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Neurofeedback Training in the Treatment of Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Tedavisinde Neurofeedback Eğitimi

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Abstract

Identified with symptoms of deficits in attention, hyperactivity and impulsivity, Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood and adolescence. With its neurobiological underpinnings, most effective treatment of the disorder has so far been reported as drug therapies. In addition to pharmacological interventions, other non- pharmaco-logical treatment strategies have also been suggested, in order to efficiently improve symptoms and overall functioning. Among nonpharmacological ADHD treatment techniques, neurofeedback has long been phrased as a treatment strategy for the condition since early 1970s. Preliminary studies showed that neurofeedback was effective in treatment of ADHD. However, well-designed studies and meta-analyses show that the efficacy of neurofeedback is not clear.

Keywords*:* ADHD, neurofeedback, treatment.

Öz

Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB), dikkatsizlik, hiperaktivite ve dürtüsellik ile ayırt edilen, çocukluk çağının en sık görülen psikiyatrik bozukluklarından biridir. Nörobiyolojik bir hastalık olarak kabul edilen ve tedavi gerektiren bu bozuklukta ilaç tedavileri en etkili tedavi yaklaşımıdır. Buna ek olarak, belirtilerin en iyi şekilde azaltılması ve genel işlevselliğin iyileştirilmesi için ilaç ve farmakolojik olmayan girişimlerin birlikte kullanıldığı tedavi yaklaşımları da önerilmektedir. Neurofeedback, farmakolojik olmayan tedavi yaklaşımları arasında 1970'lerin başından beri DEHB'de bir tedavi stratejisi olarak kendisini göstermektedir. Erken çalışmalar neurofeedback'in etkinliğine yönelik olumlu sonuçlar bildirmektedir. Ancak, iyi tasarlanmış güncel çalışmalar ve meta-analizlerden gelen veriler bu olumlu sonuçlara şüphe getirmektedir.

Anahtar sözcükler: DEHB, neurofeedback, tedavi.

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ATTENTION Deficit Hyperactivity Disorder (ADHD), is identified with symptoms of deficits in attention, hyperactivity and impulsivity, that are inconsistent with the developmental level and age of the individual, and is among the most common psychiatric disorders of childhood (Pliszka 2007). Many clinical practice guidelines have a consensus on pharmacological treatments as being the most efficient treatment approach for this disorder, that is known to have neurobiological underpinnings (Taylor et al. 2004, Pliszka 2007, Ercan et al. 2008, Kooij et al. 2010). In addition to this, non-pharmacological interventions are also recommended as augmentation strategies, in order to decrease symptoms efficiently, and improve overall functioning (Majewicz-Hefley and Carlson 2007, Puride et al. 2002). Among non pharmacological treatment strategies, Neurofeedback (NF, EEG- biofeedback) have long been regarded as a treatment approach for ADHD, since early 1970s (Lubar and Shouse 1976, Holtmann et al. 2014, Arns et al. 2015).

EEG, is identified as rythmic activity, in terms of hertz (Hz) that reflects the number of waves per second. These rhythmic activities are grouped as delta (δ) waves, up to 4 Hz; teta (θ), between 4-8 Hz, alfa (α); between 8-12 Hz, and beta (β); between 12-30 Hz. Within each rhythmic activity, there are also recognisable and functionally significant rhythms. For instance, a certain type of beta activity observed over sensorymotor cortex (12-15 Hz) is defined as sensorymotor rhythm (SMR).Of these rhythmic activites, delta waves are linked to sleep state; theta waves, to inattention and a state of drowsiness; alpha, to relaxing state, being awake and vigilant; while beta, to being active and attentive. On the other hand, magnitude of SMR amplitude is linked to sensorymotor inhibition. When sensorymotor regions are inactive, the amplitude tends to be higher (i.e, at resting state), whereas when aforementioned regions are activated (i.e, during motor tasks), the amplitude decreases (Hurt et al. 2014).

Through the end of 1960s, it was learned that regulating and renewal of brain wave patterns was possible (Kamiya 1968). This brainwave training has been named, what we know asNF, of today.A preconception that NF might be utilized in the clinical setting was actually based on the observation that cats who had been conditioned to produce a certain EEG frequency (SMR), maintained a higher seizure threshold when exposed to methylhydrazine, as convulsant agent (Sterman 1969). As the process evolved,it was also thought NF might be used in treating ADHD. Researchers have reasoned the use of NF (theta/beta training) in ADHD specifically, based on the findings derived from prior resting state EEG studies, where children with and without ADHD, were typically compared (Heinrich et al2007). Various studies have shown prominent slow wave activity in ADHD, especially in posterior regions (θ, 4-8 Hz) and/or decline in alpha and/or beta activity during resting state EEG, as well as during attention task processes. This neurophysiological deviation provides a logical ground for using theta/beta training in ADHD children (Gevensleben et al2012). However, most recent findings oppose to conceptualize theta/beta ratio at resting state EEG, as a reliable biomarker of EEG, to be used in the course of ADHD. This might be interpreted as among children with ADHD, at least one subgroup might be presenting with high theta/beta ratio, at resting state (Arns et al. 2013). For example, Heinrich and colleagues (2014), have reported higher theta/beta ratios among ADHD children, with predominantly attention deficit type, as opposed to the viewpoint that declared an increased theta/beta ratio, among all ADHD subtypes, during attentive states (Hein-

rich et al. 2014). Therefore, high theta/beta ratio or high theta values, do not seem possible to characterize all clinical presentations of ADHD (Ogrim et al. 2012). Due to such findings in children with ADHD, the question whether theta/beta training would be appropriate to be used in children with different ADHD subtypes or not, remains unclear. However, it is apparent that many relevant studies used theta/beta training. Other than that, although SMR activity has been regarded as another significant variable in ADHD, the very first article that suggested efficacy of NF in ADHD, had actually used the SMR protocol (Lubar and Shouse 1976).

