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Neurofeedback Treatments for Depression Disorders- Review of Current Advances

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ABSTRACT

Depression is one of the most common and debilitating diseases worldwide, especially in industrialized countries. Depression is traditionally managed with psychological, pharmacological, or physical interventions alone or in combination forms. However, all of the conventional methods have various limitations, such as medication side effects, frequent relapse, and high economics costs. In addition, a significant portion of the depressive disorders are treatment-refractory that do not respond to the usual medications. These different challenges emphasize the need for effective alternative treatment for depression. Neurofeedback technique (NFT) is a noninvasive and non-drug treatment through which patients learn to modulate their brain activities using repeated practice to eliminate the disease-specific patterns in electroencephalogram (EEG) of the patient. NFT emphasizes on the correlation between EEG and cognitive and behavioral disorders. There are several clinical protocols for NFT in treatment of Depression. All of these protocols aim to shift the brain activities, EEG waves, from disorder into normal state. Therefore, in developing efficient NFT for depression or any other disorders, determining the EEG based indices which are specifically correlated with different cognitive states is necessary. Several protocols have been developed based on these indices for depressive disorders and some of them are clinically used. Left to the right hemisphere alpha predominance, decreasing Theta/Beta ratio in left prefrontal cortex, decreasing left- or increasing right- hemispheric alpha activity, shifting an asymmetry index toward the right to rebalance activation levels in favor of the left hemisphere are some of the main protocols. This paper reviews the basic principles of NFT, its procedures and protocols for the treatment of depressive disorders and clinical outcomes.

Key words: Neurofeedback, Biofeedback, Depression, Electroencephalography, Quantitative electroencephalography, Treatment.

INTRODUCTION

It has been estimated that by the year 2020, depression will be the second leading cause of disability worldwide. Regarding the current prevalence and growth rates, depression is reported as the most important disease in the WHO'S global statistics for 2020. It affects up to 15% of the population of industrialized countries. The health and social impacts of depression are not confined to the patients themselves, but frequently involve their families, social and occupational relationships [1].

Currently, depression is managed with psychological, pharmacological, or physical interventions alone or in combination forms. Studies have shown that almost all the conventional treatment options have different drawbacks such as medication side effects, frequent relapse, and high economics costs. In addition, a significant portion of the depressive disorders are treatment-refractory who do not respond to the usual medications[2]. Even patients who respond to antidepressant treatment are often reluctant to take medication in the long term and thus experience an increased relapse risk [3]. These different challenges highlight the need for developing new effective alternative treatment for depression which can be used as adjunctive or stand alone treatment.

In this regard, different approaches have been proposed that highlight the correlation between electroencephalogram (EEG) and cognitive or behavioral disorders. An interesting article published in a journal of the "Nature Group" in 2003, stated possibility of using EEG based markers of depression acquired in REM sleep, as a predictor of therapeutic success of subsequent pharmacological treatment[4]. In line with this approach, another study in 2006 demonstrated that it is possible to predict the potential effects of different antidepressants, 48 hours before any perceived effect, using and analyzing EEG for choosing the best pharmacological treatment[5]. Bruder et al. (2008) proposed Alpha asymmetry index as an EEG based index to predict the antidepressants response prior to pharmacologic treatment in choosing the best treatment[6]. In cognitive disorders like depressive disorders one of the main challenges in the management of the disease is the subjective approach in the treatment and diagnosis of disease. It is clear the answering the standard questionnaires for assessing the depression is strongly dependent on the current mood of patient and also the interpreting and analyzing the answers are affected by the physician backgrounds. As a result, different diagnoses and thus different prescription for the same patient is probable. To resolve the problems of subjective approach, we can use more objective indices in diagnosis and management of cognitive disorders like depression. EEG is the recording of electrical activities of brain containing various types of physiological and hemodynamic information of different regions of the brain. Recent advances in the signal processing as well as insights into the connections with different parts of the brain have enabled scientists to extract useful clinical and physiological information from EEG[7-10]. We can extract functional information from EEG associated with specific cognitive functions[10-13].

Neurofeedback technique (NFT) is a direct training of brain function, through which the person learns to function more efficiently and direct the brain activities towards the desired state. The brain's activity is monitored and the corresponding information is presented for the person; they receive a reward when they changes brain activities towards an appropriate pattern they will be rewarded. This is a gradual learning process that can be applied to any measurable aspect of brain function.

