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Efficacy of Neurofeedback Versus Pharmacological Support in Subjects with ADHD

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Abstract Behavioral training in neurofeedback has proven to be an essential complement to generalize the effects of pharmacological support in subjects who have attention deficit with hyperactivity disorder (ADHD). Therefore, this investigation attempts to analyze the efficacy of neurofeedback compared with pharmacological support and the combination of both. Participants were 131 students, classified into four groups: control (did not receive neurofeedback or pharmacological support), neurofeedback group, pharmacological support group, and combined group (neurofeedback + pharmacological support). Participants' executive control and cortical activation were assessed before and after treatment. Results indicate that the combined group obtained more benefits and that the neurofeedback group improved to a greater extent in executive control than the pharmacological support group. It is concluded that this kind of training may be an alternative to stimulate activation in subjects with ADHD.

Keywords ADHD · Neurofeedback · Cortical activation · Pharmacological support · Intervention

Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders-5* (American Psychiatric Association 2013), attention deficit with hyperactivity disorder (ADHD) affects about 5 % of students. Historically, pharmacological supports have been considered the only efficacious treatment. However, in recent years, diverse studies have shown the effectiveness of neurofeedback training because as levels of cortical activation increase, symptoms of inattention, impulsivity, and hyperactivity decrease (Fuchs et al. 2003; Holtmann et al. 2014; Maurizio et al. 2013; Mayer et al. 2015; Monastra et al. 2005).

Training in neurofeedback emerged as a complementary or alternative treatment to pharmacological support (Bakhshayesh et al. 2011) aimed to stimulate cortical activation (Arns et al. 2012; Duric et al. 2014), especially in disorders that require increasing intervals of attention, self-regulation and control skills, such as ADHD (Monastra et al. 2005). Previous studies justify the increase in activation by neurofeedback training, not only due to the immediate feedback provided by the instrument (Mayer et al. 2015), but also due to the establishment of new neural pathways and connections (Toomim et al. 2004). In this sense, clinicians commonly utilize three basic types of neurofeedback training protocols, based on the alterations in ADHD (Holtmann et al. 2014). First, a conventional protocol to reduce inattention and impulsivity, which consists on operant suppressing of theta activity and enhancement of beta activity (Bakhshayesh et al. 2011; Lubar et al. 1995). Second, a protocol to reduce hypermotoric symptoms and enhance sensorimotor rhythm (SMR), which is sometimes used in addition to the previous theta-beta protocol (Monastra et al. 2005; Russell-Chapin et al. 2013). Third, based on the electrophysiologic evidence of altered slow cortical potentials (SCPs) in ADHD, other protocol has emerged, which is aimed at modifying SCPs in order to regulate cortical excitation thresholds (Christiansen et al. 2014). Among the varieties of NF protocols, the classic theta-beta procedure is one of the best scientifically evaluated (Zuberer et al. 2015) and will therefore be the focus of the present study.

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Furthermore, neoconnectionist models of learning are another theoretical referent, according to which, the frequency field of each brain activity correlates with the cortical areas involved (Congedo and Lubar 2003; Orlando and Rivera 2004). Thus, when the subject is distracted, the frequency field of the electroencephalograph measures delta or theta waves with a frequency of 0.5–4 or 4–8 Hz, respectively. When the subject is relaxed with dispersed attention, brain waves have a frequency of 8–12 Hz. Lastly, when the subject is alert, the frequency field is of 15–25 Hz, beta waves. An increase in theta activity is accompanied by decreases in blood flow and in metabolism (Lubar et al. 1995), so high frequencies of theta activity are observed in not very active brain areas (Álvarez et al. 2008). ADHD is specifically characterized by an abnormal pattern of electrocortical activity at rest, in particular, an increase in theta activity and a decrease in beta activity (Lansbergen et al. 2011). In this sense, Toomim et al. (2004) states that the beta/theta ratio is a better indicator of brain activity than each wave taken separately.

