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ACCEPTED MANUSCRIPT

NEUROFEEDBACK IN ADHD

Neurofeedback and standard pharmacological intervention in ADHD: a randomized controlled trial with six-month follow-up

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Abstract

The present study is a randomized controlled trial that aims to evaluate the efficacy of Neurofeedback compared to standard pharmacological intervention in the treatment of attention deficit/hyperactivity disorder (ADHD). The final sample consisted of 23 children with ADHD (11 boys and 12 girls, 7-14 years old). Participants carried out 40 theta/beta training sessions or received methylphenidate. Behavioral rating scales were completed by fathers, mothers, and teachers at pre-, post-treatment, two-, and six-month naturalistic follow-up. In both groups, similar significant reductions were reported in ADHD functional impairment by parents; and in primary ADHD symptoms by parents and teachers. However, significant academic performance improvements were only detected in the Neurofeedback group. Our findings provide new evidence for the efficacy of Neurofeedback, and contribute to enlarge the range of non-pharmacological ADHD intervention choices. To our knowledge, this is the first randomized controlled trial with a six-month follow-up that compares Neurofeedback and stimulant medication in ADHD.

Keywords: attention deficit/hyperactivity disorder (ADHD); EEG biofeedback; methylphenidate; neurofeedback; pharmacological intervention.

Introduction

Neurofeedback (NF) is an operant conditioning procedure that aims at developing skills for self-regulation of brain activity (Heinrich, Gevensleben, & Strehl, 2007).

Simultaneous and contingent feedback of neurophysiological signals is provided during the training, with the aim to learn to control the processes underlying these signals and thereby enhance cognitive, emotional and behavioral self-regulation. Feedback is usually presented as a computer game in which participants earn points whenever certain neurophysiological patterns change in the desired direction (Gevensleben, Rothenberger, Moll, & Heinrich, 2012). NF started more than 30 years ago in the area of Child and Adolescent Psychiatry, and has been extensively studied as a treatment for attention deficit/hyperactivity disorder (Heinrich et al., 2007).

Two distinct NF protocols are typically used in ADHD (Gevensleben et al., 2009; Wangler et al., 2011). Theta/beta training is one protocol based on the spontaneous electroencephalogram (EEG), and consists of inhibiting theta and enhancing beta, sometimes overlapping with the sensoriomotor rhythm band (Egner & Gruzelier, 2004; Lubar, 1991; Lubar, Starwood, Starwood, & Timmermann, 1995). This training, also called EEG frequency band (FREQ) training, addresses the tonic aspects of cortical arousal (Liechti et al., 2012). The other protocol is the training of slow cortical potentials (SCP), a type of event-related potential (ERP), and it is directed to phasic regulation of cortical excitability (Gevensleben et al., 2009; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Strehl et al., 2006).

Several studies have reported consistent deficits in the electrophysiology of ADHD children in comparison to children without the disorder (Clarke, Barry, McCarthy, & Slikowitz, 2001). Studies show that increased frontal theta activity is one

of the most commonly reported EEG abnormalities in ADHD. Less consistent, but also reported in several studies, are increased delta and reduced alpha and beta activity (Barry, Clarke, & Johnstone, 2003; Clarke, Barry, McCarthy, & Selikowitz, 2011). Increased slow wave/fast wave ratios have been considered a well-established phenomenon in ADHD (Putman, van Peer, Maimari, & van der Werff, 2010). Specifically, theta/beta ratio (TBR) has shown to be a sensitive marker of ADHD in several studies (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke, Barry, McCarthy, & Selikowitz, 2002, 2011; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Lubar, 1991; Monastra, Lubar, & Linden, 2001). Nevertheless, a recent meta-analysis concluded that excessive TBR cannot be considered a reliable diagnostic for ADHD (significant heterogeneity was found related to increase TBR in control groups); however a substantial sub-group of ADHD patients do deviate on this measure (Arns, Conners, & Kraemer, 2012). In addition, recent studies have reported that more rigorous analysis of the EEG is required to reliably dissociate a slowed individual alpha peak frequency (iAPF) from real excess theta (Arns, 2012; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011). Neurophysiologic abnormalities also characterize the ERP of ADHD patients (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008). Attenuations of P300 components, which reflect attention, inhibition and cognitive control, as well as deviant slow cortical potentials like the contingent negative variation (CNV) during preparation and activation of a motor or cognitive response, are reported in ERP studies (Barry, Johnstone, & Clarke, 2003).

Previous studies have reported a decrease of behavioral problems and improved cognitive performance in ADHD children after theta/beta and SCP training (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Drechsler et al., 2007; Fuchs Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Gevensleben et al., 2009;

Gevensleben et al., 2010; Heinrich et al., 2004; Monastra, Monastra, & George, 2002; Leins et al., 2007). Moreover, some studies have found that improvements are maintained after six months (Gevensleben et al., 2010; Leins et al., 2007), and even after two years after completing the training (Gani, Birbaumer, & Strehl, 2008). Additionally, several studies have found certain normalization of EEG and ERP after NF training (Bakhshayesh et al., 2011; Doehnert et al., 2008; Heinrich et al., 2004; Kropotov et al., 2005; Monastra et al., 2002). Nevertheless, NF efficacy in comparison to medication, gold standard ADHD treatment, is still not well established. The existing studies have several methodological shortcomings that need to be addressed in order to consider NF as efficacious as standard pharmacological intervention for ADHD.

Rossiter and La Vaque (1995) conducted the first controlled group study to compare NF and stimulant medication, using a sample of 46 participants, with a broad age range (8-21 years old). This study presented some important limitations such as lack of randomization and absence of follow up data. A replication of this study was made with a larger sample (N = 62), expanded age range (7-55 years old) and improved statistical analysis (Rossiter, 2004). Nevertheless, no randomization assignment was done. Monastra et al. (2002) conducted another study examining the effects of NF, stimulant medication, and parenting style on primary ADHD symptoms, neuropsychological, and electrophysiological variables. Children, aged 6-19 (N = 100), participated in a one year program that included medication, parent counseling, and academic support at school. Fifty-one participants also received NF intervention. Although this study included a large sample, control over important variables, and an examination of treatment effects one year after initial evaluation, it was not a randomized control trial. Fuchs et al. (2003) compared the effects of NF and stimulant medication in a smaller sample (N = 34) of children aged 8-12 years. In this study, no randomization

was conducted, and no follow-up assessments were included. In 2011, another study compared methylphenidate with NF in a sample of 39 children (7-12 years old) that included an age-matched healthy control group to control test-retest effect (Ali Nazari, Querne, De Broca, & Berquin, 2011). The main strength of this study was the inclusion of behavioral and neuropsychological variables. Nevertheless, it lacked randomization as the previous studies.

Recently, Duric, Assmus, Gundersen, and Elgen (2012) conducted a controlled study in which 91 ADHD participants (aged 6-18 years) were randomly assigned to three groups. The first group received NF, the second received medication, and a third group received both NF and medication. This is the first randomized controlled study that analyzed not only the separate effects of NF and medication, but also the interaction between both of these treatments. Nevertheless, this study did not include teacher reports (which is very important given that ADHD diagnosis relies on the fulfillment of symptom criteria according to DSM-IV at least in two settings: e. g. school), and only included a short-term follow-up assessment (one week after the treatment was completed).

In spite of the positive effects of NF reported in these studies, more research should be conducted in order to conclude that NF and pharmacological intervention have similar effects on ADHD children. The present study aims to compare the efficacy of NF and standard pharmacological intervention in ADHD based on teacher and parent reports using a randomized controlled trial design with a two and six- month follow-up.

Method

Participants

Sixty-three children aged 7-14 years were recruited through a semi-structured clinical interview (Barkley, Murphy, & Bauermeister, 1998) from the Unit of Children's

Psychological Assessment (UAPI) at University of Balearic Islands, the Neuropediatric Department from Hospital Son Llatzer, and the Still ADHD Association in Palma de Majorca (Spain). Children with comorbid disorders (other than oppositional defiant disorder) evaluated through the Child Behavior Checklist (CBLC; Achenbach & Recorla, 2001), were excluded from the study. All participants had an IQ higher than 80 according to their results in the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2004). Children were not receiving medication, at least for two weeks before starting treatment, or concurring psychotherapy. This study was approved by the Bioethics Committee of the Faculty of Psychology of the University of Balearic Islands.

