Efficacy of Neurofeedback treatment in ADHD: The effects on Inattention, Impulsivity and Hyperactivity: A meta-analysis.

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ABSTRACT
Since the first reports of Neurofeedback treatment in ADHD in 1976 many studies have been carried out investigating the effects of Neurofeedback on different symptoms of ADHD such as inattention, impulsivity and hyperactivity. This technique is also used by many practitioners, but the question as to the evidence-based level of this treatment is still unclear. In this study selected research on Neurofeedback treatment for ADHD was collected and a meta-analysis was performed.
Both prospective controlled studies and studies employing a pre- and post-design found large effect sizes (ES) for Neurofeedback on impulsivity and inattention and a medium ES for hyperactivity. Randomized studies demonstrated a lower ES for hyperactivity suggesting that hyperactivity is probably most sensitive to non-specific treatment factors.
Due to the inclusion of some very recent and sound methodological studies in this meta-analysis potential confounding factors such as small studies, lack of randomization in previous studies and a lack of adequate control groups have been addressed and the clinical effects of Neurofeedback in the treatment of ADHD can be regarded as clinically meaningful. Four randomized controlled trials have shown Neurofeedback to be superior to a (semi-active) control group, whereby the requirements for Level 4: Efficacious are fulfilled (Criteria for evaluating the level of evidence for efficacy established by the AAPB and ISNR). Three studies have employed a semi-active control group which can be regarded as a credible sham control providing an equal level of cognitive training and client-therapist interaction. Therefore, in line with the AAPB and ISNR guidelines for rating clinical efficacy, we conclude that Neurofeedback treatment for ADHD can be considered 'Efficacious and Specific' (Level 5) with a large ES for inattention and impulsivity and a medium ES for hyperactivity.

Keywords: Neurofeedback, EEG Biofeedback, ADHD, meta-analysis, inattention, impulsivity, hyperactivity.

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INTRODUCTION

In 1976 Lubar and Shouse [16] were the first to report on EEG and behavioural changes in a hyperkinetic child after training the Sensorimotor EEG rhythm (SMR: 12-14 Hz). The rationale behind using SMR training in hyperkinetic syndrome lays in the fact that the most characteristic behavioural correlate of this rhythm is immobility [17, 18], a reduction in muscular tension accompanying SMR training [18] and excessive SMR production in quadriplegics and paraplegics [19] suggesting that enhancing this rhythm through operant conditioning should decrease the hyperkinetic complaints. Employing a within subject ABA design, Shouse and Lubar also showed that hyperactive symptoms *decreased* when SMR was enhanced and hyperactive symptoms *increased* when SMR was inhibited [20]. Several variations of this training protocol have been developed and tested over the years such as enhancing beta and inhibiting theta, enhancing SMR and inhibiting beta etc. For a detailed explanation of these different protocols also see Monastra [21].

In 2004 Heinrich et al. [4] were the first to report positive results after Slow Cortical Potential (SCP) Neurofeedback in the treatment of ADHD. SCP Neurofeedback is different from the above mentioned approaches in that changes in the polarity of the EEG are rewarded (i.e. positivity vs. negativity in the EEG) and a discrete reward scheme is used. Interestingly both the SCP Neurofeedback and SMR Neurofeedback approaches have been successfully used in treating epilepsy as well (for an overview also see Egner & Sterman [22]) and are suggested to both regulate cortical excitability [22, 23].

The initial findings by Lubar and Shouse [16] and Heinrich et al. [4] have stimulated a considerable amount of research into the treatment of ADHD with EEG Biofeedback or Neurofeedback. Many clinicians are currently using this therapy in their clinical practice. Therefore, the question concerning the evidence-based level of Neurofeedback therapy for ADHD and its significance in the treatment of ADHD arises.

The Guidelines for Evaluation of Clinical Efficacy of Psychophysiological Interventions [24] jointly accepted by the International Society for Neurofeedback and Research (ISNR) and the Association for Applied Psychophysiology and Biofeedback (AAPB) and similar to those from the American Psychological Association (APA) specify five types of classifications ranging from “Not empirically supported” to “Efficacious and specific”. Monastra et al. [21] critically reviewed the literature and applied the above mentioned guidelines. It was concluded that Neurofeedback treatment for ADHD could be considered as ‘probably efficacious’. However, in that same year Loo and Barkley [25] published a review article where they concluded that *“…the promise of EEG Biofeedback as a legitimate treatment cannot be fulfilled without studies that are scientifically rigorous*.” [25] (page 73). The main concerns they raised were the lack of well controlled, randomized studies, the small group sizes and the lack of proof that the EEG Feedback is solely responsible for the clinical benefit and not non-specific factors such as the additional time spent with a therapist or ‘cognitive training’. In 2006, Holtmann and Stadtler [26] concluded that EEG Biofeedback has gained promising empirical support in recent years, but there is still a strong need for more empirically and methodologically sound evaluation studies. Given these different conclusions based on the same literature, a more quantitative approach might be warranted to establish the evidence-based level of neurofeedback treatment in ADHD also including some more recent studies addressing some of the concerns raised.