These theoretical references justify neurofeedback interventions with subjects with ADHD. Monastra et al. (2005), in a review, analyzed the empirical evidence of neurofeedback, applying the guidelines of efficacy concurrently established by the Association of Applied Psychophysiology and Biofeedback and the International Society for Neuronal Regulation. On the basis of these principles, they concluded that neurofeedback is "probably an efficacious instrument" for treatment of ADHD, as clinically significant improvement is observed in approximately 75 % of the cases treated in each one of the investigations analyzed.

Gevensleben et al. (2009), after studying 102 participants (8–12 years) who received 36 sessions of neurofeedback, concluded that the instrument shows contrasted clinical efficacy in the treatment of ADHD. Previously, Thompson and Thompson (1998) carried out a study with 111 participants (98 boys and 13 adults) with ADHD during 40 training sessions combining neurofeedback and metacognitive strategies. As a result, they observed significant improvements in ADHD, both in the variables contributed by the test of variables of attention (TOVA; Greenberg 1996) (inattention, impulsivity, variability and response time) and in the quantified EEG (QEEG) results. In addition to these gains, they identified better academic and intellectual functioning, so they suggest that this type of treatment is a useful intervention for students with ADHD. This should be taken into account because pharmacological support produces a benefit in behavior and attention, but does not typically improve academic performance or interaction capacity (Duric et al. 2014; Nash 2000).

Along with these lines, a good deal of research has focused on comparing the effects of pharmacological support versus neurofeedback. For instance, Rossiter (2004) compared the benefits of both treatments in a sample of 62 participants. They observed that both interventions improved performance on TOVA, with no differences between them. Meanwhile, Fuchs et al. (2003) compared both treatments during a 3-month interval, including among their assessment instruments a behavioral scale (IOWA Conner's Rating Scale) for parents and teachers. After training a sample of 34 children (8–12 years), 22 with neurofeedback and 12 with methylphenidate, they concluded that both treatments produced an improvement in the variables recorded by TOVA and in the D-2 Test (Brickenkamp 2002). Furthermore, parents and teachers also observed a reduction of symptomatology associated with the disorder in both groups.

Thus, indexes like the executive function and TOVA variables of inattention and impulsivity are modified after neurofeedback training (Fuchs et al. 2003; Othmer et al. 2000). Moreover, according to Gevensleben et al. (2010), the benefits in ADHD produced by neurofeedback training are maintained at the 6-month follow-up, in contrast to pharmacological treatment. The results of multimodal treatments (Multimodal Treatment Study for Children with ADHD -MTA- 1999) suggest that, whereas pharmacological support is effective for the symptomatology of the disorder, combination with other treatments also produces improvement at a contextual level (learning, emotional and social behavior, and family problems).

Therefore, the goal of this investigation is aimed at analyzing the differential efficacy of neurofeedback training versus pharmacological support in participants with ADHD, and whether the combination of both treatments can generate more benefits. For this purpose, we used three groups, all subjects with ADHD who either received pharmacological support or neurofeedback, or the combination of both (neurofeedback + pharmacological support). There was also a control group with ADHD that was not trained in neurofeedback and did not receive pharmacological support. The working hypothesis is that, although all three treated groups will improve performance in the variables assessed (executive control with TOVA and cortical activation with QEEG), the group with combined treatment will benefit more from the intervention. Therefore, this group will record higher cortical activation in the central (Cz) and prefrontal (Fp1) areas as well as committing fewer omissions and commissions, better response time, and less variability in the TOVA (with an ADHD score approaching standard scores), and lower recordings in the Scale of Assessment of Attention Deficit with Hyperactivity (EDAH; Farré and Narbona 2013) completed by parents. Concerning the pharmacological support and neurofeedback groups, the hypothesis is that there will be no differences in cortical activation measures between

groups, but significant differences will be found in executive control measures (because pharmacological support does not necessarily imply an improvement at the executive level), as well as in parents' evaluations of symptomatology.

