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Current Advances in Neurofeedback Techniques for the Treatment of ADHD

YADOLLAHPOUR ALI*, NARAQI ARANI MAHMUD and RASHIDI SAMANEH

Department of Medical Physics, School of Medicine,
Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
*Corresponding author E-mail: yadollahpour.a@gmail.com

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ABSTRACT

Neurofeedback (NF) or electroencephalogram (EEG) biofeedback is a biofeedback for the brain where the values of specific physiological variables or cognitive functions are voluntarily modified using the biosignals recorded from and feedbacked to the subject. This technique has been extensively investigated as a therapeutic modality for attention deficit/ hyperactivity disorder (ADHD). However, a reliable efficient clinical protocol has not been proposed. fMRI-NF and EEG-NF have shown promising potentials to be used as clinical treatments for ADHD and other cognitive disorders. The present study reviews the basic principles, recent advances and clinical considerations of NF techniques for ADHD.

Key words: Neurofeedback, ADHD, electroencephalography, Treatment protocols.

INTRODUCTION

Developing into adulthood makes the brain an anatomically and physiologically static organ. Early childhood, is the critical period of brain development where it undergoes dramatic changes[1]. Environmental induced changes such as learning in the brain were only possible in very specific areas such as the cerebellum and hippocampus. In the beginning of the 1980s, some evidence demonstrated the self-organizing principles of the brain, such as after differentiation of peripheral nerves[2]. This self-organizing principle of the brain is now beyond doubt and has become known as neuroplasticity or brain plasticity.

Based on this concept, another form of biofeedback known as electroencephalogram (EEG) biofeedback, neurotherapy or neurofeedback (NF) was proposed through which genetic and environmental tendencies are counterbalanced by learning to alter brain wave patterns. This technique alters and modulates brainwave activity and power of brain's frequency bands such as alpha (associated with relaxation and meditation) and theta (associated with focused attention). Therefore, NF can be described as biofeedback for the brain where the values of specific physiological variables or cognitive functions are voluntarily modified using the biosignals recorded from and feedbacked to the subject[3]. It is also known as a self-regulation technique through which patients develop a control what was once thought as involuntary[4]. NF involves learning to self-control brain activities largely based on operant conditioning principles, with the aim of improving mental states or processes, whether or not in clinical conditions. In the majority cases of NF, physiological signals are used as brain waves. From this perspective, it is considered more like training than a therapy that the patients play an active role and practice until developing the control skill[4]. In a brief, the patient produces an appropriate physiological signal of her/his own brain waves and

consequently the equipment is responsible for registering, transforming and enlarging it in a pattern that can be presented to the patient through volume of an attractive music, brightness of a film or a variety of games. Thus, with the aim of receiving direct feedback and information of the changes produced in the physiological signal, patient learns how to modify it through classical conditioning and/or operant processes[5].

A report published by journal of Biological Psychology (2014) stated that "The last decade has witnessed a sharp rise in the number of publications about Neurofeedback (Fig. 1), and this can be interpreted as a sign that an increasing number of research groups are now recognizing Neurofeedback as a research topic."

The main objectives of NF are: controlling a system of physiological responses through training, keeping controlled these responses in the absence of the feedback, and generalizing and maintaining the achieved self-control[6]. To achieving these purpose, in spite of spending several sessions of neurofeedback training (20-30 sessions), often the patient is given 'homework', such as listening to recordings of the weekly NF session every day, or how to confirm the new feeling of calm to maintain it outside the NF clinic[7].

In an NF system, biological sensors, usually EEG electrodes are placed on the scalp to convey the electrophysiological signals of brain into a software package where these signals are converted to a display based on the fluctuation of EEG signals. After initial preprocessing and artifact removing, the signals are separated into three main frequency bands (Fig.2): slow (up to 7 Hz); medium (8–12 Hz); fast (13–21 Hz)(7).

Higher frequencies are correlated with the more aroused mentally and physically state of the person. Frequencies above 21 Hz are associated with excessive autonomic arousal from anxiety to anger, while very fast rhythms, above 40 Hz (gamma), fulfil functions beyond arousal. The feedback software gives a signal (auditory, visual or vibratory) when the patient produces more normal brainwaves at least in 60–70% of the session.