To date no quantitative meta-analysis has been done on this topic. A meta-analysis provides a powerful approach to integrate many studies and investigate the overall effect across studies. Such an analysis could address some of the issues raised and test the effect size – and hence clinical relevance – of these methods in a quantitative manner. Since ADHD is characterized by persistent symptoms of inattention, hyperactivity and/or [27] in this meta-analysis we will investigate the effects of Neurofeedback and stimulant medication on the core symptoms of ADHD: Hyperactivity, Inattention and Impulsivity.

METHOD

Study selection

The literature was searched for studies investigating Neurofeedback or EEG Biofeedback in ADHD. For this purpose the Comprehensive Neurofeedback Bibliography compiled by Hammond [28] served as the first basis. Furthermore, a search in PubMed was performed using combinations of the following keywords: 'Neurofeedback' or 'EEG Biofeedback' or 'neurotherapy' or 'SCP' or 'Slow Cortical Potentials' and 'ADHD' or 'ADD' or 'Attention Deficit Hyperactivity Disorder' or 'Attention Deficit Disorder'. Furthermore, several authors were contacted who had presented Neurofeedback studies in ADHD on conferences (ISNR and Society for Applied Neuroscience (SAN)) during the last 2 years to obtain potential studies that are currently in press.

All these publications were obtained and screened for inclusion criteria. The reference lists of the articles were also cross-checked for any missing studies.

In order to guarantee sufficient scientific rigidity papers had to be published in a peer-reviewed scientific journal or be part of a PhD thesis.
The designs had to comply with the following criteria:

- Treated subjects should have a primary diagnosis of ADHD/ADD.
- 1) Controlled between subject design studies who have used a passive (waiting list) or active (stimulant medication; biofeedback; cognitive training) control groups either randomized or not; or 2) Prospective within subject design studies or 3) Retrospective within subject design studies with a large enough sample to provide a reliable representation of daily practice (N>500).
- The Neurofeedback treatment was provided in a standardized manner, and no more than two treatment protocols were used.

Standardized pre- and post-assessment means and Standard Deviations (SD's) for at least 1 of the following domains had to be available: Hyperactivity, Inattentiveness or CPT commission errors. When the means and SD's from a given study were not available, they were requested from the authors. Not all authors responded or were still able to retrieve this information, and if there was not sufficient information available the study was excluded from the meta-analysis.

Study grouping

In neurofeedback training several treatment protocols are used, such as SMR enhancement combined with Theta Suppression, Beta enhancement with Theta suppression, and the training of Slow Cortical Potentials (SCP). Most studies use central areas (Cz, C3, C4) as a training site and only few studies included Frontal sites (Fz, FCz). To remain in line with the majority of the literature on EEG frequency bands, for this meta-analysis we classified both SMR/Theta and Beta/Theta training as Beta/Theta training, since the SMR frequency band (12-15 Hz) is part of the Beta-1 frequency spectrum. Furthermore, several studies have compared theta-beta training and SCP training both within-subject [13] and between-subjects [12] and both neurofeedback approaches show comparable effects on the different aspects of ADHD such as inattention, hyperactivity and impulsivity. Therefore, in the current meta-analysis both SCP and theta-beta Neurofeedback protocols are investigated in the same analysis. The results from this meta-analysis will be reviewed post-hoc for differential effects of the different training protocols.

Data collection

The following pre- and post-assessment measures were collected from the included studies:

1) Hyperactivity: Assessed with a DSM rating scale such as Conners (CPRS-R); ADDES-Home, BASC, SNAP, FBB-HKS (parents) or DSM-IV Rating Scale (Lauth & Schlottke).
2) Inattention: Assessed with an inattention rating scale such as FBB-HKS, Conners (CPRS-R, BASC, ADDES-Home, SNAP/Iowa-Conners) or DSM-IV Rating Scale (Lauth & Schlottke).

3) Impulsivity: Commission errors on a CPT such as a TOVA, IVA (auditory prudence measure) or Go-NoGo test.

These measures were used as treatment endpoints.

Meta-Analysis

Two effect sizes were calculated. First, for the controlled between subject design studies the effect size of the Neurofeedback group as compared to the control group were calculated. These data were used to compare the outcome after Neurofeedback therapy with a control condition. Since some studies have used an active control group (Stimulant medication) or a semi-active control group (attention training [13, 14]), EMG Biofeedback [14] or group-therapy [11] the within-subject effect sizes were also calculated and plotted for all ADHD children treated with Neurofeedback from both the controlled and the within subject designs.

Effect sizes (ES) were calculated with Hedges' D using the pooled pre-test SD [29, 30] and the pre-post treatment differences for the outcome measures of the controlled studies. For the within-subject analysis the pre- and post-treatment means and SD's were used to calculate the ES. The Grand Mean Effect Size, 95% confidence intervals, Qt (heterogeneity of effect sizes) and Fail-safe number (Rosenthal's method: α<0.05) were calculated using MetaWin version 2.1 [31]. The fail-safe number is the number of studies, indicating how many unpublished null-findings are needed in order to render an effect non-significant.