With this review, case reports and controlled studies depicting the utility of NF in the treatment of ADHD, were addressed using a chronological framework, and efficacy of NF, that has frequently been phrased among non- pharmacological treatment strategies, and as a treatment modality in ADHD, was evaluated in the light of relevant literature.

Case Reports

As well observed within any field of practice- based clinical research, studies need to be conducted in order to develop novel treatment approaches. In that sense, preliminary data on whether NF treatment was valid in ADHD or not, was introjected into relevant literature through the presentation of a case report, in the year 1976. Lubar and Shouse (1976), presented the results of a NF training protocol, that was used for treating an 11- year old boy who had been diagnosed with predominantly hyperactive-type ADHD. In their study comprising a single subject, researchers found the patient was able to control his SMR activity, and increase it throughout his training sessions. This study concluded that pharmacological treatment along with SMR training was more efficient than treatment with only medication use, and caused better clinical improvement. Researchers also stated that the approach would be beneficial in treating children who had predominant hyperactivity symptoms (Lubar and Shouse 1976). Same researchers also presented a case series of 17 children between the ages of 8-15 years, later on. As part of this study, cases were trained in order to reduce the percentage of microvolt or theta activity within their EEGs, all while increasing the percentage of beta activity, during 30-45 sessions implemented, all aiming to overcome certain difficulties caused by ADHD. Following the training, reduction of theta activity and increase in beta activity was observed in 11 children (Lubar et al. 1995). Another study explored the effects of NF on 36 participants aged between 6-17 years. Efficacy of treatment was measured by evaluation of parent questionnaires upon completion of 30-session NF training, comparison of TOVA (Test of Variables of Attention) scores prior to onset of training and after 20-sessions of training, and measuring the alterations in quantitative-EEG (qEEG) parameters post-training, for some cases. At the end of treatment, reports on subjective observations of parents indicated an improvement of 86%, and 74%, in TOVA scores measured. A high level of correlation existed between observed clinical improvement and TOVA scores (74%), as well as alterations in qEEG parameters (78%). In the same study, it was reported that 5 of 24 patients that had been on medication before, did not require pharmacological treatment anymore, while it was possible to decrease the dose of medication in 11, and of 8 patients whose medication regimen was not altered, four were reported to have presented with an overall improvement, in

turn, causing the researchers to suggest similar doses of the medication might have been more efficient, following NF training (Alhambra et al. 1995).

After the aforementioned case studies were published, Thompson and Thompson (1998) explored the effects of NF in 111 children (where 98 of them were aged between 5-16 years old) diagnosed with attention deficit disorder (those who had hyperactivity and not), while Kaiser and Othmer (2000) aimed to assess the same, in 1089 patients collected from 32 different units (186 ADHD patients with and without hyperactivity). Both studies reported an improvement in attention and impulse control, as a result of the intervention. Additionally, Thompson and Thompson (1998) reported a 12- point increase in IQ scores (Thompson and Thompson 1998, Kaiser and Othmer 2000). In their research, Thompson and Thompson (1998) used metacognitive strategy training as the intervention, which might possibly have a confounding effect over results obtained. Moreover, 30% of their cases had also been using methylphenidate at the time of treatment (Thompson and Thompson (1998). Although the large sample size of the study by Kaiser and Othmer (2000), TOVA being the sole variable evaluated to measure the efficiency of treatment, would be considered as a main limitation. Another case study that compared the effects of NF with placebo, among 7 boys aged between 7-12 years and diagnosed with ADHD was important, since it had used the method of non-treatment feedback procedure. Subsequent sessions of treating and non-treating versions (placebo) were used in these cases, and parent/teacher ratings and cognitive tests were applied for each participant. In the end of the study, it was found that treatment and placebo sessions did not cause significant improvement, and were not significantly different from each other. Regarding this finding, researchers have suggested that therapeutic mechanisms such as behavioral techniques, unwillingly, might possibly account for some of the attributed positive effects of NF, and sometimes causing a medium- large effect size, these might be falsely interpreted as therapeutic effects of NF (Heywood and Beale 2003).

When most case reports are reviewed, one might conclude that NF would be an efficient treatment modality in ADHD. However, in most of the research published, it is striking to see that no methodology was utilized to assess possible confounding factors that might have an impact on the results obtained, such as characteristics of the therapist (understanding the patient, experience or trust), patient characteristics (intelligence and the capacity to learn new skills), treatment characteristics (i.e, inclusion of cases that have already been on medication), encounter with other therapeutic experiences (i.e, changes in parenting styles, counseling). Without controlling such confounding factors, it would be challenging and risky to have a conclusion on the efficiency of NF. For all these reasons, against all the positive results reported, data obtained through such research are not enough to suggest the efficiency of any kind of treatment, and to make generalizations. These difficulties have actually yielded to conducting controlled studies, within this field.

Controlled Studies

Scientific literature on NF has comprised of case reports solely and non-randomized or not open labeled studies for a long time, following the first case report published in 1976. The very first review published in 2005, focusing on the place of NF, in the treatment of ADHD, concluded that NF might be a viable and efficient treatment

option (Monastra et al. 2005). This piece of information constituted a significant source of motivation for subsequent research that focused on the subject. Controlled studies that were striking within this field, have emerged after mid- 1990s.