This paper reviews the basic principles of NFT, its procedures and protocols for the treatment of depressive disorders, and clinical outcomes. Recent advances in NFT for depression in clinical and research scales are reviewed. In addition, the concept of low energy NF system and its fundamental principles are discussed.

Fundamentals of neurofeedback techniques

Biofeedback (BF) is a mind-body technique that has been proposed to strengthen the communication between mind and body (NCCAM, 2007).

BF emphasizes on relaxation and stress-reducing techniques. Using these techniques, individuals can learn to control a variety of physiological responses which formerly thought to be completely involuntary. Therefore, this technique help manage anxiety and pain commonly associated with stress reactions[14-17].

The U.S. Food and Drug Administration (FDA, 2007) has a certain definition of a BF device: "an instrument that provides a visual or auditory signal corresponding to the status of one or more of a patient's physiological parameters (e.g., brain alpha wave activity, muscle activity, skin temperature, etc.) so that the patient can control voluntarily these physiological parameters".

However, there are several different types of BF. EMG BF, measuring muscle tension; is proposed for the treatment of chronic muscle stiffness, injury and pain (e.g., neck and back pain); headaches, asthma, incontinence; and intestinal symptoms. Thermal BF, measuring skin temperature; is proposed for the treatment of circulatory disorders, such as headaches, hypertension, and Raynaud's phenomenon. Galvanic skin response (GSR) BF, measures electrical conductance in the skin associated with sweat gland activity and perspiration. GSR is proposed for the treatment of anxiety disorders and phobias[18].

BF modality used for constipation treatment was EMG-based BF and positive results were reported in 69–78% of patient and in adults not children, with improvements maintained for up to two years (American Gastroenterological Association (AGA), 2000). Another disorder is urinary incontinence and BF has been proposed as a treatment modality for multiple type of urinary (FDA, 2005)[19, 20] with an improvement in incontinence for up to two years following the use of BF[21, 22]. BF is effective in reducing the severity and frequency of migraine and tension headaches in adults and children[23-26]. In addition, The National Institute for Health and Clinical Excellence (NICE, 2002), the American Cancer Society (ACS) and The National Comprehensive Cancer Network (NCCN,2007), generally state that BF is a non-pharmacological treatment option on the treatment of breast cancer and for patients who experience nausea and vomiting after or during chemotherapy and radiation".

Overall, there is a lack of randomized controlled trials using sufficient sample sizes, comparing BF to established therapeutic modalities (e.g., pharmacotherapy, behavior therapy) with long-term follow-ups.

Neurofeedback (NF) or EEG-BF is a form of BF that works based on the EEG based measures aiming to shift the disorder associated markers into healthy state associated measures.

During early 1960s, Dr. Joe Kamiya discovered that some of his research subjects could learn to control the amplitude and frequency characteristics of their own EEG if provided feedback about those characteristics. Many psychologists and medical practitioners soon sensed the possibilities such operant control of central nervous system electrical activity might have for clinical treatment. Within a few years, the term EEG-BF or NF was applied to these methods, a BF society was formed, related research was completed at several laboratories, and increasing numbers of clinicians began applying EEG-BF in the treatment of anxiety and other psychiatric disorders(7). Nowadays, EEG-BF or NF has been proposed for the treatment of multiple disorders including insomnia, attention deficit hyperactivity disorder (ADHD), anxiety disorders, epilepsy, addictions, tinnitus, brain injury, depression, and learning disabilities. However, what appeared to be an extremely promising treatment modality quite suddenly fell into disrepute[7]. During the first years after this discovery, studies on BF have been hampered partly because of prejudice on similar concepts like Zen, mind control, etc. However, advances in signal processing, knowledge in behavior-neurophysiological association and well controlled trials have drawn the research interests to BF and NF.

QEEG and Neurofeedback in Depression

There is a good consensus among neurotherapists that it is necessary to have objective assessments or indices on a subject's EEG characteristics prior to any BF intervention. In this regard, computerized EEG analysis techniques that provide measures of a large number of EEG characteristics are used. These techniques are referred to as quantified EEG or quantitative EEG (QEEG). When used in conjunction with a normative database, they are capable of providing useful information for deciding what EEG parameters to modify and for determining the degree to which such parameters have been modified successfully. As with the field of EEG-BF, the development of QEEG techniques has been rather recent. Consequently, there is considerable controversy about specific procedures to be used, the range of disorders to which they are applicable, dangers inherent in their use, and qualifications for using QEEG and NFT. There is a strong need for research addressing these issues. To date, no comprehensive source of

information has been available to anyone wishing to explore the nature of NF and its association with QEEG.