When the total heterogeneity of a sample (Qt) was significant – indicating that the variance among effect sizes is greater than expected by sampling error – studies were omitted from the meta-analysis one-by-one and the study contributing most to the significance of the Qt value was excluded from further analysis for that variable until the Qt value was no longer significant. This was done for a maximum of 3 iterations. If more than 3 studies needed to be excluded in order to obtain a non-significant Qt value, then other explanatory variables for the effects have to be assumed [31]. In such a case the results for that variable will not be interpreted further.

Post-Hoc Analysis

Post-hoc analyses were carried out to check for potential differences in methodological approaches and quality of studies. The effect sizes were submitted to a one-way ANOVA to analyse the following variables:

1) Neurofeedback protocol: SMR/Beta/Theta vs. Beta/Theta vs. SCP protocols as well as SCP protocols vs. all Beta/Theta protocols.
2) Time: studies before 2006 and studies after 2006 will be compared to check for differences in ES in newer studies.
3) Studies employing randomization vs. non-randomized studies. Since the a-priori expectation is that randomized studies will have lower ES, we considered a p-value of below 0.1 as significant (one-tailed significance) thus using a strict criterion for this dimension.

Finally, the Pearson correlation coefficient was established between the average number of sessions and the effect size. Since it is expected from learning theory that more sessions will lead to better clinical effects a one-tailed test was performed.

RESULTS

Fifteen studies met all criteria and were included in the meta-analysis. One randomized controlled trial (RCT) Linden et al [32] and one prospective study (Lubar et al. [33]) were excluded from the meta-analysis since no SD's were available for those studies. An overview of all included studies can be found in Table 1. For all controlled studies there was a total of 476 subjects included in the meta analysis and for the pre- / post-design studies there was a total of 718 subjects included in the meta-analysis. Drop-out rates were only reported in 5 studies [3, 5, 10, 13, 9] and are therefore not included in table 1. Most reported drop-out rates were around 10% for most studies for both treatment and control groups.

The following calculations were performed to make data compatible with the meta-analysis: Kropotov et al. [6] reported the data based on a group of good-performers (N=71) and a group of poor performers (N=15). Xiong et al. [7] reported the data based for 3 groups of ADHD (Inattentive, Hyperactive and Combined type of ADHD). The means and SD's for these studies were hence re-calculated for the whole sample using the formula: SD=sqrt[n*sum(x^2)-(sum(x))^2)/(n(n-1))] for standard deviations.

All data used in this meta-analysis can be downloaded from www.brainclinics.com under downloads.

Prospective controlled studies

Note that there were two types of controlled studies; studies with a passive or semi-active control group such as a waiting list control group, EMG biofeedback and cognitive training and studies using an active control group such as stimulant medication ('gold standard' treatment for ADHD). These studies have been analysed separately. Figure 1 shows the results of the meta-analysis for both the studies with a passive control group (blue) and an active control group (green). A positive effect size denotes a decrease in symptoms for that measure. For impulsivity the ES for the Neurofeedback vs. Stimulant medication group is close to 0; indicating that Neurofeedback is equally efficacious as stimulant medication. Furthermore, note the large grand mean ES for Inattention (ES=0.81) and Impulsivity (ES=0.69) for Neurofeedback compared to a control group.
For hyperactivity and inattention there were not enough data available for a valid comparison between methylphenidate and Neurofeedback.

Inattention

The test for heterogeneity was significant (Qt=43,47, p=0.0000; mean effect size: 0.9903) meaning that the variance among the effect sizes was greater than expected by sampling error. It was found that the study from Monastra et al. [2] (ES=2.22) and Holtmann et al. [14] (ES=-0.39) contributed most to the significant Qt and were hence excluded from the analysis.

The mean effect size for Inattention was 0.8097 (95% confidence interval (CI) 0.39—1.23; Total N=201). The test for heterogeneity was not significant (Qt=3,31, p=0.51). The fail safe number of studies was 52.1, indicating that at least 52 unpublished null-findings are needed in order to render the effect of Neurofeedback on attention non-significant.

Hyperactivity

The test for heterogeneity was significant (Qt=16,45, p=0.01153; mean effect size: 0.6583). It was found that the study from Monastra et al. [2] (ES=1.36) contributed most to the significant Qt and was hence excluded from the analysis.

The mean effect size for Hyperactivity was 0.3962 (95% CI 0.05—0.75; Total N=235. The test for heterogeneity was not significant (Qt=2,83, p=0.726). The fail safe number of studies was 15.4.