The aim of the NF practitioner is to encourage the production of healthier brainwaves, so that a patient who has an excessive slow wave is helped to produce a faster, higher, frequency. Therefore, for instance in attention deficit/hyperactivity disorder (ADHD) with comorbid anxiety, the patient learns to increase the amplitude (voltage) of preferential frequencies, at the same time as reducing the amplitude of the very slow (less than 7 Hz) and/or very fast (more than 22 Hz) sets of brainwaves. While all frequencies are appropriate for a given situation, the midrange frequencies (12–21 Hz) are those that most people want to be able to produce at will and benefit from the associated feelings of calm, control and mental alertness.

Neurofeedback Techniques

NF have been used in combination of several brain imaging techniques such as quantitative electroencephalography (QEEG)[8], functional magnetic resonance imaging (fMRI)[9], near-infrared spectrography (NIRS), positron emission tomography (PET)(10) and single photon emission computed tomography (SPECT). However, only fMRI-NF and EEG-NF have acceptable applications in clinical studies. In addition, NIRS[11] may offer advantages in terms of targeting well-defined brain regions, and such studies are ongoing[12]. NIRS is used by Kober et al. (2014) to increase motor-related brain activities aimed at training patients with focal brain lesions[13].

Electroencephalograph Neurofeedback (EEG-NF)

Electroencephalogram-neurofeedback (EEG-NF) has different advantages including being widely available and accessible in mobile settings. It is a popular procedure especially in child and adolescent mental health settings for ADHD managements[14, 15], although a recent meta-analysis has raised doubts about the specificity of the effects in ADHD[16].

However, EEG-NF has some disadvantages such as low spatial resolution, source localization problem induced by volume conductance effects and the attenuation of electrical signals from the source to the scalp[17]. In addition, the considerable inter-individual variability of EEG asymmetry limits its usefulness as a NF target (18).

Functional Magnetic Resonance Imaging Neurofeedback (fMRI-NF)

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. fMRI scans acquired from patients with chronic schizophrenia during the experience of auditory verbal hallucinations (i.e. as a type of NF) show activation in the auditory cortex, very similar to that during stimulation with actual sounds[19]. In addition, Beauregard and Levesque in a clinical trial (2006), investigated the effects of NF training on the neural bases of selective attention and response inhibition in children with ADHD using fMRI. They concluded "NF training has the capacity to functionally normalize the brain systems mediating selective attention and response inhibition in ADHD children"[9].

The high spatial resolution and access to deeper brain structure make fMRI an attractive tool for network mapping in psychiatric disorders and NF[20]. The best advantage of fMRI-NF, compared with other NF techniques, is its better access to deep sub-cortical brain structure. Other particular strengths of this technique are its high spatial resolution and flexibility, noninvasiveness, and accuracy compared with deep brain stimulation[21, 22]. These features make fMRI particularly suitable for investigations on mental disorders where deep structures play a major role like dopaminergic midbrain[23] and cortical regions[24] that are involved in ADHD.

However, fMRI-NF is not very real time and has a delay in the second range compared with the millisecond temporal resolution of electrophysiological based techniques such as EEG and MEG. The fMRI signal is created by the hemodynamic delay of five seconds between the actual neural activity and the vascular response; thus, it is not a truly "real-time" feedback. When participants are informed of this delay, it does not pose an obstacle to NF training[25]. Another disadvantage of fMRI-NF system is a technical limitations, so that it can be performed only when the subject is within a magnetic resonance system[26].

Advances in technology have greatly simplified EEG recordings, so that researchers can focus on more advanced topics, use and develop more sophisticated research designs, and could apply the NF methods to a variety of clinical groups with a low cost and easy to use NF. These developments have dramatically developed EEG-NF field during recent years.

Advantages of NF

Both stimulant medication and behavior therapy are the most often applied and accepted treatments for cognitive disorders. However, these