In an early-term study conducted by Rossiter and LaVaque (1995), effects exerted by a 20-session NF training model was compared to that obtained by the treatment with psychostimulant drugs, and no significant difference was found between two groups in terms of treatment-response rates (Rositter and La Vaque 1995). Another study by Linden et al. (1996) is significant, as it was the first randomized controlled study conducted in this field. As part of this aforementioned study, 18 ADHD patients aged between 5-15 years old (where 6 of the participants had a comorbid diagnosis of Specific Learning Disorder) were recruited, and with the condition that each group had equal number of patients, the sample was randomly divided into two subgroups as 40-session NF group and wait- list control group. As a result of the study, researchers have reported significant increase in IQ scores of the cases within NF group, and reduction in symptoms of attention deficiency, rated by parental reports. Same reduction was not observed for the symptoms of hyperactivity and impulsivity. Moreover, no significant difference was observed between two groups at posttreatment phase, in terms of agressive behavior and oppositional- defiant behavior. Even though randomization of groups, presence of a control group and elimination of possible confounding factors (such as being on medication) were maintained and strengths of the study, the fact that neither children nor their parents were blind to the study methodology, failure to provide a placebo control for possible confounders such as the time spent with the therapist and variables related to the treatment setting, were among significant methodological limitations. Again, while small sample size would not allow generalization of the findings to general population and extraction of reliable conclusions, results of the study actually reported a reduction in only attention- deficiency. Albeit such methodological limitations, this study is still important, as it involved randomization (Linden et al. 1996). In another randomized study that had a control group as the wait- list, conducted with 16 ADHD children aged between 8-10 years old, the NF-treated group completed a 35-47 session training throughout a treatment period of 6 months. As a result of the study, treatment group showed reductions in impulsivity symptoms, measured by using TOVA. On the other hand, teachers have reported improvements in attention, though no changes in impulsivity and hyperactivity. Along with this, electrophysiological improvement models have not been demonstrated consistently, on qEEG measures, selected by the research team (Carmody et al. 2001).

Monastra and colleagues' study (2002) comes to attention as they lack randomization, albeit maintaining a large sample size. As part of this study, a total of 100 patients who were all diagnosed with ADHD and all treatment naive, were assessed. All patients were included in a comprehensive clinical program that encompassed drug management, parental counseling, and school visits, and based on parental choice, 51 cases had also received NF training. NF sessions were continued for 34-50 weeks, with one session per week. Patients were tested a year later, when they were on methylphenidate and not. While on methylphenidate (15-45 mg/day), significant improvements measured by ADHD rating scales, TOVA and qEEG were observed in both groups, and it was reported that the group receiving only NF actually preserved these benefits, as measured with tests, after the medication was stopped. Researchers have stated that

their findings supported the efficacy of multimodal treatment models including parental counseling and NF, in addition to stimulant treatment (Monastra et al. 2002). However, because of methodological limitations such as lack of randomization, blindness, uncontrolled therapeutic effect of the time spent with the therapist; findings of this study does not provide a clear explanation as to whether it would be necessary to add-on NF to a multimodal treatment program, in order to maintain clinical benefits that had emerged following treatment with stimulants.

Table 1: Controlled studies that assess efficacy of neurofeedback in the treatment of ADHD.

Study	Method (Random assignment/ placebo control)	Treatment (NF) group	Control group	N (Age)	NF (sessions)	Result (significant improvement in ADHD symptoms, within NF group)
Rositter &La Vaque 1995	-/-	SMR/theta/beta	Stimulants	46 (8-21)	20	-
Linden et al. 1996	+/-	Theta/beta	Wait list	18(5-15)	40	+
Carmody et al. 2001	+/-	SMR/theta/beta	Wait list	16 (8-10)	35-47	+
Monastra et al. 2002	-/-	Theta/ beta +stimulant treatment+ other strategies	Stimulant treatment+ other strategies	100 (6-19)	34-50	- (clinical improvements pursued following cessation of medications, within NF group)
Fuchs et al. 2003	-/-	Theta/beta	Stimulants	34 (8-12)	36	-
Levesque et al. 2006	+/-	SMR/theta/beta	Wait list	15 (8-12)	40	+
Drechsler et al. 2007	-/-	SCP	Group training program	30 (9-13)	30	+
Leins et al. 2007	+/-	SCP	Theta/beta	38 (8-13)	30	-
Gevensleben et al. 2009b	+/-	Theta/beta/SCP	Attention skills training	102 (8-12)	36	+
Gevensleben et al.. 2010	Results of 6-month follow up of 2009 study					+ (clinical improvements have continued during 6-month follow up).
Holtmann et al. 2009	+/-	Theta/beta	Attention skills training	34 (7-12)	20	+
Perreau-Linck et al. 2010	+/+	Theta/SMR	Placebo NF	9 (8-13)	40	-
Lansbergen et al. 2011	+/+	Individualised frequency band training	Placebo NF	14 (8-15)	30	-
Arnold et al. 2013	+/+	Theta/beta	Placebo NF	39 (6-12)	40	-
van Dongen-Boomsma et al. 2013	+/+	Individualised frequency band training	Placebo NF	41 (8-15)	30	-
Bakhshayesh et al.. 2011	+/-	Theta/beta	EMG-biofeedback	35 (6-14)	30	+ (no significant difference was found via assessment by the teachers)
Maurizio et al. 2014	+/-	Theta/beta/SCP	EMG-biofeedback	25 (8.5-13)	36	-
Strehl et al. 2017	+/-	SCP	EMG-biofeedback	150 (7-9)	25	+ (no significant difference was found via assessment by the teachers)

Another study that lacked randomization was conducted by Fuchs and colleagues (2003). Researchers have compared methylphenidate use and NF among 34 children, aged between 8-12 years old; and no additional treatment intervention was applied to any of the groups. Groups were formed according to the parents' choices, and NF group had a 36-session training throughout 12 weeks. Significant improvements measured by psychometric and behavioral test groups, as well as parent and teacher assessment reports were obtained, in both treatment groups. Researchers of this study have concluded that NF, as a non- pharmacological treatment option, was efficient in improving certain behavioral components of ADHD (Fuchs et al. 2003). Although this study was important due to elimination of confounding effects of add-on treatment strategies, the fact that treatment strategy to be used was based on parent's choice might be a confounding factor on results. Since financial burden of NF would be totally on the family, results reported by families that would be willing to pay for the treatment and those that would not, might be a source of bias. Such bias could only be disregarded through employing random assignment and inclusion of a placebo control group. Researchers have actually drew attention towards lack of randomization, as a limitation, and they have also stated that it would not be possible to implement such a treatment, without the consent of the parents (Fuchs et al. 2003).