Computerized analyses of EEG signals involve a number of factors: (1) frequency distribution, (2) voltage (as amplitude of the electrical signals), (3) locus of the phenomena, (4) waveform or wave shape morphology, (5) Interhemispheric symmetries (symmetry of voltage, frequency, wave shapes for homologous sites), (6) character of waveform occurrence (random, serial, continuous), (7) regulation of voltage and frequency, and (8) reactivity (changes in an EEG parameter with changes in state). In an effort to visualize better the distribution of specified frequency band powers and amplitudes and symmetries of these measures, computerized display programs have been developed. These methods utilize certain features of the EEG, such as digitized amplitudes, in a computerized game-like form in which the patient attempts to use feedback concerning these features to achieve a specified goal of EEG change consistently by maintaining a certain "correct mental state." These "correct states" are those that have been shown by QEEG measurements to correlate with a "normal" state of brain functioning. Thus, for example, if QEEG findings reveal a disproportionate ratio of theta to beta amplitudes in a given brain region (compared to the normal), a computer game in which one needs to keep a "Pac-Man" moving solely by developing a more normal theta/beta amplitude ratio is conducted during a therapeutic session. Over a series of sessions, the ease of maintaining this correct ratio by the patient usually increases and, upon psychometric testing of attention abilities, a corresponding improvement in scores is commonly seen. The number of sessions required to achieve a stabilized effect appears to vary from patient to patient, but anecdotal reports indicate positive effects are considered stable over years.

Current protocols of neurofeedback for depression

There are several clinical protocols used to apply EEG-NF such as the alpha predominance in the left hemisphere to the right and decrease left-hemispheric alpha activity, increase right-hemispheric alpha activity, shift an asymmetry index toward the right in order to rebalance activation levels in favor of the left hemisphere, and the reduction of Theta activity (4-8 Hz) in relation to Beta (15-28 Hz) in the left prefrontal cortex (i.e. decrease in the Theta/Beta ratio on the left prefrontal cortex)[27, 28]. Dias and Deusen (2011) applied a new NF protocol that simultaneously capable of providing the training demands of Alpha asymmetry and increased Beta/ Theta relationship in the left prefrontal cortex[29].

However, limitations of the previous studies including small sample size, inadequate or no controls, lack of randomization or comparison to conventional therapies, and/or long-term follow-up, as well as inconsistent outcome measures and incomplete reporting of data, make the NF therapy no effective for the treatment of disorders such as depression, statically.it must be noted that the field still has space for substantial evolution, especially in regard to the elaboration of new and more complete training protocols that may be capable of maximizing this potential.

EEG measures for neurofeedback assessment

The EEG is categorized in frequency bands with differing amplitudes: Delta (2-4 Hz) and Theta (4-8 Hz) bands as slow, Alpha (8-12 Hz) as intermediary, and Beta (12-38 Hz) and Gamma (38-42 Hz) as fast frequency bands. it is acquired that greater Alpha activity on the left hemisphere is correlated with the inhibition of local neural networks, and hence that the EEG is asymmetric to the right[29]. In line with recent advances in the field of EEG-based marker for identifying depression and anxiety; the therapeutic values of EEG have also been entered in the related research in two main fields: 1- identifying the exact place of given clinical complaints by the process of mapping brainwave patterns. 2- synthesis the normal activation or normal wave activity in a cranial place where the EEG abnormality has been observed, by stimulating the client to increase or decrease power in specific EEG bands, as read from electrodes positioned over specific areas on the scalp. This technique is called neurofeedback or EEG-BF or EEG-neurofeedback. In addition, we can produce the same absent frequency and amplitude of the brain wave and convey it to the scalp directly. NF represents a form of operant conditioning, through which an individual may learn to modify the electrical activity of his own

brain (Thatcher, 2000). It is widely believed to be free of any side effects or health risks, however, it is important to determine with caution the presence of paroxysmal activity in the frequency bands to be amplified to avoid the amplification of the same paroxysmal phenomenon[29].

