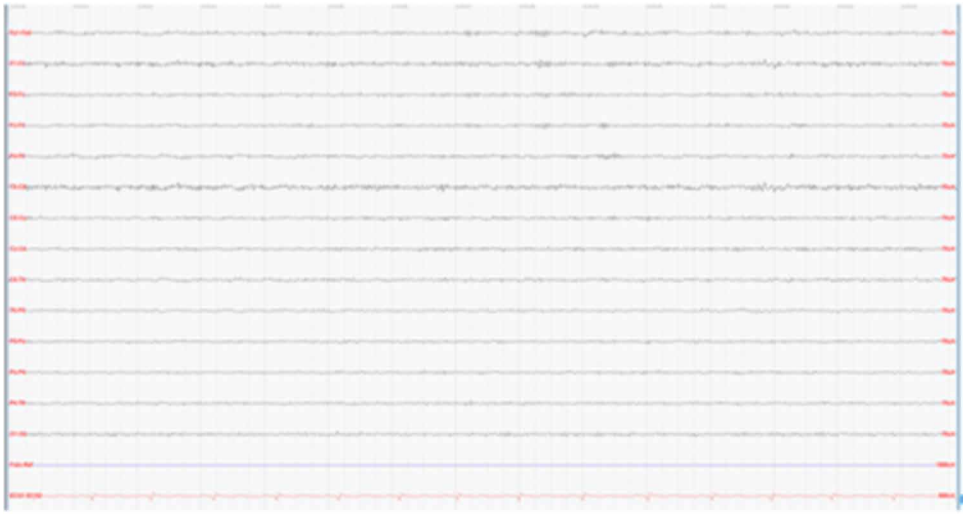
In adult population, mood disorders in which anxiety and depression take part of main symptomatology, NFB and BFB are considered one of non-pharmacologic therapeutical approaches. Major depression, post-traumatic stress disorder (PTSD), obsessive-compulsive disturbance (OCD), insomnia and others belong to neuropsychiatric disturbances whose changes in cellular dynamics of several brain areas induces a down-regulation of mood and emotions. For example, in case of PTSD, real-time MRI neurofeedback can help in self-regulation of hippocampal formation (Misaki *et al.*, 2021), dorsomedial prefrontal cortex, middle cingulate cortex, amygdala, parietal cortex and insula (Misaki *et al*., 2019, Misaki *et al*., 2021)

Despite the growing number of patients looking for alternative non-pharmacological therapies, majority of cases have been previously treated with pharmacological drugs whose target is the synaptic neurochemical modulation, what can be associated, in EEG patterns, at faster frequencies and lower amplitude brain signals (Figure 10).

In opposite, soft or mild symptoms in non-pharmacological-treated patients can show slower brain activity (Figure 11) in their EEG pattern.

There are a relatively accordance in psychiatric NFB application, in which Theta/Beta ratio and SMR reinforcement protocols should be explored (Batail *et al*., 2019). In each patient, this possibility should be previously confirmed by qEEG recordings. Additionally, alpha asymmetry protocol is identified as a promising EEG-biomarker (Choi *et a.l*, 2011; Wang *et al*., 2019), meaning and excessive beta or theta

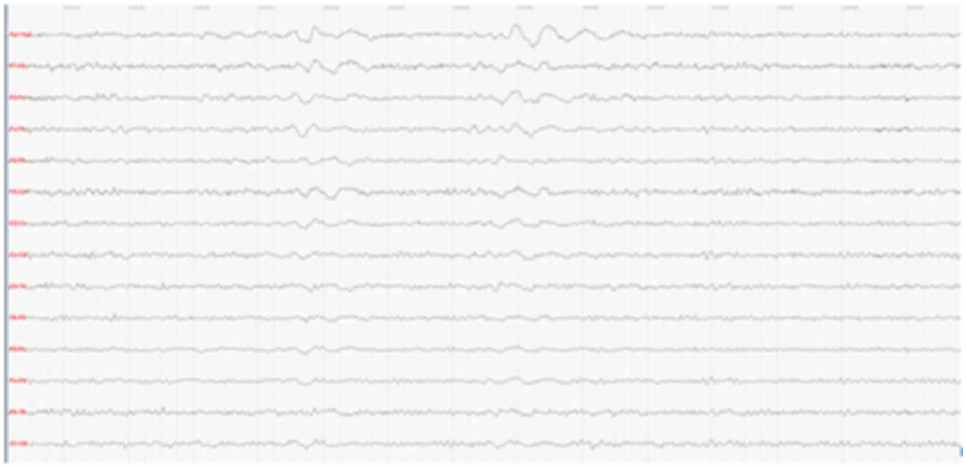
Figure 10. Electroencephalogram pattern recorded in an adult woman with depressive symptomatology after some years with antidepressant therapy. A fast and low-voltage pattern is recorded in all brain areas.



frequency in a given brain area, while contralateral homologous region remains in alfa domain. In these cases, and high beta downtraining (Wang *et al*., 2019) or Alpha/Theta training could be applied (Cheon *et al*., 2016) to control major depression and anxiety symptoms of OCD, sleep disturbances and PTSD. Because alpha rhythm of parietal and occipital brain areas is recorded in eyes-closed condition, an auditory feedback is given; in this case, positive feedback in linked to a completely clear and normal volume of sounds and, in opposite limit, negative feedback is associated with no sound.

Neurofeedback, despite not being a recent technique, still presents capacity and opportunity for expansion, as is the case of applying the technique to some sleep disorders (it is known that restorative

Figure 11. Electroencephalogram pattern recorded in an adult woman with depressive symptomatology. No previous antidepressant-drug therapy was administrated. Note, especially in frontal areas, slower brain activity.



sleep is essential for the physical and psychological well-being of any individual), or to addictive states such as alcoholism. Anyway, what stands out from the most recent literature is the combination of this neurotherapy with functional magnetic resonance, thus emphasizing, once again, that science will always be multidisciplinary (Tang *et al.*, 2016; Dousset *et al.*, 2020; Thibault *et al.*, 2018).

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