Methods

Participants

Participants in this investigation were 131 students with ADHD, 48 girls and 83 boys, between 8 and 11 years of age. Participants were classified into four groups: Control group, students with ADHD who did not receive either pharmacological support of neurofeedback ($n = 33$, 11 girls and 22 boys); neurofeedback group ($n = 33$, 11 girls and 22 boys); pharmacological support group ($n = 34$, 15 girls and 19 boys), and combined group ($n = 31$, 11 girls and 20 boys). They all had an IQ of 80 or higher (see Table 1), as assessed by the orientation team of their school with the Wechsler Intelligence Scale for Children (WISC-IV, Wechsler 2004). Participants attended diverse public and subsidized schools in Asturias (Spain) and had been diagnosed with ADHD by their neuropediatrician of reference. They were assigned to a specific treatment group depending on the preferences expressed by their parents.

The analyses carried out on the participants of this investigation showed that the sample is homogeneous, with no statistically significant differences among the participants as a function of IQ ($p = 0.996$) or age ($p = 0.952$).

Instruments

Participants were assessed at three levels (assessment of symptoms -EDAH-assessment of execution -TOVA- and assessment of cortical activation -QEEG-) at two different moments (before treatment initiation and after treatment). The EEG-spectrum was used for the neurofeedback intervention.

Table 1 Means and SD of IQs and age of the groups

Groups	N	IQ		Age	
		M	SD	M	SD
1. CG	33	98.24	10.78	9.63	1.14
2. NF	33	98.66	11.85	9.63	1.20
3. PS	34	98.02	10.83	9.67	1.10
4. NF + PS	31	98.25	9.88	9.52	1.02
Total sample	131	98.29	10.75	9.61	1.11

CG control, *NF* neurofeedback, *PS* pharmacological support; *M* mean, *SD* standard deviation

Scale of Assessment of Attention Deficit with Hyperactivity (EDAH)

Assessment of ADHD symptoms was performed with the EDAH scale (Farré and Narbona 2013) for parents. The scale has 20 items providing information about attention deficit (AD; 5 items), hyperactivity-impulsivity (H; 5 items), and conduct disorder (CD; 10 items). Items are scored on a 4-point Likert-type format, ranging from 0 to 3. The reliability of the instrument, using Cronbach's Alpha, is high for the whole scale ($\alpha = 0.929$) and its components: DA ($\alpha = 0.898$), H ($\alpha = 0.849$), and CD ($\alpha = 0.899$). There were also found high and significant correlations ($r = 0.679$; $p < 0.001$) between the whole scale and the ADHD diagnostic criteria established by DSM-III-R (APA 1987). Given the purpose of the present study, only AD and H subscales were used. Attention deficit and/or hyperactivity-impulsivity are considered to exist when the score in one of the subscales is higher than 90 %.

Test of Variables of Attention (TOVA)

Execution was assessed with the TOVA (Greenberg 1996). This test presents two different alternative stimuli on a computer screen, for an average of 22.5 min. The first stimulus is a black square on the upper border, and the subject should press a button when it appears. The second stimulus is a black square on the lower border, and the subject should not perform any action. The TOVA controls omissions (OM), commissions (COM), response time (RT), and variability (VAR). Obtaining a SD below the mean in omissions and response time indicates attention deficit; if this occurs in commissions, it indicates impulsivity; and, lastly, if it occurs in variability, it is an indication of hyperactivity. Other indicators to be taken into account in the TOVA are the D value (D′) and the ADHD score. D′ is obtained from the subject's performance across the test, so that the more errors committed, the higher will be this index, attributable to hyperactivity. ADHD score is the result of the sum of the response time of the first half, D′ of the second half, and the total variability. If ADHD score is lower than −1.80, it indicates a deficit in executive control (González-Castro et al. 2013).