Another study in which randomization was insufficient due to certain reasons (i.e, the need to have a smaller age gap between the children that participated in the group program, etc.), was conducted by Drechsler et al. (2007). Researchers recruited 17 children with ADHD (13 boys and 4 girls) to a NF training program, and control group that comprised of 13 children (10 boys and 3 girls) diagnosed with ADHD were enrolled in a group training program that was based on cognitive behavioral therapy principles. Results of the study have indicated more improvement within attention and cognitive domains specifically, in NF group, compared to parent and teacher reports. Similar improvements were observed via neuropsychological measures (Drechsler et al. 2007). Although this study has reported positive outcome with NF, insufficient randomization and very small sample size were the main limitations.

In a meta-analysis that included functional brain imaging studies in individuals with ADHD, functional abnormalities in various regions of the brain, including anterior cingulate cortex (ACC) were reported (Hart et al. 2013). Although Levesque and colleagues (2006) conducted their study with a small sample, the study was important since it was the first to demonstrate neurophysiological alterations pre- NF training and post- training, in aforementioned brain regions that were reported to have been affected due to the disorder. This study had used functional magnetic resonance (fMRI) technique, along with psychometric tests. In this study where 15 (8-12 years old) children were recruited, the group who had received NF treatment demonstrated significant activation of the right ACC, shown via fMRI, along with an improvement in attention- related performances. The presence of randomization, control group and exclusion of comorbid diagnoses were strengths of the study. None of the participants were using psychostimulants; however, no data on other simultaneous interventions during the study period was available. Again, it was also not reported whether the participants and researchers were blind to treatment, or not (Levesque et al. 2006).

In addition to general rhythmic activities in EEG, more specific wave patterns might as well be observed. Such patterns identified as event-related potentials (ERPs)

are electrical representations of certain sensory and cognitive processes that emerge in the brain, in response to a stimulation or an event. A certain type of ERPs involve slow cortical potentials (SCPs) (Lofthouse et al. 2012). While negative SCPs reflect increased arousal (e.g, states of behavioral or cognitive readiness), positive SCPs indicate a reduced cortical stimulation of underlying neuronal network (e.g, during the state of behavioral inhibition) (Gevensleben et al. 2009a). A type of SCP that is related to cognitive readiness is defined as contingent negative variation (CNV). Various ERP studies that suggest a dysfunctional regulation of energy resources in ADHD, CNV was shown to have decreased among children with ADHD. In that context, SCP-NF training was conceptualized to possibly aid in improving the aforementioned dysfunctional regulation of energy resources (Gevensleben et al. 2014). While majority of the research focused on inhibition of theta, and reinforcement of beta and/or SMR, Leins et al. (2007) have attempted to explore the efficact of SCP-NF, based on the aforementioned conceptualization. This study is important, in the sense that it has used SCP-NF, and compared SCP-NF and theta/beta NF, at the same time. According to the directory of the study, 38 children with ADHD (8-13 years old) were randomly assigned to two groups, with equal number of participants in each group. While children, their parents and teachers were blind, NF trainers were not. Measures were carried out at the start, post- treatment and following 6- month follow-up. In the end of the study, both groups have succeeded in regulating cortical activity consciously, and demonstrated improvements in attention and IQ. Both parents and teachers have reported significant behavioral and cognitive improvements. Along with that, clinical effects resumed for both groups, 6 months after the treatment. Groups did not show differences regarding behavioral and cognitive outcomes. Along with the comparison of two different NF protocol, presence of randomization, paying attention to blindness, other than NF trainers, exclusion of individuals with comorbid neurological and psychiatric diagnoses, use of standardized assessment tools might be considered among the strengths of the study. Whereas, NF trainers not being blinded, and a lack of a placebo control group would be main limitations to the study. Contributing effects of motivation and expectations of participants over the process, could only be assessed with the presence of a placebo control. Moreover, the fact that confounding factors possibly related to changes detected 6 months after the last NF session left unmeasured or uncontrolled, might also be counted among significant limitations of the study (Leins et al. 2007).

Similar to the study of Leins et al. (2007), in their study where 6- month follow up results were assessed, has been conducted by Gevensleben and his colleagues (Gevensleben et al. 2009, 2010). With this study, effects of NF were compared to a computerized attention skills training, and initial and 6- month follow up results were analyzed. Contrary to other studies, treatment of control group was designed to be as similar as possible to NF treatment, and a larger sample size was used. In total, 102 children with ADHD, aged between 8-12 years old were included in the study. Groups were formed via random assignment, and pre-, peri- , and posttreatment results were evaluated through assessing various behavior assessment and rating scales completed by parents and teachers of participants. Evaluations carried out by parents and teachers suggested superiority of NF treatment in the reduction of ADHD symptoms (Gevensleben et al. 2009b). Approximately a year later, the researchers published follow-up results of remaining 61 children, upon exclusion of lost data and cases that were on medication

(Gevensleben et al. 2010). These findings were solely based on parent assessments. Due to changr of teachers and motivational loss observed among teachers regarding completion of measurement tools, in turn higher rates of dropping out, teacher evaluations were not included in the analysis during the follow-up period. When findings were published, it was seen that improvements in ADHD children, as a result of NF, continued throughout 6-month follow- up period. In order to overcome limitations of previous studies, exclusion of confounding factors such as parental counseling, medication and skills training, and blindness of teachers constitute the strengths of the study. Along with these, it would also be important to carry out an assessment in multiple domains and settings, such as at home, at school, and following 6- month of monitorization. However, gradually shrinking sample dize due to drop outs and lost data during the follow- up period (35%) and the decision to let only parent's complete assessment tools during follow- up might be considered among the limitations of the study. It is questionable that data derived from a different source of information, such as a teacher, would support the information reported by the parents, via measurement tools applied. Moreover, starting children who do not respond well to NF on medication, would raise the question whether NF could be counted as a treatment model for ADHD children, on its own. These results might as well indicate that not all children with ADHD got better, following NF treatment. As a conclusion, researchers have stated that NF might be proposed as a treatment model for children with ADHD, along with traditional behavior training and medication use. However, this study failed to put forward a perspective on whether NF could be considered as a treatment model on its own or not, in children with ADHD and/or how it should be added on multimodal treatment strategies (Gevensleben et al. 2009b, 2010).