Study	Country	Conditions		n	Age	Measure	Instrument	NF Site	Treatment	Mean # Ses.	Notes
PROSPECTIVE CONTROLLED STUDIES											
1) Rossiter & La Vaque 1995	USA	Stimulant control Group	ADHD: Control:	23 23	12,9 12,9	Hyperactivity Impulsivity Inattention	BASC TOVA BASC	Cz, FCz, CPz	Beta/Theta	20	
2) Monastra et al. 2002	USA	Control group	ADHD: Control:	51 49	10 10	Hyperactivity Impulsivity Inattention	ADDES TOVA ADDES	CPz and Cz	Beta/Theta	43	Comprehensive Clinical Care and Ritalin as additional therapy for both groups. Less cortical slowing
3) Fuchs et al. 2003	USA	Control group	ADHD: Control:	22 11	9,8 9,6	Impulsivity	TOVA	C3 or C4	Beta/Theta	36	
4) Heinrich et al. 2004	DE	Waiting list control	ADHD: Control:	13 9	11,1 10,5	Hyperactivity Impulsivity Inattention	FBB-HKS CPT FBB-HKS	Cz	SCP	25	↑ CNV ERP
5) Rossiter 2004	USA	Stimulant control Group	ADHD: Control:	31 31	16,6 16,7	Hyperactivity Impulsivity Inattention	BASC TOVA BASC	C3 or C8	Beta/Theta	50	
8) Levesque et al. 2006	CA	**RCT** Control Group	ADHD: Control:	15 5	10,2 10,2	Hyperactivity Impulsivity Inattention	CPRS-R IVA CPRS-R	Cz	Beta/Theta	40	fMRI showed activation of the right ACcd, left caudate and left substantia nigra during Counting Stroop test
10) Bakhshayesh, 2007	DE	**RCT** Control group EMG Biofeedback	ADHD: Control:	18 17	9,61 9,06	Hyperactivity Impulsivity Inattention	FBB-HKS CPT Commissions FBB-HKS	FCz-CPz	Beta/Theta	30	
11) Drechsler, 2007	CH	Group therapy Control Group	ADHD: Control:	17 13	10,5 11,2	Hyperactivity Impulsivity Inattention	FBB-HKS TAP: Go-NoGo FBB-HKS	Cz	SCP	30	Doehnert (2008): Post-QEEG: Theta decreased at Oz
13) Gevensleben et al. In Press	CH	Group therapy Control Group	ADHD: Control:	59 35	9,1 9,4	Hyperactivity Inattention	FBB-HKS FBB-HKS	Cz	SCP and Beta/Theta	36	
14) Holtman et al. In press	DE	**RCT** Captain's Log Control Group	ADHD: Control:	20 14	10,3 10,2	Hyperactivity Impulsivity Inattention	FBB-HKS Go-NoGo FBB-HKS	Cz	Beta/Theta	20	Normalization of Frontal No-Go N2 ERP
			Total N:	**476**							

Study	Country	Design		n	Age	Measure	Instrument	NF Site	Treatment	Mean # Ses.	Notes
PROSPECTIVE PRE- / POST-DESIGN STUDIES											
6) Kropotov et al. 2005	Russia	Pre-/post-design	ADHD:	18	11,4	Hyperactivity Impulsivity Inattention	SNAP-4 Go-NoGo SNAP-4	C3-Fz or C4-Pz	Beta (C3) SMR (C4	17	Normalization of ERP's for good-performers
7) Xiong et al. 2005	China	Pre-/post-design	ADHD:	60	>6	Omissions	IVA	?	Beta/Theta	40	
9) Strehl et al. 2006	DE	Pre-/post-design **Randomized** to SCP or Beta/Theta	ADHD:	23	9,3	Hyperactivity Impulsivity Inattention	DSM-IV RS TAP: Go-NoGo DSM-IV RS	Cz	SCP	30	
12) Leins et al. 2007	DE	Pre-/post-design **Randomized** to SCP or Beta/Theta	ADHD:	19	9,2	Hyperactivity Impulsivity Inattention	DSM-IV RS TAP: Go-NoGo DSM-IV RS	C3f and C4f	Beta/Theta	30	
RETROSPECTIVE PRE-/POST-DESIGN STUDY											
15) Kaiser & Othmer, 2000	USA	Multisite naturalistic pre-/postdesign	ADHD:	530 *	17,3	Impulsivity	TOVA	C3, C4	Beta/Theta		
			Total N:	**718**							

RCT = Randomized Controlled Trial; DSM-IV RS = DSM-IV Rating Scale (Lauth & Schlottke)

* The original Kaiser & Othmer sample consisted of 1089 subjects, however means and SD's were only available for N=530 (Kaiser, personal communication).

Impulsivity

Neurofeedback vs. Control Group

The mean effect size for Impulsivity was 0.6862 (95% CI 0.34—1.03; Total N=241). The test for heterogeneity was not significant (Qt=2,63, p=0.757). The fail safe number of studies was 37.7.

Neurofeedback vs. Methylphenidate

The mean effect size for Impulsivity was -0.0393 (95% CI -0.45—0.37; Total N=240). The test for heterogeneity was not significant (Qt=0,26, p=0.967. The fail safe number of studies was 0.