Quantified EEG (QEEG)

Cortical activation is recorded with QEEG, providing levels of cortical activation through the beta/theta ratio. It measures attention capacity, independently of the task to be performed. For this purpose, an electrode is placed on the corresponding cortical areas (central area of the cortex -Cz-, and left prefrontal area -Fp1-) to record the beta/theta ratio. Two more control electrodes are placed on the left

and right earlobes. The QEEG is administered to each participant, with open eyes, for a maximum duration of 10 min. An EMG system is placed on the right forearm to control the degree of movement. Once the electrodes are placed, participants are asked to remain relaxed, without emitting any movement, breathing slowly and evenly, and concentrating exclusively on the computer screen, on which the theta and beta waves emitted by them are displayed successively. Once the degree of cortical activation is registered, the results obtained are interpreted. A beta/-theta ratio lower than 50 % at Cz is indicative of sustained attention deficits, whereas if the ratio is below 50 % at Fp1, the deficit is associated with a lack of executive control, linked to hyperactivity (González-Castro et al. 2013).

Neurofeedback (EEG Spectrum)

Initial activation, assessed through the beta/theta ratio, was enhanced by means of neurofeedback, specifically, using the *EEG spectrum* (www.neurocybernetics.com), designed by Howard Lightstone for Neurocybernetics, Inc. The instrument is made up of two apparatuses: one for the person who guides the training and the other for the person being trained. The trainee is connected to the apparatus through an EEG preamplifier with wires connected by simple electrodes: signal, ground, and reference. The electrode signal is fixed to the prefrontal area (Fp1) with conductor gel, and the reference and ground electrodes are placed on the earlobe. Samples of the EEG signal are taken 256 times per second and digitalized. The trainer's software processes the samples of the transformed digital signals and stores, filters, and separates them into various frequency bands, and visualizes both the unprocessed signals and the filtered signals on the computer at a rate of 160 samples per second. The data of the brain wave amplitudes at each frequency band are transmitted by the trainer's computer to the subject's computer as a game. For this purpose, the trainer monitors the activity of the brain waves and sets the goals, while the patient visualizes the feedback through the game.

Procedure

This study was conducted in accordance with the Helsinki Declaration of the World Medical Association (Williams 2008). After obtaining parents' consent, each child was assigned to a reference group (control group, neurofeedback, pharmacological support, combined). Then, we administered pretreatment assessment with QEEG and TOVA. To assess with the QEEG, participants were instructed to remain relaxed, without moving, with eyes open, and looking at the computer screen. Next, TOVA was applied, after giving participants the following instructions: "During the next few minutes, you will see a sequence of figures on the computer. You should press the key as fast as possible when you see the rectangle with the square near the top border of the screen, but not when the square is near the lower border". Participants carried out an initial 3-min practice session.

Students with pharmacological support received methylphenidate, which was administered according to neuropediatricians recommendations, based on evolutionary parameters such as age and weight. For students that received neurofeedback training, the intervention consisted in a 15 min session, 3 days per week, during 3 months. The training began with the rocket game of the EEG spectrum. After 3 months, participants were assessed again with the described instruments (posttreatment assessment) to appraise the effects of the intervention.

Design and Data Analysis

We used an ex-post-facto descriptive design with four treatment groups (pharmacological support, neurofeedback, combined) and a control group that did not receive intervention initially.

As the goal of the investigation was to determine potential differences between the four groups after treatments, the data obtained were analyzed with multivariate analysis of variance (MANOVA) and covariance (MANCOVA), the latter when the effect of the pretest variables was statistically significant. The dependent variables were: measures of cortical activation, executive control, and symptomatology recordings. We used the value of Wilks' λ to determine possible significant differences in all the dependent variables taken conjointly. In those cases where Wilks' λ was significant ($p < 0.05$), the results of the individual analyses of variance (ANOVAs) were interpreted. For effect sizes interpretation, Cohen's (1988) criterion was used, which establishes that the effect is small when $\eta p^2 = 0.01$ ($d = 0.20$), medium when $\eta p^2 = 0.059$ ($d = 0.50$), and high when $\eta p^2 = 0.138$ ($d = 0.80$). SPSS v.17 was used to conduct statistical analyses.

In addition, given that one of the hypothesis was related to the absence of differences in cortical activation measures between the groups with neurofeedback versus pharmacological intervention, the gain in Cz and Fp1 was calculated (posttreatment − pretreatment), and the differences among the three treatment conditions (pharmacological support, neurofeedback and combined) were analyzed with ANOVAs.