Holtmann et al. (2009) have evaluated 34 children between the ages 7-12 years, who had been diagnosed with ADHD, upon an assessment carried out in a psychiatry unit of a university hospital. Of participants, 27 continued their psychostimulant treatment regimen, throughout the study period. Similar to that in the study of Gevensleben et al. (2009), a computerized attention skills training was applied to the control group. In addition to that, all parents received parental training. Even though randomization was maintained, no attention was paid towards blindness. As a result of the study, significant reductions in impulsivity were observed within NF group. Researchers have suggested theta/beta training might be associated with corrected inhibitor control, and this might be the reason why the training specifically had an impact on impulsivity. However, lack of blindness and presentation of any result, directed towards follow-up period, similar to that observed in the study of Gevensleben et al. (2010), as well as reporting results for only impulsivity, among cardinal symptoms of ADHD were limitations of this study. Additionally, multimodal approach did not allow assessing the effects of NF, in an isolated pattern (Holtmann et al. 2009).

A study designed by paying attention to the limitations of previous studies that focus on ADHD of childhood, was conducted by Perreau-Linck et al. (2010). In line with the study aims, 9 children (8-13 years old) who were diagnosed with ADHD, by using Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (K-SADS- PL) semistructured interview were recruited. Participants without any comorbidity and medication free were separated in active and placebo NF groups, via random assignment. Pre- and post-training assessments consisted of scales

completed by parents and neuropsychological tests. Blinding was maintained for children, parents, and NF trainers; however specialists that were responsible for pre- and post- treatment neuropsychological testing were not blinded. Results of this study indicated significant improvement in both groups, measured by the results collected from some subscales, especially hyperactivity, that were filled out by parents, with a more generalized improvement observed within the placebo NF group, compared to measures obtained during the pre-treatment phase. All participants showed improvement in at least one, from a series of neuropsychological measures. This improvement was much more prominent in Stroop Task Inhibition/ Variability condition sub-task for active NF group, while in placebo NF group, it was more prominent in Strrop Task Inhibition Condition and Continous Performance test- II (CPT-II) variability measure. As a result, no significant difference was found between groups. This study makes an important contribution to this field, since triple blinding of children, their parents and NF trainers, as well as using placebo control. In addition to this, diagnosing ADHD by using a valid and reliable instrument, carrying out the control for comorbid diagnoses and medication, and using standard ADHD treatment outcome criteria, altogether increase the strength of the study. On the other hand, sample size was very small, no data related tp follow up was present, and specialists conducting neuropsychological tests being not blind might have affected the results obtained. Nevertheless, other factors such as presence of a response to placebo, motivation or expectations were also thought to contribute to the results of NF training in children with ADHD (Perreau-Linck et al. 2010).

Results of another placebo-controlled study that was published approximately a year after the study conducted by would be important due to the clinical doubt it posed on other studies that report positive outcome. In this study that consisted of 14 children (8-15 years old) diagnosed with ADHD, participating children were classfied with respect to their ages, medication use and EEG subtypes; and then using random assignment method, were divided in two groups, identified as NF group (n=8), and placebo NF group (n=6). Individualized NF treatment protocol was applied to NF group. Even though analyses suggested significant improvement in ADHD symptoms over time, changes obtained were similar for both groups. In other words, individualized NF treatment protocol was not superior to placebo NF treatment protocol, regarding symptomatic improvement in children with ADHD. This study was a randomized, double-blind, and placebo- controlled study. However, the small sample size makes it challenging to generalize the findings, to overall population. Moreover, the fact that it has used individualized NF treatment protocol that would be individually tailored for each child makes it even harder to compare the results to other study findings, where standardized NF treatment was applied to participants (Lansbergen et al. 2011).

Another randomized, placebo controlled study that was conducted, by taking methodological limitations of previous studies into account, has been published by Arnold and colleagues, in 2013. In fact, this aforementioned study was a work of feasibility, aiming to address possible issues, before conducting another study that would focus on the given subject. Thirty- nine participants diagnosed with ADHD (6-12 years old), who did not meet any of the determined exclusion criteria (IQ <80, mental age <6, history of any comorbid disorder that would require use of psychoactive medication, former history of NF treatment, and the history of using different types of

psychotropic drugs for certain time before the onset of the study, etc.), were divided in active (n=26), and placebo (n=12) groups, with a ratio of 2:1, via random assignment. Evaluations were made right before the initiation of treatment, immediately after 12th, 24th and 40th NF sessions, and following 2- month follow- up period. Various measurement tools that were filled out by parents, teachers, and clinicians; as well as neuropsychological tests have been among instruments for assessment. In general, through an interpretation of clinical and neuropsychological results, it was reported that active treatment was not significantly favorable, compared to placebo. Indeed, though statistically insignificant, placebo group had better results on many symptom-related criteria. Even though this study was identified as a work of feasibility, it is important with its reported findings. This is because albeit the small sample size used, the study was designed as a randomized, placebo- controlled and double- blind study, the condition of blindness was verified, and variables such as comorbidity, medication use were taken into consideration, at the time of sampling (Arnold et al. 2013). Again, another randomized, placebo- controlled study conducted in 2013, reported insignificant results. As part of this study, 41 children diagnosed with ADHD (8-15 years old) were randomly assigned to be either included in 30-session NF treatment group (n = 22), or placebo NF (n = 19) group. The research was designed as a double- blind study, and the condition of blindness was verified. As a result, NF was not found to be superior to placebo, with respect to treatment efficacy (van Dongen-Boomsma et al. 2013).