From the initial sample, 14 participants were excluded because parents were not interested and 19 children did not fulfill one of the following inclusion criteria: (a) scoring over 90th percentile in the ADHD rating scale-IV (ADHD-RS) teacher version and over 80th percentile in parent version (DuPaul, Power, Anastopoulos, & Reid, 1998), (b) scoring over 7 points (from 24) in ODD scale, and (c) scoring under 5 (1 to 10 scale) in any academic area. Informed consent was obtained from parents of 30 children in an individual meeting where a psychologist (any of the three first authors) explained the study conditions. Before starting treatment, one participant was not interested in participating, and in two cases parents did not accept randomization because they had preference for NF. In sum, 27 children were randomly assigned to the two treatment conditions. During the two months of treatment, four participants were excluded from the study. In the NF group, one participant was excluded for taking medication while receiving NF, and another participant presented aggressive behaviors at school and very poor academic performance that required the use of medication. In the pharmacological group, two participants were also excluded. One showed negative secondary effects during the use of medication, and the other participant was excluded because the mother

was suspected of having Diogenes Syndrome. Therefore, the final sample consisted of 23 children, 11 received pharmacological intervention and 12 went through 40 sessions of NF (see Figure 1).

Design

The present study is a randomized controlled trial that compares the efficacy of two treatments: NF and standard pharmacological intervention. Figure 2 illustrates the design of the study. A random number table was used as a randomization method in order to avoid bias, as described in San Martín, Espinosa, and Fernández (1987).

Behavioral measures were assessed at different points: pre-treatment (Pre), post-treatment (Post), two-month follow-up (FU1), and six-month follow-up (FU2). The Pre assessment was conducted approximately one week before starting the treatment. The Post assessment was conducted five months after starting medication for children in the pharmacological group, and after completing 40 sessions of training for children in the NF group. After post treatment assessment, parents of NF group children were free to choose medication (naturalistic follow-up).

Treatment phase

Pharmacological intervention. Patients received the standard treatment for ADHD determined by the same neuropediatrician in Son Llatzer Hospital. This standard treatment was based on the Guide of clinical practice for ADHD children and adolescents of the National Health System in Spain (2010). All patients received an inferior dosage of 1 mg/kg/day of Methylphenidate in its different formulations (immediate, intermediate release, and OROS). Children in the pharmacological group continued receiving medication during post-treatment and follow-up assessments.

Neurofeedback training. NF was conducted using Atlantis II 2x2 equipment from Brainmaster. This equipment uses an impedance check (below 5 Kohms) and controls artifacts automatically (> 120 microvolts). The EEG was analyzed in two frequency bands (theta: 4-7 Hz, beta: 15-20 Hz). EEG recordings were obtained from a monopolar electrode site situated on Cz for participants between 7-11 years old. For older participants it was calculated at FCz, based in the International 10/20 System, with ear references (Arns, Ridder, Strehl, Breteler, & Coenen, 2009; Lubar & Lubar, 1999; Monastra et al., 2005).

The 40 theta/beta training sessions were conducted by trained last-year psychology undergraduates supervised by the first author. Participants had two sessions per week. Each session consisted of six runs of four minutes each. Baseline values were determined at the beginning of each session (30 seconds). Participants had short pauses between runs that enabled them to relax. In sum, a session had a length of 35 minutes approximately.

The training was presented to the child as a computer game (puzzles, races, Pacman, etc.) in which he/she had to concentrate to win. Specifically, children were instructed by the trainer to develop and prolong the strategy that best helped them to win points in the game. The child received visual and auditory reinforcement contingent on his/her success in controlling microvolts of theta and/or beta. The program calculated individual thresholds according to daily baseline values, and had the following reinforcement plan: 70% of the time below the threshold in theta, and up to 20% of the time below the threshold in beta (or 80 % above the threshold) was rewarded. Throughout the session these reward thresholds were manually adjusted by the trainer when it was too difficult or too easy for the child to meet the criteria.

Trainers verbally reinforced participants when concentration states were prolonged. Additionally, performance graphs were shown to participants during pauses. This enhanced motivation and engagement to the task. Another motivational factor proved to work very well for almost all participants: daily scores were written on a chalkboard. Participants were eager to compete with other members of the group and worked harder for getting the top scores. Independent of these scores, every week candies, picture cards or sketches of their favorite character/subject were given to all participants.

Behavioral assessment

Table 1 summarizes all the instruments used at the different assessment points throughout the study.

ADHD rating scale-IV (ADHD RS-IV). This scale is an 18-item scale with one item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD: nine items make up the inattention subscale and the other nine the hyperactivity-impulsivity subscale. Each item is scored on a 0 to 3 scale (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). The scale presents a cut-off point according with age, sex and source of information (DuPaul et al., 1998). Fathers, mothers, and teachers answered the Spanish version of this scale (Servera & Cardo, 2007) to evaluate attention and hyperactivity/impulsivity.

Oppositional defiant disorder rating scale based on DSM-IV (ODDRS-IV). This scale, proposed by Hommersen, Murray, Ohan, and Johnston (2006), and used by Molina, Smith, and Pelham (2001), consists in eight statements of criterion A of the DSM-IV for the diagnosis of ODD formulated as questions. Parents and teachers are asked to rate the extent to which each symptom is descriptive of their child/student's

behavior over the past six months on a 4-point rating scale (0 = not at all; 1 = just a little; 2 = pretty much; 3 = very much). A symptom is clinically significant when the score is two or higher. A child is considered ODD if four or more symptoms are clinically significant.

Academic performance. Reading, reading comprehension, writing, math, and oral expression were assessed by the class teacher using a Likert scale from 1 to 10 (1 = very bad to 10 = excellent).

Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). This scale measures the impact of ADHD on the child's functioning in multiple domains (Weiss, Wasdell, & Bomben, 2005). It consists of 50-item and rates impairment in six domains of functioning: family (10 items), learning and school (10 items), life skills (10), self-concept (3 items), social activities (7 items) and risky activities (10 items). This scale has a 4-point Likert scale from 0 to 3 (0 = never or not at all; 1 = sometimes or somewhat; 2 = often or much; 3 = very often or very much). Parents were instructed to answer this scale together.

Data Analysis

Statistical analyses were made using the Statistical Package for the Social Sciences (SPSS) version 19.0. A repeated measures ANOVA with a between-subject factor GROUP with two levels (NF and pharmacological groups) and a within-subject factor TIME with four levels (Pre, Post, FU1, and FU2) was conducted. Since the GROUP x TIME interaction was not significant in any of the variables, we focused on the analysis of the factor TIME, and the comparisons that were interesting according to our objectives (i.e. comparisons between Pre and the other three assessments). These contrasts were corrected for multiple testing by Bonferroni. Normality was not fulfilled

in 29 measures according to Shapiro-Wilk Test (16 in the NF and 13 in the pharmacological group) of a total of 144. Since results in these variables were not significantly different when using non-parametric tests, we decided to conduct parametric tests in all variables. Student's *t*-tests were applied to conduct between-group comparisons. Effect sizes were calculated with Cohen's *d* using the following formula for independent mean comparisons:

 $d = |\operatorname{M_1-M_2}| / \sqrt{(n_1 - 1)} \operatorname{SD_1}^2 + (n_2 - 1) \operatorname{SD_2}^2 / n_1 + n_2 - 2$. And for dependent mean comparisons: $|\operatorname{M_1-M_2}| / \sqrt{(\operatorname{SD_1}^2 + \operatorname{SD_2}^2)} - (2r \times \operatorname{SD_1} \times \operatorname{SD_2})$. Equivalence analyses were not conducted due to the small number of the sample.

Results

There were no significant differences between the NF and pharmacological groups according to sex, age, IQ, and ADHD subtype (see Table 2). Means and standard deviations for all dependent measures at Pre, Post, FU1, and FU2 for NF and pharmacological groups are presented in Table 3.