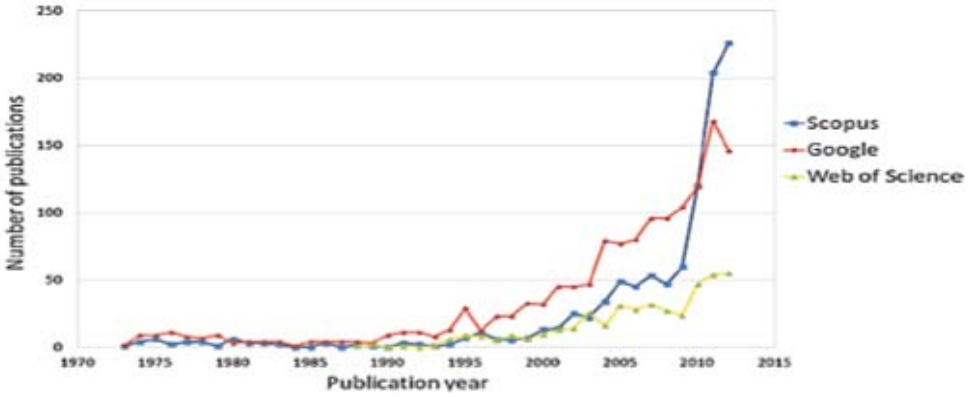

Fig. 1: Boxtel and Gruzelier report in Biological Psychology(2014);Number of publications by publication year for the search terms "Neurofeedback" and "EEG Biofeedback" in records of Scopus, Google Scholar and Web of Science

treatments have limitations that recently have been demonstrated. For example, Matousek et al (1984) in a large-scale, long-term study showed that after 14 months of prescribing stimulant medication for ADHD, in many cases, there are less effective than they had been initially[27]. In addition, limited long-term effects of stimulant medication[28] and behavior therapy have been reported[29, 30]. In addition, increasingly concerns are existed about long-term side-effects of medication on growth, cardiovascular and neurophysiological systems.

However, comparisons of the effectiveness of NF versus medication have generally shown NF remains a safe, non-invasive alternative to medication and can be at least as effective as, if not better than medication with better long-term effects[7, 31]. The two main advantages of the NF system, as several non-randomized studies have stated, are the same effects of NF and stimulant medication on measures of inattention and impulsivity in ADHD[32-35], and the long persistence of these effects[33].

Neurofeedback as a Therapeutic Modality

EEG biofeedback has been proposed for the treatment of various dysfunctions including insomnia, ADHD, anxiety disorders, epilepsy, addictions, tinnitus, brain injury, depression, and learning disabilities. However, the evidence in the literature does not support the efficacy of EEG biofeedback in all of these conditions.

NF differs from electroconvulsive therapy, transcranial magnetic stimulation or any other techniques that force the brainwaves to alter. It simply provides a signal as a feedback to reorganize the brain waves so that the patients are the only ones that can voluntarily learn, recognize and produce their optimum brainwave state. Therefore, brain resets itself to a new steady state and many patients will recognize this sensation, as a real reward, after three or four sessions. Session by session the neural network is involved and strengthens, as the amplitude increases or decreases according to the needs of the individual patient, and any changes are recorded[7]. The NF practitioner expects to see the EEG normalized after 20 sessions.

These non-pharmacological therapies may be useful for patients who have failed or are intolerant to drug therapy; patients with a history of long-term, frequent or excessive use of analgesics or other acute medications; patients with significant stress; or for patients who are pregnant, planning to become pregnant or are nursing (The American Academy of Family Physicians- AAFP, 2000).

There are also individual differences in one's ability to conditioning its own brain activity.

Typically, at least for children, the signal used in NF will be very much like a computer game, so that points are scored for keeping a car on a road, a monkey climbing a tree, a boat reaching to an end, and so on. For adults, if the patients maintain the 70% of desired threshold, the signal presented in NF may play an attractive music or even demonstrate a graphical interaction of their own

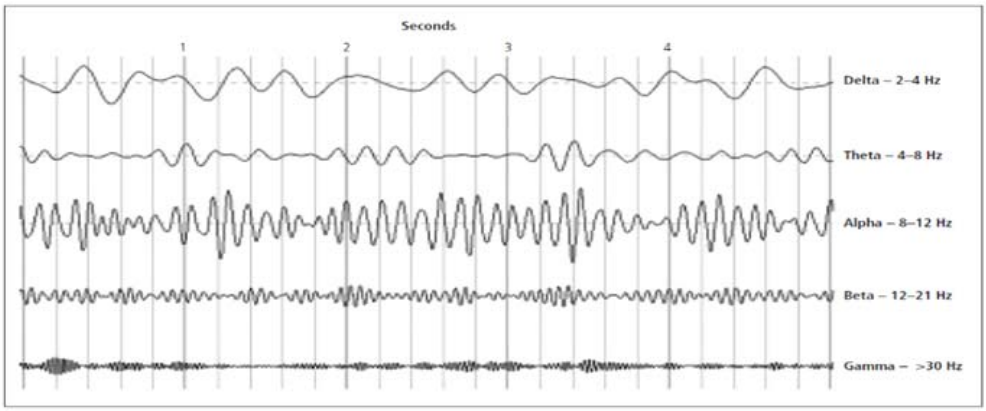

Fig. 2: Electroencephalography frequency bands

brainwaves. The reward is either the calmer or else more alert feeling that the production of these healthier brainwaves can bring and it is held to be a case of operant conditioning of the brain[7].