Various studies that explored non-pharmacological interventions in the treatment of ADHD, have compared NF to other feedback strategies, such as electromyography (EMG) - biofeedback. Examples to research that employed this aforementioned perspective would be studies conducted by Bakhshayesh et al. (2011), Maurizio et al. (2014), and Strehl et al. (2017), respectively. While the first one of these studies used theta/beta in NF group, the second one used SCP, and the third one used SCP-NF. One superiority of the third study mentioned, was its large sample size (n=150). While the first study (n=35) reported NF was superior only on the attention-deficiency domain, as measured by parent assessments, teacher assessments revealed no such difference was present (Bakhshayesh et al. 2011). In the second study (n=25), while there were similar improvements, as a result of assessments conducted separately for each group, there was no significant superiority for adopting NF method for treatment (Maurizio et al. 2014). As for the last study, there was a reported reduction of core ADHD symptoms in children from both groups, with more favorable outcomes with NF; however, similar to the results of the first study, the same were not obtained when assessments of teachers were analyzed (Strehl et al. 2017). Although different NF training protocol were used in these aforementioned research, the fact that they have ended up with different results while using the same control group should be interpreted cautiously. Research where efficacy of NF treatment in ADHD was measured, are presented in Table 1.

Metanalysis studies that have aimed to assess the efficiency of NF, in the treatment of ADHD have also been conducted. The very first metanalysis that focused on the subject was published in 2009, by Arns and colleagues (Arns et al. 2009). This metanalysis comprised of 15 studies in total, where 10 were of prospective- controlled (n=476), and 5 were of pre-post intervention (n=718) design. Researchers of this metanalysis have reported effect size of NF, for attention-deficiency, hyperactivity, and impulsivity,

as 0,81, 0.40, and 0,69, respectively. With its high effect size for attention deficiency and impulsivity; and medium effect-size for hyperactivity, the researchers have suggested NF might be an "efficient and specific" treatment strategy, for ADHD. It would be important to underline that Arns and colleagues (2009) have used systematic and comprehensive methods for the metanalysis, such as study selection procedures, inclusion criteria, identification of pre- and post- measure data. However, including studies that had used random assignment technique and those that had not, at the same time, might hinder the safe interpretation of results obtained. On the other hand, it is striking that most studies they included, were not blinded. Possible bias that might be derived from this non-blinded condition and the effect it might pose on the overall results cannot be predicted. Another limitation to their study, was the lack of placebo control groups, included in the studies for their metanalysis. Needless to point out, if we pay attention to the year the study was published, and bear in our minds that studies included in this metanalysis had certain methodological limitations at those days, this might explain many of the difficulties. This might have caused the researchers to include studies that were not randomized, not blinded and lacking placebo control groups, in their metanalysis. However, without encompassing studies with aforementioned rigorous design, one needs to think over the statement suggesting NF is an "efficient and specific" treatment strategy, in ADHD, again (Arns et al. 2009).

In a latter meta-analysis following Arns et al. (2009) that had aimed to explore non- pharmacological intervention strategies for ADHD, the researchers have included 8 randomized controlled studies, in their analysis. Of these RCTs, only one had a placebo control group, while three had used a wait- list; one used an EMG- biofeedback; two used an attention skills training; and one used a non-treatment, as the control group. Four of the eight studies, involved possibly- blinded evaluations. According to the analyses that were carried out by using mostly the assessments of parents that were not blinded to the distribution of treatment, statistically significant reductions in symptoms were obtained, and standardized mean difference (SMD) was calculated as 0.59. Reported results reflect those similar to the ones priorly published by Arns et al. (2009), though smaller. Besides, when only possibly- blinded assessments were used in analyses, the effect was insignificant (SMD=0.29). Differing from the conclusion Arns and colleagues have derived in their meta-analysis, these researchers have underlined the need for more evidence that would include blinded assessments, before one is able to recommend NF, as a plausible strategy, among non-pharmacological treatment interventions of ADHD (Sonuge-Barke et al. 2013).

Results of another meta-analysis conducted in 2016, have also pointed out to different findings that has been reported by that of Arns et al. (2009). This meta-analysis comprised of 13 studies in total, and as a result of the analysis, NF was not found as an efficient option, in treating ADHD. The meta-analysis encompassed randomized controlled studies, solely. Inclusion criteria were; recruiting participants aged between 3-18 years, being diagnosed with ADHD or obtaining a score above the cut-off points as measured by ADHD rating scales, and exclusion of rare comorbid diagnoses (i.e, Fragile-X syndrome). Acknowledged control conditions were listed as "resuming routine treatment", "wait- list", "active", or "placebo". Among outcome measures, ADHD symptoms (all ADHD symptoms, and attention-deficit and hyperactivity/ impulsivity symptoms; separately), neuropsychological laboratory derived measures, academic func-

tioning measures, and severity of symptoms related to comorbid diagnoses (e.g, oppositional defiant disorder or anxiety disorder), might be identified. As a result of the analyses conducted, initially significant results, with a small- to medium effect size on attention deficiency, impulsivity/hyperactivity and all ADHD symptoms (SMD<0.5), were reduced to statistically insignificant levels, when sensitivity analyses were repeated, with the inclusion of solely placebo- controlled studies. Although a significant effect resumed for hyperactivity/impulsivity, small effect size was measured (SMD=0.25). When possibly blinded assessment results were analyzed, effect size for ADHD measures decreased even further, losing its statistical significance for overall ADHD, attention deficiency, and hyperactivity/impulsivity symptoms. Moreover, inclusion of possibly blinded assessments only, as part of the analyses from placebo controlled studies, still failed to create a statistical difference. Analyses of neuropsychological test performances yielded to insignificant effect- sizes. Researchers have reported that the type of NF did not have any effect over the differences observed among obtained results. In summary, this meta-analysis conducted by Cortese et al. (2016), indicates that evidences derived from controlled studies that encompass possibly blinded assessments, did not support NF, as an efficient treatment strategy for ADHD (Cortese et al. 2016).