For greater clarity, in the results section, we present pre- and posttreatment data of the variables recorded by the instruments separately.

Results

Results are presented for each group of variables (in the two assessments: pre- and post-treatment): cortical activation with QEEG (central and left prefrontal), executive control with TOVA (omissions, commissions, response time, variability, D′, and ADHD score), and observation with EDAH.

Cortical Activation with QEEG

Table 2 presents the data of the assessment of cortical activation at Cz and Fp1.

The MANOVA for the pretreatment measures showed that the main effects of the independent variables (treatments) on the dependent variables (central and prefrontal activation) were statistically non significant, Wilks' $\lambda = 0.940$, F (6, 252) = 1.318, $p = 0.249$, $\eta p^2 = 0.030$. Thus, there were no pretreatment differences between the four groups in any of these two variables.

With regard to posttreatment measures, the MANOVA showed that the main effects of the independent variables on the dependent ones were statistically significant, Wilks' $\lambda = 0.639$, F (6, 254) = 10.54, $p < 0.001$, $\eta p^2 = 0.201$. The effect size of the relation was relevant, as 20.1 % of the variability is attributable to group differences. Concerning inter-subject effects analysis (ANOVAs), results revealed the existence of statistically significant differences among the four groups of participants, regarding both Cz, F (3, 127) = 20.67, $p < 0.001$, $\eta p^2 = 0.328$, and Fp1, F (3, 127) = 12.68, $p < 0.001$, $\eta p^2 = 0.231$.

Results of the post hoc multiple Scheffé comparisons indicated that, in the variable Cz, there were statistically significant group differences between control group and the three treatment groups: neurofeedback ($p < 0.001$), pharmacological support ($p \leq 0.001$), and combined ($p < 0.001$). Moreover, the differences between combined and pharmacological support were statistically significant ($p = 0.006$). Also for the variable Fp1, there were statistically significant group differences between control group and the three treatment groups: neurofeedback ($p < 0.001$), pharmacological support ($p = 0.005$), and combined ($p < 0.001$). In both variables, the direction of the differences indicated that the combined group improved cortical and left prefrontal activation to a greater extent. There were no statistically significant differences between pharmacological support and neurofeedback groups, although the latter obtained higher activation in both areas.

Lastly, in order to analyze the differences pre-posttreatment between the treatment groups, the gain in the three conditions (NC, AF, NC + AF) was calculated. The results of the ANOVAs showed that there were differences between the gain observed in NC and NC + AF groups in the both Cz, F (1, 62) = 31.420, $p < 0.001$, $\eta p^2 = 0.336$; and Fp1, F (1, 62) = 10.280, $p = 0.002$, $\eta p^2 = 0.142$. Similar differences were also found in the case of AF and NC + AF in Cz, F (1, 63) = 34.559, $p < 0.001$, $\eta p^2 = 0.355$; and Fp1, F (1, 63) = 11.656, $p < 0.001$, $\eta p^2 = 0.156$. However, no significant differences were found between NC and AF groups, showing these groups a similar gain in both Cz, F (1, 65) = 0.180, $p < 0.673$, $\eta p^2 = 0.003$; and Fp1, F (1, 65) = 0.183, $p = 0.670$, $\eta p^2 = 0.003$.

Executive Control with TOVA

Table 3 presents the means and SD of the six indicators of executive control (omissions, commissions, response, time, and variability) at the two assessment moments (pre- and post-treatment). To interpret this information correctly, it should be taken into account that lower scores indicate a higher deficit.

Upon analyzing the pretreatment measures, statistically significant group differences were observed, Wilks' $\lambda = 0.691$, F (18, 245) = 2.676, $p < 0.001$, $\eta p^2 = 0.116$. Analysis of the between-subject effects revealed differences in the variable commissions, F (3, 127) = 5.97, $p = 0.001$, $\eta p^2 = 0.124$, and D′, F (3, 127) = 4.73, $p = 0.004$, $\eta p^2 = 0.101$. The results of the post hoc multiple Scheffé comparisons revealed statistically significant differences in the variable commissions between control group and the neurofeedback group ($p = 0.002$) and between the neurofeedback and combined groups ($p = 0.021$). For the variable D′, statistically significant differences between control group and the neurofeedback group were found ($p = 0.007$). These variables (commissions and D′) were considered covariates in the posttreatment analysis described below.