The evidence in the clinical trials has not established clinical efficacy and effectiveness of NF (36-39). A Hayes (2003) review of six studies that met inclusion criteria concluded that "there is insufficient evidence from the available peer-reviewed literature to conclude that EEG biofeedback therapy is effective for the treatment of disorders such as ADHD, epilepsy, insomnia, depression, mood disorders, posttraumatic stress disorder, alcoholism, drug addiction, or menopausal symptoms. No definitive conclusions regarding the efficacy of EEG biofeedback can be drawn." In a subsequent literature search (2008), Hayes' conclusions have not changed.

However, the effects of NF remain controversial. In addition to the methodological defects of the clinical trials, it is unclear whether the positive outcomes following NF are due to the electrophysiological mechanisms or other factors such as parental intervention or properties of the therapeutic setting and content[38-41].

Historical review of neurofeedback

Neurofeedback, as a cognitive therapy technique to teach or improve self-regulation of brain activity can already be traced back to the finding indicating the human EEG is susceptible to classical conditioning principles in the early 1930s[42-44]. Early experiments showed that the EEG alpha-blocking response could be classically conditioned[42, 43], which was subsequently confirmed by more systematic investigations in the 1940s[(44, 45]. Then, its principles were first applied to the EEG in the early 1960s[46-48] where Sterman reported the first successful application of operant conditioning of EEG with clinical effects. He performed the training of an EEG rhythm with the same frequency and topographical distribution as SMR during wakefulness in the cat, which increased sleep spindle density during sleep and improved sleep quality[49] also replicated in humans[50]. In addition, during early 1960s, Dr. Kamiya discovered that some of his research subjects could learn to control the amplitude and frequency characteristics of their own EEG if they receive appropriate feedback on those characteristics. Many psychologists and medical practitioners soon sensed the possibilities such operant conditioning of central nervous system electrical activity might have for clinical treatment[51].

In 1976, Lubar described the application of SMR neurofeedback in a child with hyperkinetic syndrome and found improvements in hyperactivity and distractibility[52]. He applied an ABA design, i.e. at first he increased SMR band with producing mediated wave activity (12-14 Hz) in absence of slow wave activity (4-7 Hz) and found significant effect of movement enhancement. Then, he reversed the trend and witnessed that symptoms worsened when reversal training was employed. These findings were subsequently replicated several years later in a larger open label study(53). These studies are the earliest demonstration of clinical effects of neurofeedback in what is now called ADHD[54]. Alpha enhancement neurofeedback (6–13 Hz) protocols have also been tested in these earlier years, but failed to find a specific effect on hyperkinetic behavior[55] .

The whole idea of abnormally slow or fast brainwaves is built on years of research, first on EEG sleep patterns and, later, on the correlation of the level of arousal to particular frequency bands. It is accepted by all neuropsychologists that there is an inverted U-shape to emotional state, with slow frequencies associated with drowsiness and fast frequencies associated with anxiety, anger or hyper vigilance[7]. The NF technique became a viable alternative to medication in the USA, especially in cases where drugs did not decrease symptoms or the side-effects required withdrawal[56, 57]. Many Eastern European countries, do not allow the use of stimulants for children and NF has a greater use in these locations.

Initial work on clinical application of NF was the most developed in the field of attention disorders such as ADHD[58-60]. However, because of some failed replications, absent or poor control conditions in some early studies, insufficient insight of understanding the mechanisms, overstatement of clinical benefits and fast procedure of acceptance in society, the field of NF has long been encountered by an aura of mystery that have prevented from

progress. Thus, the above factors, all may have contributed to a certain caution in the adoption of NF as a research theme by university laboratories.

ADHD and NF

ADHD is one of the most common neurodevelopmental and psychiatric disorders of childhood with neurobiological basis. The general rate of prevalence is reported between 3% and 7% of school age children[61] and 4.1 to 5% of children and teenagers[62] (APA, 2000; WHO, 2011). Torres et al (2010) reported the prevalence rates of 3.1 %[63] and 15.86 % in school-age childre[64].