NF is different technique in comparison to all external stimulation techniques in that it enables patients to control their brain activity and thus to contribute in an important therapeutic factor that is their experience of self-efficacy[30]. Principally, there are at least two methods of NF in which self-regulation of brain activity may be beneficial for depression, ADHD, mood disorders, posttraumatic stress disorder, and other mental disorders:

1. A primary abnormal process may be addressed by self-regulation training, such as Hyperactivition or Hypoactivition of specific brain areas or networks. In this approach, identifying such abnormal activation patterns in individual patients beforehand will necessary.
2. Neuromodulation can also act in a different way, by activating or suppressing circuits that are not primarily abnormal, but whose modulation may nevertheless produce clinical benefits[31].

There are two main trends in developing NF applications in depression: the first is based on asymmetry of Alpha activity to the left prefrontal cortex or the increased left prefrontal cortex Alpha activity acquired in depression. In this protocol patient is instructed to train Alpha predominance in the right prefrontal cortex and decrease of Alpha activity in the left prefrontal cortex. This protocol is the most mentioned protocol in several literatures [6, 32-35] and Derubeis et al. (2008) stated that "finding in the diverse studies on the EEG spectral suggest the existence of decreased metabolic activity of left prefrontal cortex or in fact, increased Alpha power in this area of depression individuals, both in relation to their right frontal activity and in relation to the left prefrontal EEG activity in healthy individuals[36].

The second trend focuses on Theta/ Beta ratio in the left prefrontal cortex that in the depression patients it is more than healthy one [27, 28]. The Beta activity is related to motivational and executive functions and in depression it is diminished. In addition, an increase in Theta activity is associated with a lower brain activity which worsens the depression disorder. Therefore, the goal is decreasing the Theta activity, increasing the Beta activity or decreasing Theta/Beta ratio in the left prefrontal cortex of depressed one. However, the close relations of depression and anxiety implies the necessity for careful programming in order to eliminate the possibility that a training protocol for depression lead to increased anxiety. Because the high activity of Beta3 (23-38Hz) in both hemispheres is directly associated with anxiety, in applying the Theta/Beta ratio, it is critical to increase just the Beta1 (15-20Hz) activity on the left hemisphere. In the new protocol of Dias and Deusen, presented three parameters for the brain to train: increase of the asymmetry of Alpha (9-14Hz) to the right, increase of the Beta/Theta relationship (Theta 4-8Hz) on the left prefrontal cortex, and reduction of the Beta 3 component (23-38 Hz) over the entire prefrontal cortex[29].

Although studies with the fMRI and metabolic imaging with positron emission tomography (PET) have indicated several potential disease-relevant features for depression including significant imbalances between prefrontal and limbic areas[37, 38], none of these have been validated as biomarkers for use in individual patients[39]. Similarly, although some positive results have been obtained with EEG mapping techniques, especially in relation to hemispheric asymmetries in depression, the clinical trials have not established clinical efficacy and effectiveness of EEG -BF in depression, ADHD or other mental disorders[32, 40-42]. To date, there is insufficient evidence to identify any reliably abnormal, local, or distributed brain activation patterns in individual patients specially with depression that could be targeted with NF[39].

DeRubeis et al indicated that NF has “revealed promising effects in recent clinical trials” for depression treatment[36]. A study with a five-year follow-up period claimed that the therapeutic effects last five years[43], while other study, with a two-year follow-up, indicated a treatment effectiveness

of 92% of NF for depression in comorbidity with alcoholism[35]. Despite these promising findings, the field still needs more substantial evolution, especially in developing new and more comprehensive training protocols of NFTs for depression.

Neurofeedback Techniques in Depression

There are two major methods of NF for clinical settings: A functional imaging approach with fMRI and EEG-NF.

EEG-NF in depression

EEG-NF studies of depression were originally based on Davidson's approach(i.e. withdrawal model of emotion)[44]. In this approach, the left and right frontal cortex respectively serve appetitive and aversive emotional behaviors[45], and hypoactivity of left frontal areas would be associated with depression[46, 47].

Alpha activity of the EEG is associated with relaxation and meditation, it means lower metabolic activation. this relative left hypoactivity would be associated with relatively higher left than right frontal alpha power[48]. In consequence it is necessary to train patients to decrease left-hemispheric alpha activity, and increase right-hemispheric alpha activity.