Table 2 Cortical activation pre- and post-treatment means and SD assessed with QEEG at Cz and Fp1

	CG ($n = 33$)		NF ($n = 33$)		PS ($n = 34$)		NF + PS ($n = 31$)	
	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)
Cz	0.40 (0.07)	0.41 (0.07)	0.44 (0.07)	0.49 (0.06)	0.42 (0.07)	0.47 (0.06)	0.41 (0.07)	0.53 (0.04)
Fp1	0.42 (0.07)	0.43 (0.07)	0.44 (0.07)	0.52 (0.05)	0.42 (0.06)	0.50 (0.09)	0.40 (0.07)	0.53 (0.04)

CG control, *NF* neurofeedback, *PS* pharmacological support, *M* mean, *SD* standard deviation

Table 3 Executive control pre- and post-treatment means on executive control in the four groups

	CG ($n = 33$)		NF ($n = 33$)		PS ($n = 34$)		NF + PS ($n = 31$)	
	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)
OM	77.12 (8.27)	77.33 (8.589)	80.33 (12.47)	90.76 (8.17)	79.32 (7.54)	84.94 (5.82)	77.74 (7.60)	91.35 (4.57)
COM	85.39 (7.57)	87.73 (8.13)	91.33 (6.22)	100.76 (10.10)	8.47 (5.53)	94.47 (5.93)	86.48 (4.67)	97.45 (5.83)
VAR	79.55 (8.94)	79.12 (9.35)	79.82 (10.42)	89.76 (9.18)	80.09 (6.92)	84.74 (7.51)	76.45 (7.97)	91.55 (5.27)
TR	76.48 (8.73)	75.33 (8.84)	80.79 (9.25)	89.39 (12.25)	79.26 (7.79)	85.74 (7.56)	78.45 (7.78)	92.39 (3.80)
D′	−1.90 (0.66)	−1.70 (0.66)	−1.34 (0.67)	−0.77 (0.60)	−1.74 (0.61)	−1.05 (0.56)	−1.79 (0.62)	−0.68 (0.45)
ADHD score	−4.13 (1.40)	−3.87 (1.58)	−3.46 (1.44)	−1.87 (1.19)	−4.21 (1.78)	−2.47 (1.07)	−4.19 (1.45)	−1.75 (0.63)

CG control, *NF* neurofeedback, *PS* pharmacological support, *M* mean, *SD* standard deviation

The posttreatment data revealed statistically significant group differences, Wilks' $\lambda = 0.691$, F (18, 339) = 6.906, $p < 0.001$, $\eta p^2 = 0.255$. The effect size of the relation was relevant, as 25.5 % of the variability is attributable to group differences. The effect of the covariates was significant for both commissions, F (6, 120) = 13.950, $p < 0.001$, $\eta p^2 = 0.411$; and D′, F (6, 120) = 11.794, $p < 0.001$, $\eta p^2 = 0.371$. Analysis of between-subject effects showed that these differences occurred in the six variables recorded: omissions, F (3, 125) = 26.24, $p < 0.001$, $\eta p^2 = 0.386$, commissions, F (3, 125) = 14.46, $p < 0.001$, $\eta p^2 = 0.258$, response time, F (3, 125) = 22.24, $p < 0.001$, $\eta p^2 = 0.348$, and variability, F (3, 125) = 16.34, $p < 0.001$, $\eta p^2 = 0.282$, D′, F (3, 125) = 14.55, $p < 0.001$, $\eta p^2 = 0.366$, and ADHD score, F (3, 125) = 23.30, $p < 0.001$, $\eta p^2 = 0.359$.