In their meta-analysis that aimed to assess long-term effects of NF, J Van Doren et al. (2018) have only included follow- up studies. Studies were assessed, in the context of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). According to this checklist, 10 randomized controlled studies, that had met the inclusion criteria, were included. This meta-analysis has specifically explored the immediate effects of NF treatment, and throughout the follow-up phase. In order to carry out a much more efficient evaluation, researchers divided their control groups in two, as active and inactive. While active group was identified as the one that used evidence-based treatment strategies that were proven to be efficient in treating ADHD (methylphenidate and self- management training), other group has made up the inactive control group. Two hundred fifty-six individuals from NF group, and 250 cases from the control group were included in the analysis. Follow-up data at 2nd, 3rd, 6th and 12th month were evaluated. As part of the results obtained, post-treatment effect size of NF was moderate, for attention deficiency (SMD=0.64), and hyperactivity/impulsivity (SMD=0.50). This aforementioned effect size tended to increase for attention problems (SMD=0.80), while remained at moderate levels for hyperactivity/impulsivity (SMD=0.61). As a result of comparative analyses with inactive group, NF seems to be significantly supported. However, this significance observed is caused by very small differences, statistically. On the other hand, the study has implicated that NF had similar efficacy as a treatment option, similar to treatment that were used in active groups. Additionally, another remark stressed out was that clinical improvements caused by NF treatment continued, following cessation of treatment. All these findings have been reported to support the notion that NF had a different and specific impact. Attention was drawn to the impact of treatment would not have been due to therapeutic relationship between the patient and the therapist, or treatment-related expectations, non-specific characteristics of the method, or its placebo- like effects. Inclusion of 506 cases in total, and having used PRISMA method, this study was considered as a valuable contribution to relevant literature. However, researchers have also implied that

in most of the studies included in the meta-analysis, simultaneous use of medical treatment might mask the actual effects of NF. In addition to this, the researchers have also identified possible bias caused by lack of blinded NF studies, as a limitation (J Van Doren et al. 2018).

Conclusion

Due to methodological flaws and limitations of available research (insufficient or undetermined condition of blindness, failure to measure therapeutic effect of the time spent with the therapist, presence of confounding factors, small sample sizes in some studies, lack of randomization in some studies, etc.), limited number of placebo- controlled studies, unclear results of long-term treatment, inconsistent and discrepant findings obtained with different studies, efficiency of NF as a treatment strategy in ADHD, remains vague. Besides, the costly nature of the method as a treatment option, and considering many companies that wish to market NF as a treatment technique are readily available, studies that focus on the subject would especially have to give detailed information, with respect to their conflict of interest situations. Moreover, when studies that explore this subject are reviewed, it is seen that long treatment duration and more number of sessions were needed to obtain a sufficient treatment response, with the use of NF. Taking NF-related time spent and financial burden into account, studies that would employ a much more rigorous methodology and meticulous design, that aim to measure the efficiency of treatment, are warranted. Currently, NF is not recommended as a treatment option, in ADHD treatment guidelines.

References

Alhambra MA, Fowler TP, Alhambra AA (1995) EEG biofeedback: A new treatment option for ADD/ADHD. J Neurotherapy, 1:39–43.

Arnold LE, Lofthouse N, Hersch S, Pan X, Hurt E, Bates B et al. (2013) EEG neurofeedback for ADHD: double-blind sham-controlled randomized pilot feasibility trial. J Atten Disord, 17:410-419.

Arns M, Conners CK, Kraemer HC (2013) A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. J Atten Disord, 17:374–383.

Arns M, Heinrich H, Ros T, Rothenberger A, Strehl U (2015) Editorial: Neurofeedback in ADHD. Front Hum Neurosci, 9:602.

Arns M, de Ridder S, Strehl U, Breteler M, Coenen A (2009) Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta analysis. Clin EEG Neurosci, 40:180-189

Bakhshayesh A, Hansch S, Wyschkon A, Rezai MC, Esser G (2011) Neurofeedback in ADHD: a single-blind randomized controlled trial. Eur Child Adolesc Psychiatry, 20:481–491

Carmody DP, Radvanski DC, Wadhwani S, Sabo MJ, Vergara L (2001) EEG biofeedback training and attention-deficit/hyperactivity disorder in an elementary school setting. J Neurotherapy, 43:5–27.

Cortese S, Ferrin M, Brandeis D, Holtmann M, Aggensteiner P, Daley D et al. (2016) Neurofeedback for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry, 55:444-455.

Drechsler R, Straub M, Doehnert M, Heinrich H, Steinhausen HC, Brandeis D (2007) Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention-deficit/hyperactivity disorder (ADHD). Behav Brain Funct, 3:35.

Ercan ES, Avcı A, Mukaddes NM, Semerci B, Şenol S, Yazgan Y (2008) Dikkat Eksikliği Hiperaktivite Klinik Uygulama Kılavuzu Tűrkiye-2008. İstanbul, Janssen-Cilag.

Fuchs T, Birbaumer N, Lutzenberger W, Gruzelier JH, Kaiser J (2003) Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. Appl Psychophysiol Biofeedback, 28:1–12.

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P et al.(2009a) Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. Int J Psychophysiol, 74:149-157.

Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O et al. (2009b) Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. J Child Psychol Psychiatry,50:780-789.

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P et al. (2010) Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial. Eur Child Adolesc Psychiatry, 19:715–724.