Currently, the disorder is primarily diagnosed by referring to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or the International Statistical Classification of Mental Disorders (ICD- 10). According to the DSM-IV, the disorder presents itself in three primary subtypes: predominantly inattentive type, predominantly hyperactive-impulsive type and the combined type[65]. Therefore the core symptoms of ADHD, characterized by having difficulties with attention, impulsivity and hyperactivity. In 40–60% of all cases ADHD persists into adolescence and adulthood(66).

ADHD is associated with learning disorders and leads to impairment in various domains, including negatively affects academic performance or poor academic performance in childhood, lower occupational success, poor social relationships, and higher risk-taking behavior or risk for antisocial disorders and drug abuse in adulthood[67].

Because of the significant impact of ADHD on children's functioning, considerable effort has been directed at developing effective treatments[12]. Currently, both stimulant medication (psychostimulant and non-psychostimulant) and behavior therapy are the most often applied and accepted treatments for ADHD[66] and widely used, but recent large-scale studies and meta-analyses have demonstrated limitations of these treatments. For example, a considerable minority of children treated with stimulants either fail to show an improvement in ADHD symptoms or suffer adverse effects on sleep, appetite, growth, and, less commonly, the cardiovascular system[68, 69] and limited long-term effects of stimulant medication[28] and some limitations in behavior therapy have been reported[29, 30].

Some parents, patients, and/or clinicians have a preference for non-pharmacologic treatments. In summary, these limitations highlight the need for therapeutic innovation in ADHD to develop effective non-pharmacologic interventions that can improve short-term and long-term outcomes. Therefore, developing new treatments with better long-term effects for ADHD is necessary.

NF as a new non-pharmacological treatment has shown promising potential for the treatment of ADHD as an alternative or adjunctive treatment.

EEG Characteristics of ADHD

NF is based on brain imaging studies, such as quantitative electroencephalography (QEEG)[8], positron emission tomography[10] and single photon emission computed tomography (SPECT)[70-73] which all show cortical brainwave slowing in the majority of attention deficit hyperactivity disorder (ADHD) patients as well as too much or too little coherence across functional areas of the brain. EEG based NF is proposed for the treatment of ADHD under the hypothesis that can correct the abnormal brain wave activity correlated with this disorder. The NF has a purpose that the patient, by means of operant conditioning, learns to control and alter the abnormal brain's electrical activity, so that, increase the frequency of desired brainwave and decrease the unwanted one[74].

The brain areas mediating inattention, impulsivity and hyperactivity have been of particular interest to neuroscientists specializing in ADHD. These are the right prefrontal cortices and anterior cingulate gyrus responsible for attention and the basal ganglia and cerebellum involved in movement control.

Brain topology of ADHD can be obtained using EEG and, in particular, QEEG which demonstrates the interaction between the frequency (Hz) and amplitude (¼V) of the electrophysiology of the brain. The major pattern

associated with the inattentive type of ADHD is excessive low frequency (known as Theta,4–7 Hz) combined with too little high frequency (known as Beta, 18–21 Hz) in midline and frontal cortices[27, 75]. Thus this mentioned as a higher proportion of waves Theta / Beta, i.e. a high level of Theta waves and low level of Betha waves[76-78].

The most protocol in self-regulating, used in ADHD is the decreasing of theta/Beta ratio which is typically higher than normal person (Harvard Mental Health Letter, 2010). However, the brain's rhythms have an organizing principle so that each person has her or his own pattern and an optimum 'set point' of oscillation. Given the consistency of findings that brainwave excesses/deficits are associated with ADHD[1,13,14], and that these abnormal cortical rhythms can be normalized with NF to reduce symptoms[15,16].

In addition, the EEG in children with ADHD has shown a positive correlation with the levels of cerebral perfusion associated with hypoperfusion in the frontal lobe that is related to an alteration in the rate of Theta waves[79]. These results have supported the development of NF as a technique that would change the typical EEG patterns of ADHD and also improve its symptoms.

Another protocol is based on training Slow Cortical Potential Training (SCP), in order to regulate the phasic cortical activity rather than the tonic. Drechsler et al. (2007) found that less than a half of the participants who received SCP training were able to differentiate their cortical activation in transfer trials, so that the effects could not be fully attributed to the electrophysiology training[40],

The third protocol widely used is the Rhythm Sensory Motor. Training with SMR protocol, succeeded in reducing ADHD symptoms in all studies in which it was used(80, 81).in addition, Alpha enhancement neurofeedback (6–13 Hz) protocols have also been tested in the earlier years of NF progress, but failed to find a specific effect on hyperkinetic behavior[55]. In line with the earlier lack of clinical effects of alpha-neurofeedback in ADHS[55], these results do not contribute to the question of efficacy of well-investigated neurofeedback protocols such as TBR, SMR and SCP neurofeedback protocols.