The results obtained with the post hoc multiple Scheffé comparisons indicate that, in the variable omissions, there were statistically significant group differences between control group and the three treatment groups: neurofeedback ($p < 0.001$), combined ($p < 0.001$), and pharmacological support ($p < 0.001$). The differences between the neurofeedback and pharmacological support groups ($p = 0.011$) and between the combined and pharmacological support groups ($p = 0.005$) were statistically significant. Statistically significant differences were found for the variable commissions between control group and the three treatment groups: neurofeedback ($p < 0.001$), and pharmacological support ($p = 0.007$), and combined ($p < 0.001$) and also between neurofeedback and pharmacological support ($p = 0.014$). The same result was obtained in variability between controls and the treatment groups, as well as between the combined and pharmacological support groups ($p = 0.011$). In response time, differences were found at $p = 0.027$ between the combined and pharmacological support groups. With regard to D′ and ADHD score, statistically significant differences were observed between the control group and the three treatment groups.

Observation with EDAH

Table 4 shows the means and SD of the indicators of hyperactivity, attention deficit, and hyperactivity with attention deficit.

The analysis conducted with the pretreatment data showed that the main effects of the independent variables (treatments) on the dependent variables (hyperactivity, attention deficit, and their sum) were statistically significant, Wilks' $\lambda = 0.854$, F (9, 304) = 2.26, $p = 0.018$, $\eta p^2 = 0.051$. Analysis of the between-subject effects yielded by the MANOVA revealed that these differences occurred in the H + AD variable, F (3, 127) = 5.25, $p = 0.002$, $\eta p^2 = 0.110$. Specifically, the post hoc multiple Scheffé comparisons indicated statistically significant differences between the neurofeedback group and the combined group ($p = 0.005$). The variable H + AD was considered as a covariate in the posttreatment analyses, in which the MANCOVAs showed that the main effects of the independent variables on the dependent variables were statistically significant, Wilks' $\lambda = 0.665$, F (9, 301) = 6.11, $p < 0.001$, $\eta p^2 = 0.127$. The effect of the covariate was significant, F (3, 124) = 54.12, $p < 0.001$, $\eta p^2 = 0.567$.

Analysis of the between-subject effects of the ANCOVAs showed that these differences were found in the variables H, F (3, 126) = 7.45, $p < 0.001$, $\eta p^2 = 0.151$), AD, F (3, 126) = 12.20, $p < 0.001$, $\eta p^2 = 0.225$, and H + AD, F (3, 126) = 13.42, $p < 0.001$, $\eta p^2 = 0.242$. The effect of the covariates was eliminated to perform the post hoc analyses, and statistically significant differences were subsequently observed between the control group and neurofeedback groups ($p \leq 0.001$) and between the control group and combined groups ($p = 0.003$), but not between the control group and pharmacological support groups ($p = 0.128$). For the variable AD, there were statistically significant differences between control group and the three treatment groups: neurofeedback ($p < 0.001$), pharmacological support ($p = 0.034$) and combined ($p < 0.001$).

Table 4 Pre- and post-treatment means and SD of the EDAH

	CG ($n = 33$)		NF ($n = 33$)		PS ($n = 34$)		NF + PS ($n = 31$)	
	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)
H	89.94 (5.83)	88.52 (4.67)	89.94 (5.61)	83.36 (7.53)	90.71 (5.38)	85.47 (3.51)	92.32 (5.22)	83.61 (3.99)
AD	92.30 (4.63)	90.88 (4.40)	89.24 (9.83)	81.12 (11.42)	91.06 (6.61)	85.62 (4.51)	91.13 (7.91)	82.55 (6.04)
H + AD	89.48 (7.26)	88.55 (6.77)	84.00 (14.84)	79.73 (14.36)	90.71 (5.06)	84.35 (5.52)	92.29 (4.54)	81.32 (5.01)

CG control, *NF* neurofeedback, *PS* pharmacological support, *M* mean, *SD* standard deviation

Lastly, for the variable H + AD, there were significant differences between control group and neurofeedback ($p \leq 0.001$), between control group and combined ($p = 0.016$), but not between control group and pharmacological support ($p = 0.289$).