As explained above, no significant GROUP x TIME interaction was observed in any of the variables, so data analysis was mainly based on the comparisons between Pre assessment phase and the other three assessments of the factor TIME. Moreover, due to the small sample size we focused on effect sizes.

Pre-Post Comparisons

Results are presented in Table 4. NF group showed a significant improvement on children ADHD symptoms according to mothers. Particularly, mother ADHD-RS total score was highly significant (p < .001), with a very large effect size (d = 1.90). Fathers reported no significant improvements, but medium effect sizes are observed in inattention and total scores of ADHD-RS. Mothers and fathers reported larger effect sizes for

ADHD-RS inattention scales than for hyperactivity/impulsivity scales. ODD does not improve significantly according to any of the evaluators. Nevertheless, a medium effect size is observed in the case of mothers (d = 0.68). Parent ratings of children functional impairment (WFIRS) significantly decreased after the training with a large effect size (d = 1.02). Teachers do not report significant improvements, but medium effect sizes are observed in ADHD-RS. Moreover, significant improvements in all areas of academic performance, except for math and oral expression, were reported. Writing showed a very large effect size (d = 1.54), and reading and reading comprehension showed large effect sizes (d = 1.01 and d = 0.90, respectively).

In the pharmacological group, ADHD symptomatology improved significantly according to the different evaluators. ADHD-RS total score improvements were significant for mothers and teachers, showing large effect sizes. In the inattention subscale of the ADHD-RS, mothers reported a higher significant improvement (p = .001, d = 1.50) than fathers (p = .042, d = 0.95) and teachers (p = .014, d = 0.87). Hyperactivity/impulsivity symptoms according to teachers was significantly reduced, showing a large effect size (d = 0.92). Oppositional defiant behavior was only reduced significantly according to teachers (d = 0.92). Negative impact in the child's daily life (WFIRS) showed a significant improvement, with a very large effect size (d = 1.25). However, none of the academic performance variables improved significantly showing small effect sizes

Pre- Follow-up comparisons

At the follow-up assessment children receiving pharmacological intervention continued the use of medication during both follow-ups, while children from NF group did not continue NF training. Two participants from the NF group were medicated before FU1 and six were medicated before FU2 (i.e., eight participants were taking medication

during FU2). Nevertheless, we maintain comparisons with all subjects because their removal does not cause significant changes in the results, as discussed later.

In the NF group (Table 4), inattentive and hyperactive/impulsive symptoms show significant improvements at FU1 and FU2 as stated by mothers and teachers. These improvements were particularly high for total scores, showing very large effect sizes. Fathers saw no significant improvement in ADHD-RS at follow-ups, but medium effect sizes can be observed for inattention. A significant reduction of child's functional impairment (WFIRS) was reported, showing a large effect size (d = 1.04) at FU1, and a medium effect size (d = 0.78) at FU2. ODD symptoms improved significantly according to mothers at FU1 (d = 1.09). Teachers reported significant improvements in ODD behaviors, with a large effect size at FU1 (d = 1.02) but not significant at FU2, with a medium effect size at FU2 (d = 0.78). Writing showed a significant improvement, with a large effect size (d = 0.95) at FU1. Math also showed a significant improvement at FU1 and FU2 with large effect sizes (d = 1.25 and d = 0.86 respectively). Although reading comprehension did not improve significantly, it showed a medium effect size at FU1 and FU2.

At FU1 when the two participants who receive medication from the NF group were not included in the analysis, significant differences in all variables remain (although slightly lower effect sizes are observed), except in two cases: hyperactivity/impulsivity in teacher ADHD-RS, and reading. Moreover at FU2, *t*-test comparisons (both parametric and non-parametric path) show no significant differences between the four children in the NF group who received no medication and the eight children who did.

In the pharmacological group, ADHD-RS reductions were observed for all evaluators at FU1, with the largest effect sizes in total ADHD-RS according to fathers (d

= 1.65) and inattention ADHD-RS according to mothers (d = 1.32). At FU2 fathers and teachers showed a significant improvement with large effect sizes. Mothers also reported significant improvements in inattention and total scores of ADHD-RS at FU2 with large effect sizes. No significant decrease in functional impairment, assessed through WFIRS, could be observed at FU1, however at FU2 a significant improvement in this area with a large effect size was observed (d = 1.11). Oppositional defiant symptoms were significantly reduced at FU1 according to teachers (d = 0.93). Fathers only reported a significant reduction in ODD at FU2, with a large effect size (d = 1.41). Academic performance did not improve significantly in any of the participants, displaying low effect sizes.

Comparison between NF and pharmacological groups

No significant differences were found before treatments between the two groups in the different measures of inattention, hyperactivity/impulsivity, functional impairment, and ODD (see Table 5). However, the pharmacological group showed significant higher scores at baseline in comparison to the NF group in two areas: Math (p < .001, d = 2.18), and reading (p = .043, d = 0.90). In the Post assessment, the pharmacological group had significant lower levels of inattention according to teachers (d = 0.86), and better scores in math (p = .001, d = 1.55). At FU1, ADHD-RS inattention according to fathers (d = 0.93) and math scores (d = 1.19) were significantly better for the pharmacological group. At FU2, no significant differences were found between the two groups in inattention, hyperactivity, functional impairment, or ODD. Only in math the pharmacological group scored higher (d = 1.17) than the NF group.

Figure 3 shows the average of informants' ADHD-RS total scores (i.e., mothers, fathers, and teachers). Participants in the NF and pharmacological groups present a

similar tendency of improvement in ADHD symptoms from Pre assessment through FU2 assessment.

Discussion

In general, NF reduces ADHD primary symptoms and ADHD associated functional impairment to a similar extent as pharmacological intervention. Nevertheless, our sample was limited, making it unfeasible to conclude that NF and medication are equivalent treatments for ADHD. Concerning follow-up assessments, we observed that overall participants receiving NF maintain the achieved improvements two months and even six months after completing treatment. However, given that not all subjects remained free of medication mainly at FU2, we must interpret these results carefully.

We will begin to discuss our results based on effect sizes at three levels: (1) treatments, (2) evaluators, and (3) behavioral ratings and academic performance.

Concerning the effect of treatments on behavioral ratings, pharmacological intervention seems better than NF at Post, presenting nine large effect sizes, while NF only three (however in other six variables medium effect sizes were observed). Second, NF seems more effective than medication at FU1, displaying large effect sizes for eight variables, while pharmacological group descends to seven. Third, at FU2 pharmacological group exhibits large effect sizes in 10 measures, while NF only in five (however in other five variables medium effect sizes were displayed), repeating the same tendency as in Post. Overall, taking in consideration large and medium effects sizes throughout the different behavioral evaluations, NF and medication effects are comparable. Related to evaluators, our data suggests that mothers and teachers detect more behavioral improvements (15 large effect sizes each, evenly distributed across treatments) than fathers (only present

seven). Therefore, both treatments have shown positive results in two different settings, home and school.

In terms of behavioral measures, inattention improves more than hyperactivity/impulsivity across evaluators, time and treatments: all the effects sizes are large or medium. One possible explanation for these results is that more inattention than hyperactivity/impulsivity problems was reported at baseline. Consequently, a more pronounced improvement in inattention could be expected. Another explanation would be that both treatments better address inattention than hyperactive/impulsivity symptoms. Functional impairment has improved with large effect sizes in all measures across treatments and time. Regarding academic performance, significant improvements were only observed in participants receiving NF. However, children in the pharmacological group presented significantly higher scores than in the NF group at Pre, in two of the five areas assessed. Therefore, margin for pre-post improvement was lower for this group.

Duric et al. (2012) and Fuchs et al. (2003) have also found no significant differences in behavioral ratings between NF and pharmacological treatment groups. Thus, suggesting that the effects of NF are equivalent to those obtained with stimulant medication for ADHD. Others studies have also found an improvement of inattention and hyperactivity/impulsivity according to parents and teachers after NF training (Ali Nazari et al., 2011; Bakhshayesh et al., 2011; Drechsler et al., 2007; Duric et al., 2012; Fuchs et al., 2003, Gevensleben et al., 2009; Heinrich et al., 2004; Monastra et al., 2002; Rossiter, 2004; Leins et al., 2007). A larger improvement for inattention in comparison to hyperactivity/impulsivity according to parents was also consistent with previous studies (Bakhshayesh et al., 2011; Drechsler et al., 2007). Concerning follow-ups, other studies that have included long-term assessments have also found that behavioral

improvements were maintained after six months (Gevenseleben et al., 2010; Leins et al., 2007), and even after two years of completing the training (Gani et al., 2008).