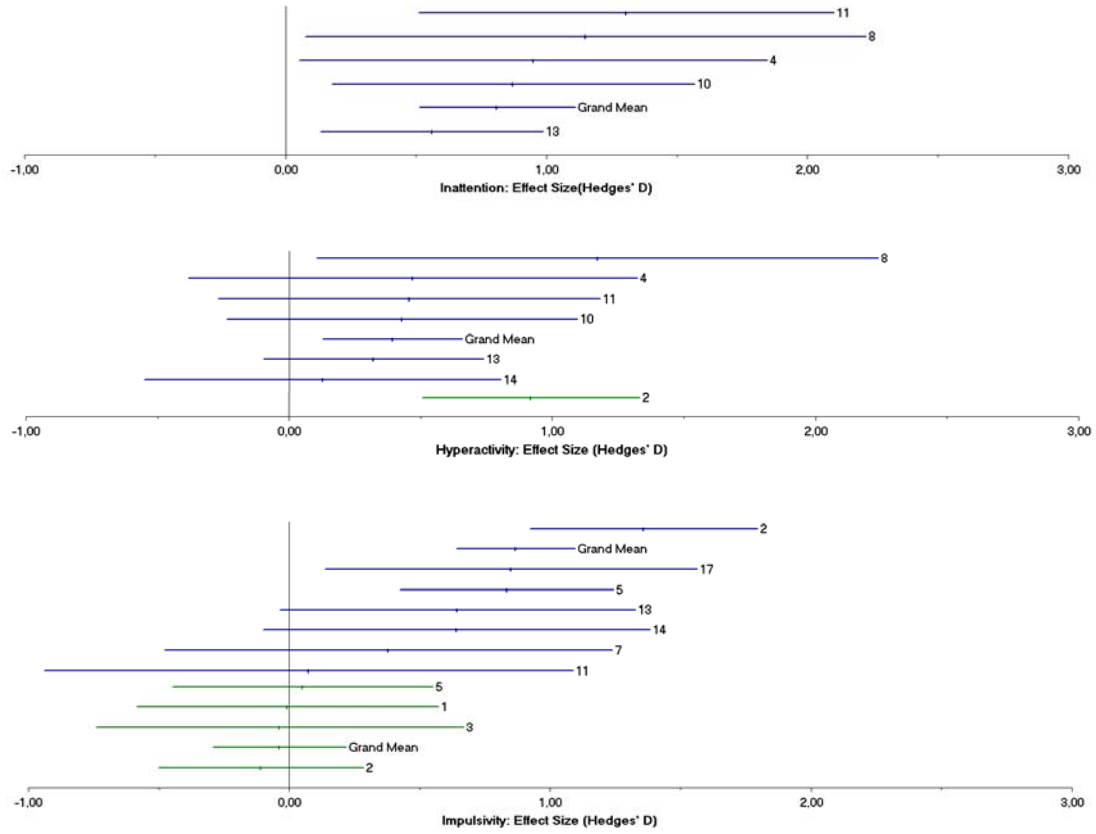

Figure 1: The effect sizes with their 95% confidence intervals for controlled studies (Blue = Neurofeedback vs. Control group; Green = Neurofeedback vs. Stimulant medication group). A positive Effect Size denotes a larger decrease in symptoms for the Neurofeedback group as compared to the control group

Within-subject effects
In figure 2 the within-subject effect sizes are shown for all studies included in the meta-analysis. Note the high Grand Mean ES for all 3 domains. The study by Strehl et al [9] and Leins et al [12] showed relatively low ES for Hyperactivity and Inattention. This is probably caused by the DSM-IV based questionnaire they used which only employs categorical answers (yes/no) whereas all other studies used scales that employed dimensional scales.

Inattention
The test for heterogeneity was significant (Qt=26.07, p=0.006; mean effect size: 1.1126). It was found that the Monastra et al. [2] (ES=1.45)) study contributed most to the significant Qt. This study combined a Comprehensive Clinical Care plan with Neurofeedback which might partly explain this finding.

The mean effect size for Inattention after excluding this study was 1.0238 (95% CI 0.84—1.21; Total N=324). The test for heterogeneity was not significant (Qt=16.26, p=0.093) meaning that the variance among the effect sizes was not greater than expected by sampling error. The fail safe number of studies was 508.6.

Hyperactivity
The mean effect size for Hyperactivity was 0.7082 (95% CI 0.54—0.87; Total N=375). The test for heterogeneity was not significant (Qt=13.57, p=0.258) meaning that the variance among the effect sizes was greater than expected by sampling error. The fail safe number of studies was 320.3.

Impulsivity
The test for heterogeneity was significant (Qt=24.93, p=0.015; mean effect size: 0.7487). It was found that the Kaiser & Othmer study [15] (ES=0.63) contributed most to the significant Qt. This was also the only naturalistic study; hence the effect size was calculated excluding this study.

The mean effect size for Impulsivity was 0.9394 (95% CI 0.76—1.12; Total N=338). The test for heterogeneity was not significant (Qt=16.15, p=0.135) meaning that the variance among the effect sizes was not greater than expected by sampling error. The fail safe number of studies was 511.7.

Figure 3 shows the grand mean effect sizes for the controlled studies compared to the within-subject effect sizes for all studies for all 3 core symptoms. Note that the ES for the controlled studies are slightly smaller, which could be due to the fact that many controlled studies used a 'semi-active' control group such as attention training [13, 14], EMG Biofeedback [10] or group-therapy [11]. Furthermore, given the 95% confidence intervals the ES for Inattention, Hyperactivity and Impulsivity are significant for both comparisons.