Discussion

The purpose of this study was to analyze the efficacy of neurofeedback training versus pharmacological support in subjects with ADHD, and to examine whether the combination of both treatments would be more efficacious. For this purpose, we used three groups of participants with ADHD who received treatment: neurofeedback, pharmacological support, or combined (neurofeedback + pharmacological support). There was also a control group with ADHD that was not trained with neurofeedback and did not receive pharmacological support. The working hypothesis was that, although all three treated groups would display a significantly better performance in the variables assessed (executive control with TOVA and cortical activation with QEEG), the group with combined treatment would obtain greater benefit from the intervention. Therefore, this group would record higher cortical activation in the central (Cz) and prefrontal cortex (Fp1) areas and would commit fewer omissions, commissions, and have better response time and less variability in the TOVA (ADHD score approaching standard scores), along with lower recordings in the EDAH. Comparing the pharmacological support and neurofeedback groups, it was hypothesized that there would be no differences in cortical activation measures (Cz and Fp1) between these groups, but there would be significant differences in executive control measures, measured with the TOVA, and in the parents' evaluations.

Taking these hypotheses into account, in effect, the treatment groups showed higher values of cortical activation, better executive control, and a reduction of the observed symptomatology. The data indicated that the combined group obtained higher benefits in all three spheres recorded. Therefore, one of the conclusions of this study is that multimodal treatments provide better results than isolated interventions, as also concluded in prior studies (MTA 1999; Álvarez et al. 2008).

Another hypothesis was that the pharmacological support and neurofeedback groups would not present differences in cortical activation, as reported in previous studies (Duric et al. 2014; Thompson and Thompson 1998). Data analysis showed the existence of no statistically significant differences in participants' cortical activation after receiving the corresponding treatments. Furthermore, the analysis of the gain in these two groups indicated that there were no statistically significant differences between them, showing that both treatments have similar effects on cortical activation measured in Cz and Fp1. With regard to executive control, our hypothesis was that the pharmacological support group would not significantly improve its performance on the TOVA in comparison with the neurofeedback group. The pharmacological support group did improve its levels of activation and, after 3 months of treatment, in the second assessment of their performance (posttreatment) (without further pharmacological treatment at the time of assessment), its performance had improved. However, the performance of this group remained worse than the observed in the combined and neurofeedback groups. These results are coherent with those found by Martínez-León (2006), and support the hypothesis that a combined treatment is more efficacious to reduce symptomatology of the disorder, but also indicate that this improvement is more consistent over time (Gevensleben et al. 2010). In this sense, as the only difference between the group with combined treatment (neurofeedback + pharmacological support) and the pharmacological support group was the training in neurofeedback, it can be concluded that the application of this type of intervention may result in a significant improvement over time, leading to better results than the pharmacological support alone.

Along these same lines, parents' recordings with the EDAH questionnaire (Farré and Narbona 2013) show pre- and post-treatment differences in the combined and neurofeedback groups, but not in the pharmacological support group. This result may be due to the fact that, although medication aims to reduce the hyperactive/impulsivity symptomatology so the child will be able to be still and

concentrate during a more or less prolonged time (depending on the type of drug), this effect is generally limited to the school schedule and study times. It therefore seems logical to think that teachers should observe a more pronounced change than parents, because by the time the child gets home, the effect of the drug will have minimized or disappeared. The benefits of neurofeedback versus pharmacological support show the utility of this kind of training and the need to continue this type of research, in order to know the efficacy of the treatment by subtypes of the disorder.

Finally, we acknowledge the following limitations. The students were assigned to a specific treatment group depending on the preferences expressed by their parents. Thus, the absence of a random assignment of the subjects is the first limitation of the present study. Second, the diagnosis of ADHD was not confirmed by using additional instruments. These aspects must be considered in further studies. Third, as the intervention program was applied during 15 min, it would be interesting to study the benefits of the intervention with periods of 30 min, and even the difference between the effects of these two periods of time. It would allow to better adjust the intervention and establish a training protocol. In this sense, following Duric et al. (2014), there is no standard recommended regarding the number, time and frequency of sessions when this type of protocols are administered.

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