An important issue must be taken into account when interpreting this data: two participants from the NF group were medicated during FU1 and eight in total were medicated during FU2. It is also important to keep in mind that at FU1 we compared a group of 11 children that continued pharmacological treatment with a group of 12 who were not receiving any treatment at the moment (with the exception of two children receiving medication). And even in this situation, NF group exhibited very positive effects compared to pharmacological group.

Could the two NF participants who received medication affect the results of this FU1? When we excluded these two cases and repeated the analyses, results were very similar. This indicates that participants who received NF maintain their improvements even two months after completing the training. This result also suggests that 83% of parents seem satisfied with the NF treatment since they did not change to pharmacological treatment.

Are there any significant differences between participants in the NF group who received medication and those who did not at FU2? There were no such differences.

Moreover, it should be noted that after 6 months of completion of the NF intervention 33% of participants did not look for an additional intervention. Therefore on the long-term, this intervention alone was sufficient for one third of the children. In sum, even if improvements were observed at FU2 for participants in the NF group, as stated before; no firm conclusions can be drawn from this assessment point due to the mixed effects of NF and medication.

Our study has implications concerning the application of NF training that we would like to emphasize. The importance of implementing principles of learning theory in NF training has been recently indicated (Arns & Kenemans, 2012; DeBeus & Kaiser, 2011; Sherlin et al., 2011). Thus, factors such as feedback animations, instructions given to participants, and reward thresholds may play a crucial role (Gevensleben et al., 2012). Our findings support the notion that feedback animations ought to be discrete but should also include a small range of options (Sherlin et al. 2011). Participants must be encouraged to strive towards achievement of regulation as recommended by Gevensleben et al. (2012). Finally, an important consideration is the use of adaptive reward thresholds vs. automatic calculation of thresholds. In our study, children were rewarded using a non-auto thresholding procedure, thus enhancing operant conditioning learning. Our findings support this procedure, and suggest that NF efficacy would be compromised when it is not implemented, as reported by other authors (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011; Sherlin et al., 2011). This again raises a question about the feasibility of double-blind, placebo- controlled trials for NF.

The main limitation of this study is its small sample. Another limitation is that NF training did not include transfer training to reach generalization of regulatory skills to daily life activities. Presumably, a better outcome could have been achieved if these strategies would have been incorporated during the training. However, other studies did not include such training and have also reported positive results for NF (Duric et al., 2012; Lubar et al., 1995). Although we found the naturalistic follow-up most ethical and appropriate to assess NF compared to pharmacological community treatment, it affected data analysis. At the same time, this design was a good indirect way to measure the degree of satisfaction for NF. Although, we did not include either neuropsychological or neurophysiologic data in this article, we did measure it and results are yet to be published.

The importance of this study relies on being the first randomized-controlled trial that compares NF and stimulant medication using parent and teacher reports, including two naturalistic follow-up assessments. These assessments have been useful to demonstrate that after two months the majority of children treated with NF are able to maintain many of their progress and even continue improving. Even more, one out three of these children are able to maintain many of the improvements after six months. These particularly positive results for NF suggest that actively training the brain may produce certain lasting beneficial effects in contrast to pharmacological intervention.

Nevertheless, there are mixed effects of medication, mainly in the second follow-up assessment, that our design has not controlled, and in the future should be taken into account. Furthermore, another important aspect of our study has been the use of multiple evaluators (mothers, fathers, and teachers) and the inclusion of a measure of academic performance. These two features have allowed a more comprehensive analysis of the effects of NF training.

In conclusion, our results suggest that NF could be long-term effective, not only as an alternative treatment, but also as a complementary treatment to pharmacological intervention in ADHD. Randomized controlled studies with larger number of participants in each condition will allow a proper equivalence analysis to determine if this preliminary conclusion is accurate. Finally, future studies should evaluate whether NF is able to decrease the dosage of medication when implemented in conjunction with pharmacological intervention.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Achenbach, T. M. &, Recorla, L. A. (2001). *Manual for the ASEBA: forms & profiles of CBCL 6-18*. Burlington, VT: University of Vermont.
- Ali Nazari M., Querne L., De Broca A., & Berquin P. (2011). Effectiveness of EEG biofeedback as compared with methylphenidate in the treatment of attention-deficit/hyperactivity disorder: a clinical outcome study. *Neuroscience and Medicine*, 2, 78-86. doi:10.4236/nm.2011.22012
- Arns, M. (2012). EEG-based personalized medicine in ADHD: individual alpha peak frequency as an endophenotype associated with non-response. *Journal of Neurotherapy*, 16, 123–141. doi: 10.1080/10874208.2012.677664
- Arns, M., Conners, C. K., & Kraemer, H. C. (2012). A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. *Journal of Attention Disorder*. Advance online publication. doi: 10.1177/1087054712460087
- 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. *Clinical EEG and Neuroscience*, 40, 180-89. doi:10.4236/nm.2011.22012
- Arns, M., & Kenemans, J. L. (2012). Neurofeedback in ADHD and insomnia: vigilance stabilization through sleep spindles and circadian networks. *Neuroscience and Biobehavioral Reviews*. Advance online publication. doi: 10.1016/j.neubiorev.2012.10.006
- Bakhshayesh, A. R., Hänsch, S., Wyschkon, A., Rezai, M. J., & Esser, G. (2011).

 Neurofeedback in ADHD: a single-blind randomized controlled trial. *European Child and Adolescent Psychiatry*, 20, 481-491. doi:10.1007/s00787-011-0208-y

- Barkley, R. A., Murphy, K. R., & Bauermeister, J. J. (1998). *Attention-deficit hyperactivity disorder: a clinical workbook* (2nd ed.). New York, NY: Guillford Press.
- Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, 114, 171-83.
- Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clinical Neurophysiology*, 114, 184-98. doi:10.1016/S1388-2457(02)00362-0
- Barry, R. J., Clarke, A. R., Johnstone, S. J., McCarthy, R., & Selikowitz, M. (2009). Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. *Biological Psychiatry*, 66, 398-401. doi: 10.1016/j.biopsych.2009.04.027
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 112, 2098-2105.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG analysis of children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. *Journal of Learning Disabilities*, *35*, 276-285.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2011). Correlation between EEG activity and behavior in children with attention-deficit/hyperactivity disorder. *Journal of Neurotherapy*, 15, 193-199. doi:10.1080/10874208.2011.595295
- DeBeus, R. J., & Kaiser, P.A. (2011). Neurofeedback in children with attention deficit and hyperactivity disorder: a randomized double-blind placebo-controlled study. In

- Coben & Evans (Eds.), Neurofeedback and neuromodulation: Techniques and applications (pp.127-152). New York, NY: Academic Press.
- Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H. C., & Dreschler, R. (2008). Slow cortical potential Neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? *Journal of Neural Transmission*, 115, 1445-56. doi:10.1007/s00702-008-0104-x
- Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H. C., & Brandeis, D. (2007). Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). *Behavioral and Brain Functions*, *3*(35), 1-13. doi:10.1186/1744-9081-3-35
- DuPaul, G., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). ADHD-Rating Scales DSM-IV for parents and teachers. New York, NY: Guilford Press.
- Duric, N. S., Assmus, J., Gundersen, D., & Elgen, I. B. (2012). Neurofeedback for the treatment of children and adolescents with ADHD: a randomized and controlled clinical trial using parent reports. *BMC Psychiatry* 12(107), 1-8. Retrieved from http://www.biomedcentral.com/1471-244X/12/107
- Egner, T., & Gruzelier, J. H. (2004). EEG Biofeedback of low beta band components: frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology*, *115*, 131-39. doi:10.1016/S1388-2457(03)00353-5
- Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003).

 Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. *Applied Psychophysiology Biofeedback*, 28, 1-12. doi:1090-0586/03/0300-0001/0
- Gani, C., Birbaumer, N., & Strehl, U. (2008). Long term effects after feedback of slow cortical potentials and of theta-beta amplitudes in children with attention-

- deficit/hyperactivity disorder (ADHD). International Journal of Bioelectromagnetism, 10, 209-232.
- Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., Studer, P., Rothenberger, A., Moll, G. H., & Heinrich, H. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. *Journal of Child Psychology and Psychiatry*, 50, 780-9. doi:10.1111/j.1469-7610.2008.02033.x
- Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., Rothenberger, A., Moll, G. H., & Heinrich, H. (2010). Neurofeedback training in children with ADHD: 6-month follow-up of a randomized controlled trial. *European Child and Adolescent Psychiatry* 19, 715-24. doi:10.1007/s00787-010-0109-5
- Gevensleben, H., Rothenberger, A., Moll, G. H., & Heinrich, H. (2012). Neurofeedback in children with ADHD: validation and challenges. *Expert Review of Neurotherapeutics*, 12, 447-460. doi: 10.1586/ern.12.22
- Guide of clinical practice in the National Health System (2010). Guía de práctica clínica sobre el trastorno por deficit de atención con hiperactividad en niños y adolescentes [Guide of clinical practice about attention deficit disorder in children and adolescents]. Barcelona, Spain: Ministerio de Ciencia e Innovación.
- Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004).

 Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry*, 55, 772-75. doi:10.1016/j.biopsych.2003.11.013
- Heinrich, H., Gevensleben, H., & Strehl, U. (2007). Annotation: Neurofeedback-train your brain to train your behavior. *Journal of Child Psychology and Psychiatry*, 48, 3-16. doi:10.1111/j.1469-7610.2006.01665.x

- Hommersen, P., Murray, C., Ohan, J. L., & Johnston, C. (2006). Oppositional Defiant Disorder Rating Scale: Preliminary evidence of reliability and validity. *Journal of Emotional Behavioral Disorders*, 14, 118-25. doi:10.1177/10634266060140020201
- Janzen, T., Graap, K., Stephanson, S., Marshall, W., & Fitzsimmons, G. (1995).

 Differences in baseline EEG measures for ADD and normally achieving preadolescent males. *Biofeedback and Self Regulation*, 20, 65-82.
- Kropotov, J. D., Grin-Yatsenko, V. A., Ponomarev, V. A., Chutko, L. S., Yakovenko, E.
 A., & Nikishena, I. S. (2005). ERPs correlates of EEG relative beta training in
 ADHD children. *International Journal of Psychophysiology*, 55, 23–34.
 doi:10.1016/j.ijpsycho.2004.05.011
- Lansbergen, M. M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase of theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuropsychopharmacology* & *Biological Psychiatry* 35, 47-52. doi:10.1016/j.pnpbp.2010.08.004
- Lansbergen, M. M., van Dongen-Boomsma, M., Buitelaar, J. K., & Slaats-Willemse, D. (2011). ADHD and EEG-neurofeedback: a double-blind randomized placebocontrolled feasibility study. *Journal of Neural Transmission*, 118, 275-284. doi: 10.1007/s00702-010-0524-2
- 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. *Applied Psychophysiology and Biofeedback 32*, 73-88. doi: 10.1007/s10484-007-9031-0
- Liechti, M. D., Maurizio, S., Heinrich, H., Jäncke, L., Meier, L., Steinhausen, H. C., Walitza, S., Drechsler, R., & Brandeis, D. (2012). First clinical trial of tomographic

- neurofeedback in attention-deficit/hyperactivity disorder: evaluation of voluntary cortical control. *Clinical Neurophysiology*, *123*, 1989-2005. doi:10.1016/j.clinph.2012.03.016
- Lubar, J. F. (1991). Discourse on the development of EEG Diagnostics and Biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback and Self Regulation*, *16*, 201-225
- Lubar, J. F., & Lubar, J. O. (1999). Neurofeedback assessment and treatment for attention deficit/hyperactivity disorder. In: J. R. Evans and A. Abarbanel (Eds), *Introduction to quantitative EEG and Neurofeedback* (pp. 103-43). San Diego, CA: Academic Press Inc.
- Lubar, J. F., Starwood, M. O., Starwood, J. N., & Timmermann, D. L. (1995).
 Quantitative EEG and auditory event-related potentials in the evaluation of attention-deficit/hyperactivity disorder: effects of methylphenidate and implications for
 Neurofeedback training. *Journal of Psychoeducational Assessment*, 34, 143-160.
- Molina, B. S., Smith, B. H., & Pelham, W. E. (2001). Factor structure and criterion validity of secondary school teacher ratings of ADHD and ODD. *Journal of Abnormal Child Psychology*, 29, 71-82. doi:10.1023/A:1005203629968
- Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback*, 27, 231-49. doi:1090-0586/02/1200-0231/0
- Monastra, V. J., Lubar, J. F., & Linden, M. (2001). The development of quantitative electroencephalographic scanning process for attention deficit/hyperactivity disorder: reliability and validity studies. *Neuropsychology*, *15*, 136-144. doi:10.1037//0894-4105.15.1.136

- Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & LaVaque, T. H. (2005). Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. *Journal of Neurotherapy*, 94, 5-34. doi:10.1300/J184v09n04_02
- Putman, P., van Peer, J., Maimari, I., van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological Psychology*, 83, 73-78. doi:10.1016/j.biopsycho.2009.10.008
- Rossiter, T. R. (2004). The Effectiveness of Neurofeedback and stimulant drugs in treating AD/HD: part II. replication. *Applied Psychophysiology and Biofeedback*, 29, 233-43. doi:10.1007/s10484-004-0383-4
- Rossiter, T. R., & La Vaque, T. J. (1995). A comparison of EEG biofeedback and psychostimulants in treating attention deficit/hyperactivity disorder. *Journal of Neurotherapy*, 1, 48-59. doi:10.1300/J184v01n01_07
- San Martín, R., Espinosa, L., & Fernández, L. (1987). *Psicoestadística. Estimación y contraste* [Psychostatistics, estimate and contrast]. Madrid, Espana: Pirámide.
- Servera, M., & Cardo, E. (2007). ADHD Rating Scale-IV in a sample of Spanish schoolchildren: normative data and internal consistency for teachers and parents. Revista de Neurología, 45, 393-399.
- Sherlin, L. H., Arns, M., Lubar, J., Heinrich, H., Kerson, C., Strehl, U., & Sterman, M. B. (2011). Neurofeedback and basic learning theory: implications for research and practice. *Journal of Neurotherapy*, 15, 292-304. doi: 10.1080/10874208.2011.623089
- Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Birbaumer, N. (2006).

 Self-regulation of slow cortical potentials: a new treatment for children with

attention-deficit/hyperactivity disorder. *Pediatrics* 118, e1530-40. doi:10.1542/peds.2005-2478

Wangler, S., Gevensleben, H., Albrecht, B., Studer, P., Rothenberger, A., Moll, G. H., & Heinrich, H. (2011). Neurofeedback in children with ADHD: specific event-related potential findings of a randomized controlled trial. *Clinical Neurophysiology*, *122*, 942-50. doi:10.1016/j.clinph.2010.06.036

Wechsler, D. (2004). *The Wechsler Intelligence Scale for Children* (4th ed.). London, England: Pearson Assessment.

Weiss, M. D., Wasdell, M. B., Bomben, M. M. (2005). Escala de clasificación del menoscabo funcional Weiss para padres (WFIRS-P). Versión 2. Retrieved from: http://www.bcchildrens.ca/NR/rdonlyres/F6C1AD32-CF47-47A7-AE97-F37FDF850DC4/20927/WFIRSParentReport.pdf

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Table 1

Behavioral Assessment

Instruments	Pre-treatment Assessment	Post-treatment Assessment	2-month Follow-up Assessment	6-month Follow-up Assessment
ADHD-RS for parents and teachers	X	x	X	x
ODD scale for parents and teachers	X	X	х	X
Academic performance rated by teachers	X	X	Ŷ	X
Semi-structured clinical interview for parents	X			
CBCL for parents	X			
WISC-IV for children	X			
WFIRS-P for parents	X	X	X	X

Note. ADHD-RS = Attention Deficit and Hyperactivity Disorder Rating Scale; ODD = Oppositional Defiant Disorder; CBCL = Child Behavior Checklist For Ages 6-18; WISC-IV = Wechsler Intelligence Scale for Children; WFIRS = Weiss Functional Impairment Rating Scale.