Gevensleben H, Kleemeyer M, Rothenberger LG, Studer P, Flaig-Röhr A, Moll GH et al. (2014) Neurofeedback in ADHD: further pieces of the puzzle. Brain Topogr, 27:20-32

Gevensleben H, Rothenberger A, Moll GH, Heinrich H (2012) Neurofeedback in children with ADHD: validation and challenges. Expert Rev Neurother, 12:447-460.

Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K (2013) Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. Arch Gen Psychiatry, 70:185-198.

Heinrich H, Busch K, Studer P, Erbe K, Moll GH, Kratz O (2014) EEG spectral analysis of attention in ADHD: implications for neurofeedback training? Front Hum Neurosci, 8:611.

Heinrich H, Gevensleben H, Strehl U (2007) Annotation: neurofeedback - train your brain to train behaviour. J. Child Psychol Psychiatry ,48:3–16.

Heywood C, Beale I (2003) EEG biofeedback vs placebo treatment for attention-deficit/hyperactivity disorder: A pilot study. J Atten Disord, 7:41–53.

Holtmann M, Grasmann D, Cionek-Szpak E, Hager V, Panzer N, Beyer A et al. (2009) Specific effects of neurofeedback on impulsivity in ADHD. Kindheitund Entwicklung,18:95-104.

Holtmann M, Sonuga-Barke E, Cortese S, Brandeis D (2014) Neurofeedback for ADHD: a review of current evidence. Child Adolesc Psychiatr Clin North Am, 23:789-806.

Hurt E, Arnold LE, Lofthouse N (2014) Quantitative EEG neurofeedback for the treatment of pediatric attention-deficit/hyperactivity disorder, autism spectrum disorders, learning disorders, and epilepsy. Child Adolesc Psychiatr Clin N Am, 23:465-86.

Kaiser DA, Othmer S (2000) Effect of neurofeedback on variables of attention in a large multi-centertrial. J Neurotherapy, 4:5–28.

Kamiya J (1968) Conscious control of brain waves. Psychology Today, 1:57-60.

Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugué M, Carpentier PJ et al. (2010) European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry, 10:67.

Lansbergen MM, vanDongen-Boomsma M, Buitelaar JK, Slaats-Willemse D (2011) ADHD & EEG-neurofeedback: a double-blind randomized placebo-controlled feasibility study. J Neural Transm, 118:275–284.

Leins U, Goth G, Hinterberger T, Klinger C, Rumpf N, Strehl U (2007) Neurofeedback for children with ADHD: A comparison of SCP and theta/beta protocols. Appl Psychophysiol Biofeedback, 32:73-88.

Levesque J, Beauregard M, Mensour B (2006) Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study. Neurosci Lett, 394:216-221

Linden M, Habib T, Radojevic V (1996) A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. Biofeedback Self Regul, 21:35–49.

Lofthouse N, Arnold LE, Hersch S, Hurt E, DeBeus R (2012) A review of neurofeedback treatment for pediatric ADHD. J Atten Disord, 16:351-372.

Lubar JF, Shouse MN (1976) EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report. Biofeedback Self Regul, 1:293-306.

Lubar JF, Swartwood MO, Swartwood JN, Timmermann DL (1995) Quantitative EEG andauditory event-related potentials in the evaluation of attention-deficit disorder: Effects of methylphenidate and implications for neurofeedback training. J Psychoeduc Assess, 34:143–160.

Majewicz-Hefley A, Carlson JS (2007) A meta-analysis of combined treatments for children diagnosed with ADHD. J Atten Disord, 10:239-250.

Maurizio S, Liechti M, Heinrich H, Jancke L, Steinhausen HC, Walitza S et al. (2014) Comparing tomographic EEG neurofeedback and EMG biofeedback in children with attention-deficit/hyperactivity disorder. Biol Psychol, 95:31–44.

Monastra VJ, Lynn S, Linden M, Lubar JF, Gruzelier J, LaVaque TJ (2005) Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder.Appl Psychophysiol Biofeedback, 30:95-114.

Monastra VJ, Monastra DM, George S (2002) The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback, 27:231–249.

Perreau-Linck E, Lessard N, Levesque J, Beauregard M (2010) Effects of neurofeedback training on inhibitory capacities in ADHD children: A single blind randomized placebo controlled study. J Neurotherapy, 14:229-242.

Pliszka S (2007) AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivitydisorder. J Am Acad Child Adolesc Psychiatry, 46:894-921.

Purdie N, Hattie J, Carroll A (2002) A review of there search on interventions for attention deficit hyperactivity disorder: What works best? Rev Educ Res, 72:61-99.

Rossiter TR, La Vaque TJ (1995) A comparison of EEG biofeedback and psycho stimulants in treating attention deficit/hyperactivity disorders. J Neurotherapy, 1:48-59.

Sterman MB, LoPresti RW, Fairchild MD (1969) Electroencephalographic and Behavioral Studies of Monomethylhydrazine Toxicity in the Cat. Virgina, Aerospace Medical Research Laboratories.

Strehl U, Aggensteiner P, Wachtlin D, Brandeis D, Albrecht B, Arana M et al. (2017) Neurofeedback of slow cortical potentials in children with attention-deficit/hyperactivity disorder: a multicenter randomized trial controlling for unspecific effects. Front Hum Neurosci, 11:135.

Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M et al. (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry, 170:275–289.

Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J et al. (2004) European clinical guidelines for hyperkinetic disorder first upgrade. Eur Child Adolesc Psychiatry, 1:I7-I30.

Thompson L, Thompson M (1998) Neurofeedback combined with training in metacognitive strategies: effectiveness in students with ADD. Appl Psychophysiol Biofeedback, 23:243–263.

vanDongen-Boomsma M, Vollebregt MA, Slaats-Willemse D, Buitelar JK (2013) A randomized placebo-controlled trial of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry, 74:821–827.

Van Doren J, Arns M, Heinrich H, Vollebregt MA, Strehl U, K Loo S (2019) Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry, 28:293-305.

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