This asymmetry model was support initially from the stroke literature because depression seemed to occur more frequently after damage to the left than the right hemisphere. But current evidence in neuropsychiatry, states that there is no such preferred association between depression and left-hemispheric damage[49]. The EEG literature has also been inconsistent in that not all authors found higher left-hemispheric alpha activity in patients with depression compared with healthy controls,[50] although a recent meta-analysis supported the asymmetry model based on resting EEG data[51]. The considerable interindividual variability of EEG asymmetry limits its usefulness as a NF target[52]. In the EEG-NF protocol, Asymmetry of alpha power is the main index that has used as feedback signal and trained patients to increase the right-to-left ratio, essentially rebalancing a considered hypoactivition of the left hemisphere. Rosenfeld et al (1996) noted This asymmetry index as A=100x(R-L)/ R+L), where R and L are the square root of power of alpha activity measured at a right and left frontal electrode respectively (Obtained by Fast Fourier Transformation)(53)

A current placebo-controlled randomized (but not blinded) study in 2010, used a NF training to increase the relative activity of the right frontal alpha band and thus would have an impact on symptoms of depressive subjects suffering from emotional, behavioral, and cognitive problems[54]. This study included 24 patients with depression who were assigned to a 5-week EEG-NF or a psychotherapy control group. Patients in the active group showed an improvement of over seven points on the 17-item Hamilton Depression Rating Scale (HDRS; from 11.33 to 4.08). In contrast, the psychotherapy group only showed minimal improvement (12.36 to 11.08).

EEG-NF has the advantage of being more widely available and including mobile settings. It is a popular procedure, especially in child and adolescent mental health settings in application to attention deficit/ hyperactivity- disorder (ADHD),[55, 56] although a recent meta-analysis has raised doubts about the specificity- of the effects in ADHD[57]. One of the disadvantage of EEG-NF is its low spatial precision, because of the volume conductance effects and the attenuation of electrical signals on their way from the source to the scalp, and the source localization problem[58]. fMRI-NF is not completely real time and has a delay in the second range compared with the millisecond temporal resolution of electrophysiological techniques such as EEG and MEG. However, the high spatial resolution and access to deeper brain structure make fMRI as an attractive tool for network mapping in psychiatric disorders and NF[59].

fMRI Neurofeedback in Depression

Functional magnetic resonance imaging (fMRI) invented 20 years ago. Particular strengths of this noninvasive technique are its spatial resolution, fidelity, and ability to reach deep subcortical structures. These features make fMRI particularly suitable for applications to mental disorders where deep structures play a major role. fMRI scans acquired from patients with chronic schizophrenia during the experience of auditory verbal hallucinations have revealed activation in

the auditory cortex, very similar to that during stimulation with actual sounds[60]. Imaging based NF follows similar principles as other NF or BF approaches. During NF training, participants receive feedback on their brain activity in real time and are instructed to change this activation. Because of technical limitations, fMRI-NF can be performed only the subject is within a magnetic resonance system[48]. The fMRI signal is created by the hemodynamic delay of =5 seconds between the actual neural activity and the vascular response, then it is not a truly "real-time" feedback. When participants are informed of this delay, it does not pose an obstacle to NF training[61]. The best advantage of the fMRI-BF compared with other NF techniques such as EEG or MEG, is its better access to deep brain structure. In addition, noninvasiveness and high spatial flexibility are other advantages of fMRI-NF compared with deep brain stimulation[62, 63].

Linden et al studied the effects of fMRI NF on drug-resistant depression patients. They informed them, without recommending any strategy; that imaging positive emotional pictures upregulates the associated areas in their mind and monitored it in the fMRI screen. Areas mostly included in the ventral prefrontal cortex and limbic system. The clinical effects of the pilot study were also promising[64]. The NF showed about 30% improvement in the depressive symptom score over the 1-month follow-up, whereas the control group did not show any improvement.

CONCLUSION

NF differs from all external stimulation techniques in that it enables the patients themselves to control their brain activity and thus to contribute to their experience of self-efficacy as an important therapeutic factor. The NFTs in depression can be categorized into three protocols: 1-decreasing left-hemispheric alpha activity, 2-increasing right-hemispheric alpha activity or shift an asymmetry index toward the right, 3- reducing Theta activity in relation to Beta in the left prefrontal cortex. Although the recent studies have shown promising outcomes in depression treatment with no adverse health effects, further randomized double blinded and placebo controlled trials are needed to introduce NF as an effective clinical treatment modality for depressants.

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