Table 2

Demographic characteristics and ADHD subtype of participants in Neurofeedback and pharmacological groups

	NF group $n = 12$	Pharmacological group $n = 11$
Age	9.53 (1.80)	8.90 (1.53)
Sex (boys/girls)	6 / 6 50% / 50%	6 / 5 54.55% / 45.45%
IQ (WISC-IV)	97.83 (12.39)	91.64 (27.57)
DSM-IV subtype		
Combined type	9 (75%)	9 (81.82%)
Inattentive type	3 (25%)	2 (18.18%)

Note: No significant differences were found between the two groups at Pretreatment assessment according to sex, age, IQ, or ADHD subtype.

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Table 3

Behavior rating descriptives by informants and assessment time in each group

		NF group	(n = 12)		Pharmacological group $(n = 11)$									
Behavior ratings	Pre M (SD)	Post M (SD)	FU1 M (SD)	FU2 M (SD)	Pre M (SD)	Post M (SD)	FU1 M (SD)	FU2 M (SD)						
				Mothers										
ADHD-RS														
Inattention	19.25 (3.70)	12.67 (6.51)	12.00 (5.39)	13.00 (7.65)	19.27 (3.26)	12.27 (4.69)	14.09 (4.21)	14.27 (4.54)						
Hyper/imp	13.00 (6.65)	10.42 (6.32)	8.50 (6.33)	7.25 (7.41)	13.09 (6.82)	10.45 (5.91)	12.73 (5.52)	11.09 (6.20)						
Total score	32.25 (6.97)	23.08 (10.20)	20.50 (9.44)	20.25 (13.07)	32.36 (7.13)	22.73 (9.10)	26.82 (7.74)	25.36 (9.94)						
ODD														
Total score	9.08 (4.17)	6.67 (4.12)	6.25 (4.61)	7.17 (6.62)	9.73 (3.77)	7.73 (4.58)	7.91 (3.62)	5.82 (3.46)						
				Fathers										
ADHD-RS				ramers										
Inattention	17.67 (3.28)	13.17 (6.25)	14.58 (4.46)	13.25 (5.59)	18.80 (4.29)	12.30 (5.96)	10.90 (3.21)	13.80 (3.05)						
Hyper/imp			9.58 (8.54)	13.60 (7.40)	10.00 (4.32)	8.80 (4.87)	10.10 (8.17)							
Total score	29.33 (6.39)	23.00 (9.54)	26.83 (9.36)	22.83 (12.46)	32.40 (9.17)	22.30 (8.38)	19.70 (5.91)	23.90 (10.60)						
ODD	_, (,						-,,,,							
Total score	6.83 (5.44)	6.50 (4.58)	7.00 (4.75)	6.33 (6.01)	8.67 (5.87)	6.11 (3.44)	4.78 (2.68)	4.67 (3.74)						
				<u> </u>										
WFIRS				Parents										
Total Score	41.50 (13.98)	27.08 (13.94)	25.58 (7.93)	27.92 (13.78)	38.18 (12.77)	23.55 (9.28)	28.18 (11.16)	30.27 (12.47)						
Total Score	41.30 (13.96)	27.06 (13.94)	23.36 (7.93)	21.92 (13.76)	38.18 (12.77)	23.33 (9.26)	20.10 (11.10)	30.27 (12.47)						
				Teachers										
ADHD-RS														
Inattention	20.42 (4.25)	17.25 (6.22)	15.58 (5.40)	14.42 (7.67)	20.18 (5.93)	11.82 (6.40)	12.27 (5.42)	12.18 (3.92)						
Hyper/imp	10.92 (8.03)	6.58 (5.58)	6.33 (6.47)	4.25 (4.97)	12.82 (8.00)	7.27 (5.80)	7.18 (7.01)	5.91 (7.23)						
Total score	31.33 (6.34)	23.83 (8.89)	21.92 (8.31)	18.67 (11.19)	33.00 (10.32)	19.09 (11.37)	19.45 (10.91)	18.09 (9.68)						
ODD														
Total score	7.67 (6.21)	6.58 (7.51)	4.58 (6.96)	4.67 (6.21)	8.18 (6.93)	4.27 (4.15)	2.36 (3.41)	4.73 (6.94)						
AP														
Reading	4.44 (1.61)	5.83 (0.83)	5.17 (1.34)	5.42 (1.51)	5.82 (1.45)	5.36 (1.50)	5.55 (1.13)	5.55 (1.04)						
Reading c.	3.15 (2.07)	5.33 (1.61)	4.92 (1.44)	4.58 (1.62)	4.89 (2.10)	4.91 (1.14)	4.91 (1.45)	5.36 (0.81)						
Writing	2.79 (1.51)	4.50 (1.51)	4.42 (1.00)	4.00 (1.12)	4.09 (2.06)	4.82 (1.40)	4.45 (1.44)	4.67 (1.41)						
Math	2.67 (1.03)	3.58 (1.31)	4.50 (1.31)	4.00 (1.76)	5.68 (1.68)	6.00 (1.79)	6.09 (1.38)	5.73 (1.10)						
Oral exp.	4.63 (2.28)	5.83 (0.83)	5.50 (1.73)	5.58 (1.68)	5.32 (2.31)	5.27 (1.62)	5.64 (1.21)	5.91 (0.94)						

Note: Pre = pre-treatment; Post = post-treatment; FU1 = first follow-up; FU2 = second follow-up; ADHD-RS = Attention Deficit and Hyperactivity Disorder Rating Scale; Hyper/imp = Hyperactivity and impulsivity; ODD = Oppositional Defiant Disorder; WFIRS = Weiss Functional Impairment Rating Scale; AP = Academic Performance; Reading c. = Reading comprehension; Oral exp. = Oral expression.

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Table 4

A priori planned comparisons based on Repeated Measures ANOVA and effect sizes for NF and pharmacological groups