Therefore, every person who suffers ADHD has one or multiple of the following abnormalities in the brain activity: The first is an increase of low frequency oscillations in the frontal lobes, predominantly in the 4–7 Hz range, known as theta rhythms and delta waves (1–4 Hz), are also observed. Secondly, an abnormal increase of frontal midline theta waves in the 5.5–8 Hz range, with its maximum amplitude in the frontal midline. The third pattern is the decrease of the Beta1 rhythm (13–18 HZ) and if we encountered with increase of Beta2 rhythm (18-30 Hz), we can concluded more associated with the overfocused, angry or anxious type of ADHD. The fourth pattern is an excess of alpha activity (8–12 Hz) at posterior, central or frontal areas of the brain[82].

Clinical considerations

In a review of the literature on NF for the treatment of ADHD, Monastra et al. (2005) summarized the results of five case studies (n=322) and five controlled-group studies (n=214) that were conducted between 1976 and 2003. The studies were reviewed by applying guidelines established by the AAPB and the International Society for Neuronal Regulation (ISNR). The authors determined that NF was "probably" an effective treatment option for ADHD (i.e., 75% of patients demonstrated significant clinical improvement), but stated that randomized controlled trials were needed to demonstrated who will benefit from this treatment[83].

In a narrative review of the literature, Holtmann and Stadler (2006) stated that NF for the treatment of ADHD has shown short-term effects comparable to the effects of medication at the behavioral and neuropsychological level. Nine studies were reviewed, including 293 subjects. Studies involved the assessment of EEG-frequency training and training of slow cortical potentials. Decreases were seen in inattention, hyperactivity and impulsivity without side effects. The authors stated that although the results were encouraging, EEG biofeedback has not been an accepted treatment modality for ADHD and there is a "strong need for empirically and methodologically sound evaluation studies[84]."

Fuchs et al. (2003) conducted a nonrandomized comparison study of children (n=34) diagnosed with ADHD. Their parents chose which treatment the child would receive, pharmaceutical management (n=12) or EEG biofeedback (n=22). The treatment was provided for 12 weeks, and both regimens were associated with improvements on all subscales of the test of variables of attention and on the speed and accuracy measures of the d2 attention endurance test. ADHD-related behaviors were noted to be significantly reduced in both groups when rated by both teachers and parents using the IOWA-Conners Behavior Rating Scale[32].

In a randomized controlled trial, Leins et al. (2007) compared ADHD children treated with slow cortical potential (n=19) to theta/beta therapy (n=19). After three phases of ten sessions, improvements were reported by parents and teachers which lasted for six months[85].

The study reported by Meisel et al (2014) found that children with ADHD benefited to an equal extent from forty theta/beta1 neurofeedback training sessions and from medication with methylphenidate, but only neurofeedback contributed to academic performance. In addition, the effects lasted for a period of at least six months.

One aspect of particular interest is the effectiveness in brainwaves modification after 20 training sessions in over 30% of patients with ADHD and the prevalence of its effects, which is estimated from one to ten years, having as a consequence the decreasing of impulsivity and hyperactivity symptoms[86]. In addition, several studies have reported a significant improvement in the levels of attention in the IQ, and the scores on the conduct scales carried out by parents and teachers (87, 88).

CONCLUSION

Although the studies on therapeutic efficacy of NF for different cognitive disorders have been controversial, it is a promising technique for different diseases. The main factors contributing to the controversial results are deficit of scientific rigurosity, limitations such as lack of control groups, small sample sizes and non-probability sampling[39, 40].

To obtain greater effectiveness, it is proposed to combine an NF technique with a multimodal therapy that combines some of the following aspects: psychoeducation, medication, behavioral intervention, parent training and/or academic support, among others[80, 89]. School and parents support have proved to be crucial in the treatment, so most studies have attempted to involve them[81].

However, further studies are needed to answer important questions in developing efficient NF based treatments for ADHD disorder: which protocols to use in which clinical or non-clinical cases; how many training sessions are necessary to exert clinical outcomes; how long these effects last, which exact brain mechanisms are involved.

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