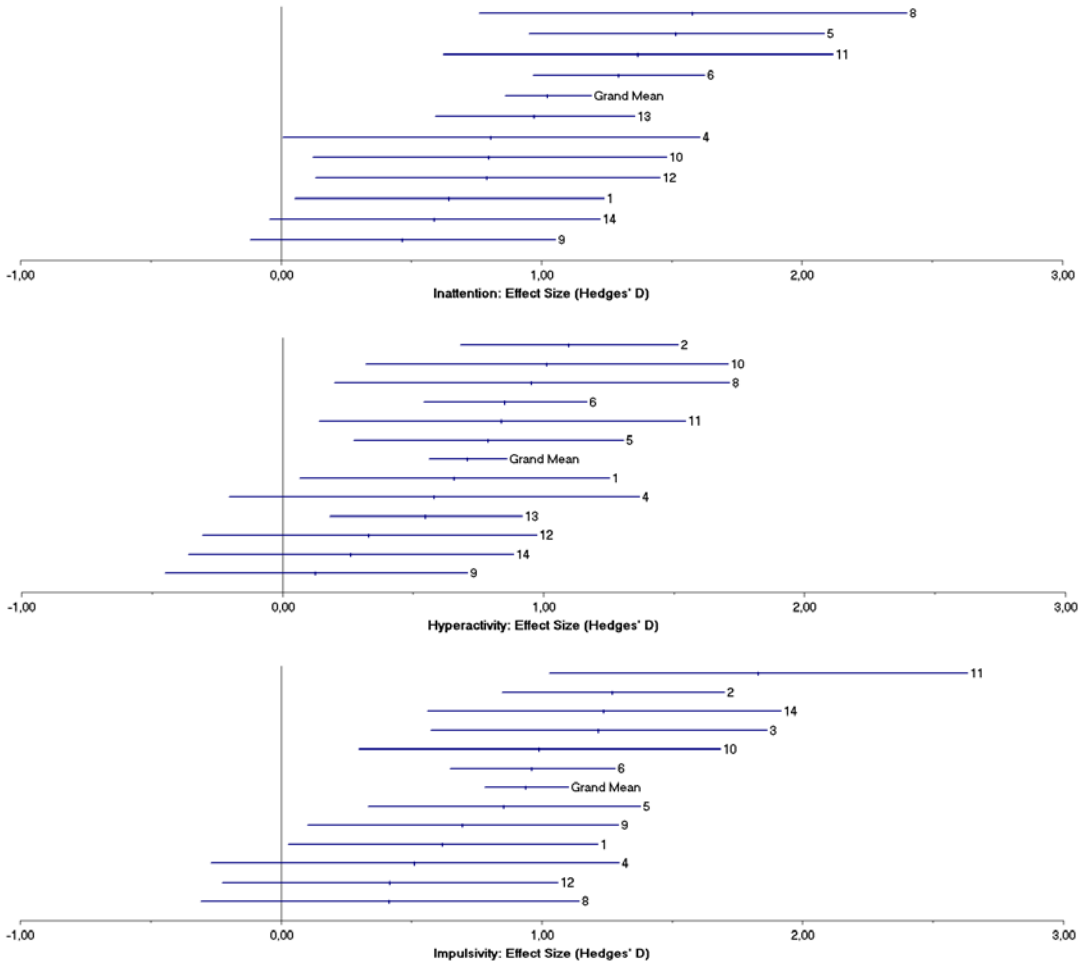

Figure 2: Within-subject design Meta-analysis: Note the large Grand Mean effect sizes for Inattention (ES: 1,02), Hyperactivity (ES=0,71) and Impulsivity (ES=0,94).