															1									
	NF group (<i>n</i> = 12)										Pharmacological group $(n = 11)$													
	Pre-Post Pre-FU1					Pre-FU2				Pre-Post				Pre-FU1				Pre-FU2						
Behavior ratings	F	p	95% CI	Cohen`s	F	p	95% CI	Cohen`s	F	p	95% CI	Cohen`s	F	p	95% CI	Cohen`s	F	p	95% CI	Cohen`s	F	p	95% CI	Cohen`s
											M	others												
ADHD-RS																								
Inattention	15.21	.002	[0.26, 1.98]	1.12	16.24	.002	[0.30, 2.02]	1.16	6.97	.023	[-0.07, 1.59]	0.76	24.70	.001	[0.55, 2.45]	1.50	19.27	.001	[0.40, 2.24]	1.32	11.29	.007	[0.12, 1.90]	1.01
Hyper/imp	2.50	.142	[-0.35, 1.27]	0.46	9.67	.010	[0.05, 1.73]	0.89	12.60	.005	[0.18, 1.88]	1.03	1.82	.206	[-0.43, 1.25]	0.41	0.04	.842	[-0.78, 0.90]	0.06	1.88	.200	[-0.42, 1.26]	0.42
Total score	43.03	.000	[0.94, 2.86]	1.90	25.91	.000	[0.57, 2.37]	1.47	15.05	.003	[0.26, 1.98]	1.12	13.54	.004	[0.21, 2.01]	1.11	7.95	.018	[-0.02, 1.72]	0.85	13.25	.005	[0.20, 2.00]	1.10
ODD	c ca	020	5 0 14 1 501	0.60	14.26	002	FO 22 1 051	1.00	2.16	170	1.0.20 1.221	0.40	1.70	221	5.0.45.1.223	0.20	4.67	056	F 0 20 1 521	0.66	7.40	021	F 0 05 1 601	0.02
Total score	5.57	.038	[-0.14, 1.50]	0.68	14.36	.003	[0.23, 1.95]	1.09	2.16	.170	[-0.39, 1.23]	0.42	1.72	.221	[-0.45, 1.23]	0.39	4.67	.056	[-0.20, 1.52]	0.66	7.40	.021	[-0.05, 1.69]	0.82
											F	athers												
ADHD-RS											1	atticis												
Inattention	5.20	.043	[-0.16, 1.48]	0.66	4.33	.061	[-0.22, 1.42]	0.60	5.52	.039	[-0.14, 1.50]	0.68	9.06	.015	[0.03, 1.87]	0.95	19.71	.002	[0.42, 2.38]	1.40	10.11	.011	[0.08, 1.94]	1.01
Hyper/imp	1.17	.302	[-0.49, 1.11]	0.31	0.14	.710	[-0.69, 0.91]	0.11	1.46	.253	[-0.46, 1.16]	0.35	2.89	.123	[-0.35, 1.43]	0.54	5.15	.050	[-0.18, 1.62]	0.72	2.69	.135	[-0.37, 1.41]	0.52
Total score	4.88	.049	[-0.18, 1.46]	0.64	1.32	.275	[-0.48, 1.14]	0.33	6.30	.029	[-0.10, 1.56]	0.73	6.97	.027	[-0.08, 1.74]	0.83	27.14	.001	[0.64, 2.66]	1.65	9.86	.012	[0.07, 1.93]	1.00
ODD																								
Total score	0.05	.834	[-0.74, 0.86]	0.06	0.05	.820	[-0.73, 0.87]	0.07	0.07	.800	[-0.73, 0.87]	0.07	1.17	.312	[-0.55, 1.27]	0.36	3.13	.114	[-0.33, 1.51]	0.59	17.98	.003	[0.40, 2.42]	1.41
											P	arents												
WFIRS									V															
Total score	12.39	.005	[0.17, 1.87]	1.02	12.96	.004	[0.19, 1.89]	1.04	7.29	.021	[-0.05, 1.61]	0.78	16.97	.002	[0.34, 2.16]	1.25	6.60	.028	[-0.09, 1.65]	0.78	13.25	.005	[0.21, 2.01]	1.11
											Te	achers												
ADHD-RS											10	acticis												
Inattention	3.10	.106	[-0.30, 1.32]	0.51	10.43	.008	[0.09, 1.77]	0.93	8.70	.013	[0.01, 1.69]	0.85	8.35	.016	[0.00, 1.74]	0.87	8.12	.017	[-0.01, 1.73]	0.86	19.36	.001	[0.40, 2.24]	1.32
Hyper/imp	4.45	.058	[-0.21, 1.43]	0.61	7.51	.019	[-0.04, 1.62]	0.79	9.42	.011	[0.05, 1.73]	0.89	9.18	.013	[0.04, 1.80]	0.92	3.88	.077	[-0.26, 1.44]	0.59	14.82	.003	[0.26, 2.06]	1.16
Total score	5.71	.036	[-0.13, 1.51]	0.69	19.80	.001	[0.41, 2.17]	1.29	25.81	.000	[0.57, 2.37]	1.47	14.44	.003	[0.25, 2.05]	1.15	9.00	.013	[0.03, 1.79]	0.91	40.07	.000	[0.91, 2.93]	1.92
ODD																								
Total score	1.44	.254	[-0.47, 1.15]	0.34	12.67	.004	[0.17, 1.87]	1.02	7.45	.020	[-0.05, 1.61]	0.78	9.18	.013	[0.04, 1.80]	0.92	9.49	.012	[0.05, 1.81]	0.93	2.89	.119	[-0.34, 1.36]	0.51
AP											•													
Reading	12.32	.005	[0.16, 1.86]	1.01	5.02	.046	[-0.53, 1.07]	0.27	2.04	.180	[-0.40, 1.22]	0.41	1.12	.314	[-0.52, 1.16]	0.32	0.71	.422	[-0.59, 1.09]	0.25	0.34	.578	[-0.67, 1.01]	0.17
Reading c.	9.80	.010	[0.06, 1.74]	0.90	7.13	.022	[-0.06, 1.60]	0.77	4.62	.054	[-0.20, 1.44]	0.62	0.00	.976	[-0.83, 0.85]	0.01	0.00	.968	[-0.83, 0.85]	0.01	0.48	.509	[-0.64, 1.04]	0.20
Writing	28.09	.000	[0.63, 2.45]	1.54	10.89	.007	[0.11, 1.79]	0.95	4.34	.027	[-0.22, 1.56]	0.67	1.23	.295	[-0.51, 1.17]	0.33	0.69	.425	[-0.59, 1.09]	0.25	3.69	.091	[-0.52, 1.26]	0.37
Math	3.39	.094	[-0.28, 1.34]	0.53	18.75	.001	[0.38, 2.12]	1.25	8.82	.013	[0.02, 1.70]	0.86	0.92	.361	[-0.55, 1.13]	0.29	0.45	.520	[-0.64, 1.04]	0.20	0.01	.923	[-0.81, 0.87]	0.03
Oral exp.	4.93	.049	[-0.19, 1.45]	0.63	1.88	.197	[-0.42, 1.20]	0.39	1.85	.202	[-0.42, 1.20]	0.39	0.01	.938	[-0.81, 0.87]	0.03	0.22	.651	[-0.70, 0.98]	0.14	0.02	.389	[-0.57, 1.11]	0.27

Note: Pre = pre-treatment; Post = post-treatment; FU1 = first follow-up; FU2 = second follow-up; CI = Confident Interval of Cohen's d; ADHD-RS = Attention Deficit and Hyperactivity Disorder Rating Scale; Hyper/imp = Hyperactivity and impulsivity; ODD = Oppositional Defiant Disorder; WFIRS = Weiss Functional Impairment Rating Scale; AP = Academic Performance; Reading c. = Reading comprehension; Oral exp. = Oral expression. Multiple comparisons have been adjusted by Bonferroni, and are considered significant at p < .017.

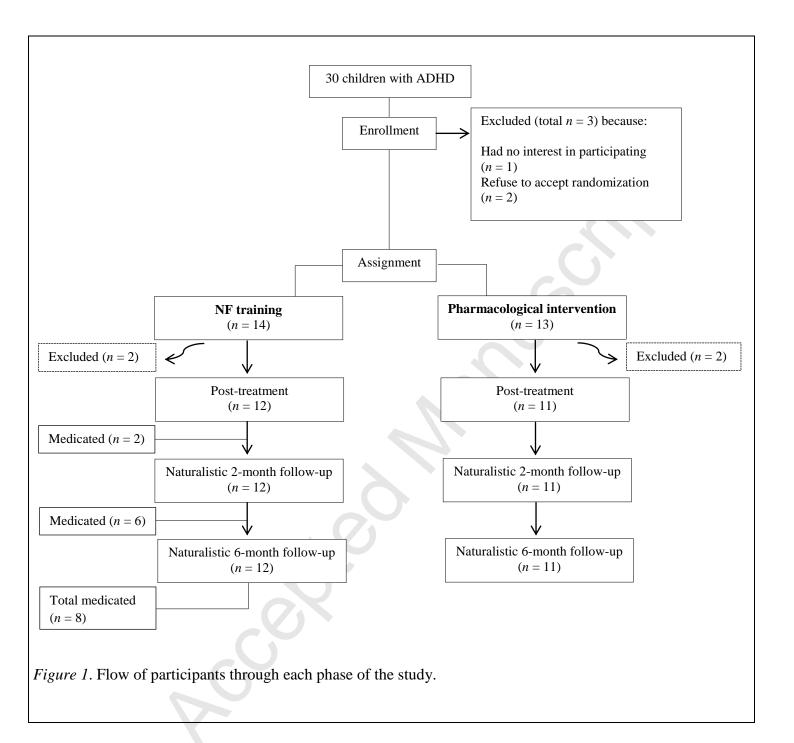
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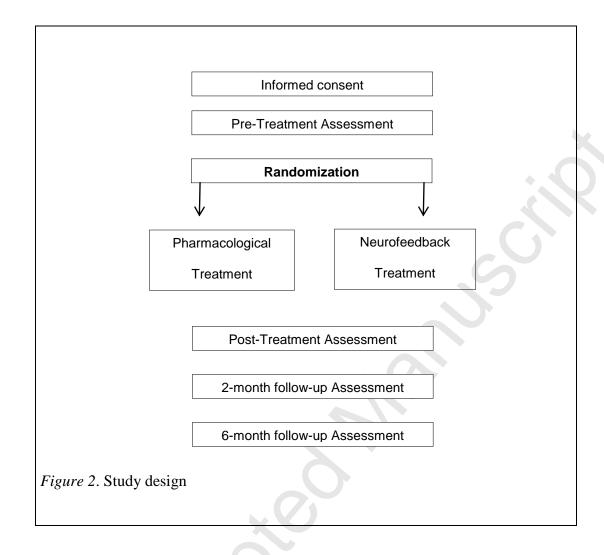
Table 5