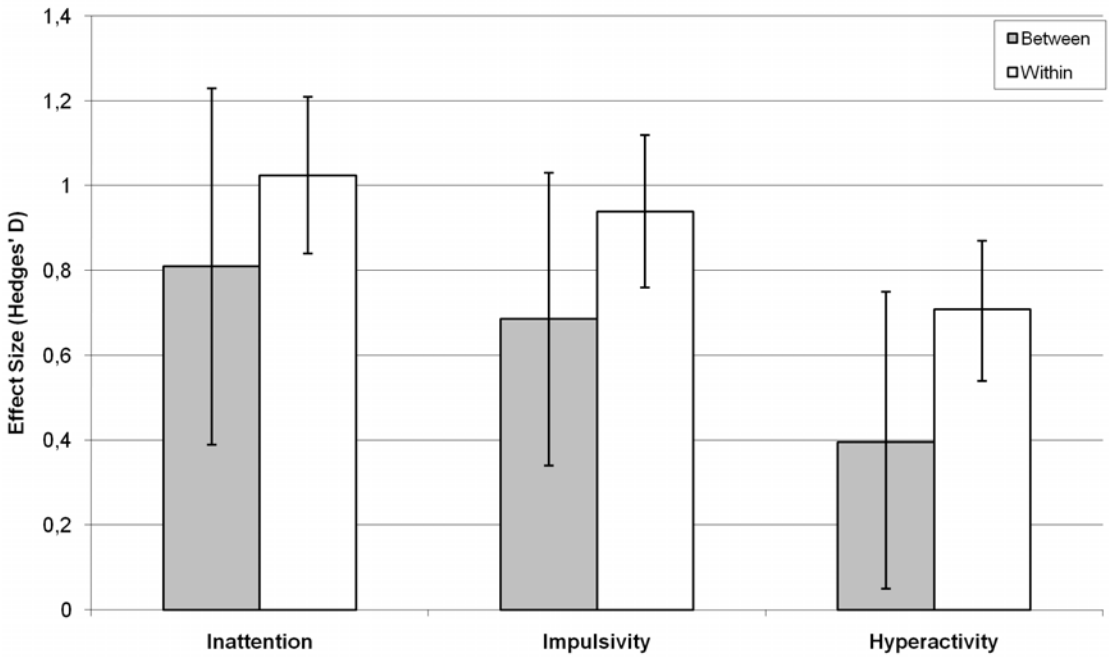

Figure 3: Effect sizes with their 95% confidence intervals for within and between subjects studies.

Post-hoc analysis

Post-hoc analysis did not reveal any differences in effect size between studies 1) employing SMR/Theta, Beta/Theta, SMR/Beta/Theta and SCP Neurofeedback protocols. Also no differences were found between SCP studies on the one hand and all Beta/Theta studies on the other hand and no effect was found for 2) Time. It can also be seen from the Forest plots that there is no clear relation between ES and time, since the studies are numbered in chronological order.

For randomization there was a significant effect for the Hyperactivity scale only (p=.080; F=3.716; df=1, 11), demonstrating that the ES for randomized studies was lower (ES=0.54) as compared to nonrandomized studies (ES=0.80). For inattention and impulsivity there were no differences.

There was a significant correlation between the average number of sessions in studies and improvement of Inattention (p=0.04; r=.550) but not for Impulsivity and Hyperactivity, meaning that for better effects on inattention are achieved with more sessions.

Placebo Controlled studies

Four (double-blind) placebo controlled studies have been performed investigating neurofeedback treatment of ADHD. These have not been published yet, and are hence not included in the meta-analysis. However, these are worth mentioning as regards to some of the critiques from the past. The first reported controlled study was mentioned in the review by Loo and Barkley [25] and was an unpublished paper by Fine, Goldman & Sandford [34]. It is of importance to note that this study used computerized cognitive training as a control condition which is not the same as sham feedback and it is known that computerized cognitive training can improve ADHD symptoms such as working memory, inattention and hyperactivity/impulsivity [35, 36]. This study showed that Neurofeedback was slightly better than the cognitive training and both were better than the waiting list control group on parent rating scales. This study should hence not be seen as a double-blind controlled, but as a placebo-controlled study.

The second study was by Orlandi & Greco [37]. This randomized double-blind placebo controlled study on 36 children with ADHD used a computer game without contingent feedback of the EEG. Clinic staff was not blinded to study group assignment, but patients and the rating physicians were. This study was presented at the ISNR meeting in 2005 and demonstrated a 47% drop-out rate for the placebo control group and 6% drop-out in the Neurofeedback group. Only the Neurofeedback group reported significant improvements on the Conners rating scale (parents: Effects size Hedges' D=0,895) and a Clinical Global Impression scale (effect size Hedges' D=1,6243). The data of this study are owned by Johnson & Johnson hence the author was not able to publish them (Greco, personal communication).

The third randomized double-blind sham controlled study in 31 ADHD children was presented at the 2006 ISNR meeting by Picard [38] and the summary of these findings have been published by Zaidel & Barnea [39]. Details of their procedure are lacking so it is hard to judge what sham control they used, and how blind the study was. This study suggests that benefits after neurofeedback training are not the result of motivational and social variables embedded in the treatment. Only the Neurofeedback group demonstrated improvements (parent rating scales) and differed significantly from both the placebo control group and the waiting list control group. There were also no differences between the placebo and the waiting list control group. The authors still plan to publish these findings (Achim & Moreau, personal communication).

The fourth randomized double-blind placebo controlled study in 53 ADHD children was presented at several international conferences by deBeus [40]. This study used a cross-over design where children first received 20 sessions of brainwave-modulated PlayStation feedback followed by PlayStation feedback which was not modulated by EEG. For the second group this was reversed. There were highly significant improvements in attention (IVA) and on rating scales for Inattention and Hyperactivity for the Neurofeedback group as compared to

the Placebo control group. This study is currently in preparation for publication (deBeus, personal communication).

In summary, the above mentioned studies demonstrate that Neurofeedback has distinguishable effects compared to a placebo condition and hence the observed effects cannot be explained by placebo.

Finally, Heywood and Beale [41] published a single-blind controlled study employing an ABAB design with a within-subject placebo design. They found a lack of effect of Neurofeedback after controlling for baseline changes and using an 'intent-to-treat design'. Due to the within-subject design with subjects serving as their own control and other methodological issues of this study we could not incorporate it into the meta-analysis.