Independent means t-tests and Cohen's effect sizes for Neurofeedback and pharmacological group comparisons

_]	Pre-Pre				Post-Post				FU1-FU1				FU2-FU2	
Behavior ratings	t	p	95% CI	Cohen's d	t	p	95% CI	Cohen's d	Ct	p	95% CI	Cohen's d	t	p	95% CI	Cohen's d
							М	others								
ADHD-RS																
Inattention	-0.02	.988	[-0.81, 0.83]	0.01	0.17	.871	[-0.75, 0.89]	0.07	-1.03	.315	[-0.40, 1.26]	0.43	-0.48	.637	[-0.62, 1.02]	0.20
Hyper/imp	-0.03	.974	[-0.81, 0.83]	0.01	-0.02	.988	[-0.82, 0.82]	0.00	-1.70	.104	[-0.13, 1.55]	0.71	-1.34	.194	[-0.27, 1.39]	0.56
Total score	-0.04	.970	[-0.80, 0.84]	0.02	0.09	.931	[-0.78, 0.86]	0.04	-1.75	.096	[-0.11, 1.57]	0.73	-1.05	.306	[-0.39, 1.27]	0.44
ODD																
Total score	-0.39	.702	[-0.66, 0.98]	0.16	-0.58	.565	[-0.58, 1.06]	0.24	-0.95	.351	[-0.43, 1.23]	0.40	0.60	.552	[-0.57, 1.07]	0.25
								.1								
ADHD-RS							F	athers								
	-0.70	401	[0 54 1 14]	0.20	0.22	.744	1 0 70 0 001	0.14	2.10	041	FO OF 1 011	0.02	0.20	.784	[0.72 0.05]	0.11
Inattention	-0.70 -0.65	.491 .521	[-0.54, 1.14] [-0.56, 1.12]	0.30 0.28	0.33 -0.08	.940	[-0.70, 0.98] [-0.81, 0.87]	0.14	2.18 1.39	.041 .180	[0.05, 1.81] [-0.27, 1.45]	0.93 0.59	-0.28 -0.14	.784 .887	[-0.73, 0.95] [-0.78, 0.90]	0.11 0.06
Hyper/imp	-0.65 -0.92				0.18	.858			2.08	.050						
Total score ODD	-0.92	.367	[-0.45, 1.25]	0.40	0.18	.858	[-0.76, 0.92]	0.08	2.08	.050	[0.01, 1.77]	0.89	-0.21	.833	[-0.75, 0.93]	0.09
Total score	-0.74	.469	[-0.54, 1.20]	0.33	0.50	.621	[-0.75, 0.93]	0.09	0.76	.454	[-0.30, 1.42]	0.56	0.22	.826	[-0.52, 1.16]	0.32
Total score	0.74	.407	[0.54, 1.20]	0.55	0.50	.021	[0.75, 0.75]	0.09	0.70	.454	[0.50, 1.42]	0.50	0.22	.020	[-0.32, 1.10]	0.32
							Pa	arents								
WFIRS																
Total score	0.59	.560	[-0.57, 1.07]	0.25	0.71	.486	[-0.52, 1.12]	0.30	-0.65	.524	[-0.55, 1.09]	0.27	-0.43	.673	[-0.64, 1.00]	0.18
							Te	achers								
ADHD-RS																
Inattention	0.11	.914	[-0.77, 0.87]	0.05	2.06	.052	[0.00, 1.72]	0.86	1.47	.158	[-0.23, 1.45]	0.61	0.89	.386	[-0.46, 1.18]	0.36
Hyper/imp	-0.57	.576	[-0.58, 1.06]	0.24	-0.29	.774	[-0.70, 0.94]	0.12	-0.30	.766	[-0.69, 0.95]	0.13	-0.65	.525	[-0.55, 1.09]	0.27
Total score	-0.47	.642	[-0.62, 1.02]	0.20	1.12	.276	[-0.36, 1.30]	0.47	0.61	.547	[-0.56, 1.08]	0.26	0.13	.897	[-0.76, 0.88]	0.06
ODD																
Total score	-0.19	.853	[-0.74, 0.90]	0.08	0.90	.378	[-0.45, 1.21]	0.38	0.96	.350	[-0.43, 1.23]	0.40	-0.02	.983	[-0.81, 0.83]	0.01
AP																
Reading	-2.15	.043	[0.04, 1.76]	0.90	0.92	.374	[-0.44, 1.22]	0.39	-0.73	.473	[-0.51, 1.13]	0.31	-0.24	.815	[-0.72, 0.92]	0.10
Reading c.	-2.00	.059	[-0.01, 1.69]	0.84	0.72	.478	[-0.52, 1.12]	0.30	0.01	.990	[-0.81, 0.83]	0.01	-1.44	.165	[-0.24, 1.44]	0.60
Writing	-1.73	.098	[-0.11, 1.57]	0.73	-0.52	.607	[-0.60, 1.04]	0.22	-0.07	.942	[-0.80, 0.84]	0.02	-1.11	.284	[-0.41, 1.47]	0.53
Math	-5.25	<.001	[1.15, 3.21]	2.18	-3.72	.001	[0.62, 2.48]	1.55	-2.84	.010	[0.30, 2.08]	1.19	-2.79	.011	[0.28, 2.06]	1.17
Oral exp.	-0.73	.477	[-0.52, 1.12]	0.30	1.06	.302	[-0.39, 1.27]	0.44	-0.22	.830	[-0.73, 0.91]	0.09	-0.57	.577	[-0.58, 1.06]	0.24

Note. Pre = pre-treatment; Post = post-treatment; FU1 = first follow-up; FU2 = second follow-up; CI = Confident Interval of Cohen's d; ADHD-RS = Attention Deficit and Hyperactivity Disorder Rating Scale; Hyper/imp = Hyperactivity and impulsivity; ODD = Oppositional Defiant Disorder; WFIRS = Weiss Functional Impairment Rating Scale; AP = Academic Performance; Reading c. = Reading comprehension; Oral exp. = Oral expression.





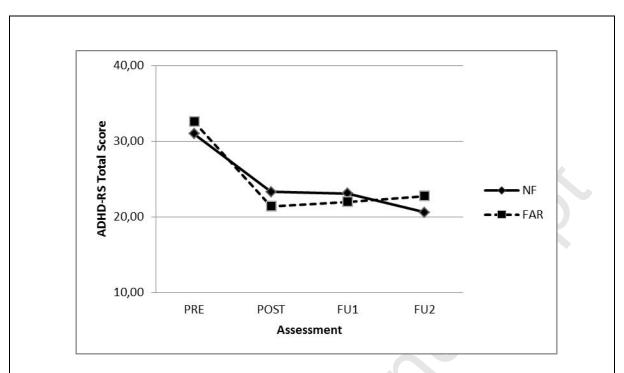


Figure 3. Mothers, fathers, and teachers ADHD-RS mean total scores in NF and pharmacological groups.

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Highlights

- We compared the efficacy of neurofeedback and standard pharmacological intervention in a randomized controlled trial.
- Neurofeedback reduces ADHD core symptoms and ADHD associated functional impairment to a similar extent as pharmacological intervention.
- Significant academic performance improvement was observed in participants receiving neurofeedback.
- Two-month and six-month follow-up assessments, based on parent and teacher reports, showed that participants receiving NF maintain their improvements months after completing the training.