DISCUSSION

This study investigated the effects of Neurofeedback therapy on core symptoms of ADHD using a meta-analytic approach. Fifteen studies were found fulfilling our criteria, with a total of 1194 subjects and the majority of studies conducted in Germany (7 studies) and the USA (4 studies). Four studies employed randomized allocation of subjects and 3 studies compared Neurofeedback with stimulant medication (the current 'gold standard' in the treatment of ADHD).

From the controlled studies in the meta-analysis it was evident that Neurofeedback had large effect sizes [42] on Inattention and Impulsivity and a medium ES for Hyperactivity. Many of these controlled studies have used semi-active control groups such as cognitive training [13, 14], EMG Biofeedback [10] or group-therapy [11]. Since it is known that cognitive training for instance can improve ADHD symptoms such as working memory, inattention and hyperactivity/impulsivity [35, 36] the within-subject ES were also calculated. These showed large effect sizes. They were significant for each of the core symptoms: Inattention, Impulsivity and Hyperactivity. For an overview of ES from controlled studies as well as those of within subject effects also see Figure 3.

From Figure 1 it can be clearly seen that the studies from Bakshayesh [10], Gevensleben et al [13] and Holtmann et al. [14] have the lowest ES for hyperactivity. These were exactly the 3 studies that all employed a semi-active control group in a randomized design. The fact that the ES for hyperactivity was significantly lower – though still a medium ES - for randomized studies suggests that hyperactivity is probably most sensitive to non-specific treatment factors. Future studies should use randomization in order to provide evidence for treatment effects on Hyperactivity.

The studies comparing Neurofeedback with stimulant medication showed that both treatments have equal effects on Impulsivity. There were not enough data for Inattention and Hyperactivity to make such a comparison.

There are several issues when interpreting meta-analytical data. For instance the selection of studies and relevant variables is directly related to the quality of the outcome of the meta-analysis. Furthermore, there is the possibility of publication bias causing a higher ES due to unpublished results of null findings also referred to as the 'file drawer problem' [31]. The fail-safe numbers in relation to the number of included studies were rather high in this study. The fail-safe number is the number of non-significant unpublished studies to be added to the meta-analysis to change the results of the meta-analysis from significant to not-significant. The fail-safe number for controlled studies was 15 for Hyperactivity, 52 for Inattention and 37 for impulsivity. The fail-safe number for within-subject studies was 320 for Hyperactivity and more than 500 for Inattention and Impulsivity. It seems rather unlikely that such numbers of studies with null-findings exist and have not been published.

This 'file-drawer problem' was further addressed by the a-priori selection of treatment end-points and requesting additional (unpublished) data from authors if required. Most studies reported many results, such as rating scale data for Inattention and Impulsivity and a range of neuropsychological tests. For this meta-analysis we specifically defined the measures to be

included for the 3 domains a priori, such as rating scale data for hyperactivity and inattention and commission errors on a CPT test as a measure of impulsivity. Since most authors will focus their papers mostly on the significant findings of their study, our approach aimed at minimizing the risk of over-estimating the effect sizes. In many cases (such as [4, 8, 9, 12,]) we requested the means and SD's for the commission errors and/or rating scale data which in some cases were not even significant for that study.

In the past several criticisms have been raised about studies investigating the efficacy of Neurofeedback in the treatment of ADHD for instance by Loo and Barkley [25] and Holtmann and Stadtler [26] as regards to small sample sizes, lack of adequate control group, no randomization, disregard of long term outcome. Below we will address these critical issues in the light of the many recently conducted studies:

Randomization
In this meta-analysis support was found for the need of randomized trials, given the fact that ES were significantly smaller for randomized trials for hyperactivity scales, but not for inattention and impulsivity. The average effect size for randomized studies was still medium (ES=0.54). Furthermore, in this meta-analysis the results of 6 randomized studies have been incorporated, with all showing medium to high effect sizes for Inattention and Impulsivity and low to high effect sizes for Hyperactivity. Indeed randomization is required in order to conduct reliable studies, but it can be concluded that randomized studies so far still show large effect sizes for inattention and impulsivity.

Sample-size
The largest studies to date are the studies by Monastra [2](N=100), Gevensleben et al. [13] (N=94) and Kaiser & Othmer [15](original study N=1089; data available in this meta-analysis N=530; Kaiser, personal communication). The results from the Monastra study [2] need to be interpreted with caution since this study was excluded from most analysis since it contributed most to the heterogeneity of effect sizes (Qt). This is probably related to the fact that subjects in that study besides Neurofeedback and Ritalin also received a Comprehensive Clinical Care program, leading to higher ES as compared to the other studies. The study by Gevensleben et al. [13] is the most methodologically sound study to date. It included randomization, a large sample size and a multi-centre approach. This study showed a medium ES for Hyperactivity (ES=0.55) and a large ES for Inattention (ES=0.97). Finally, the Kaiser & Othmer study [15] is the largest study to date. For Impulsivity the ES was medium (ES=0.63), but this value was excluded from the analysis since this study contributed most to the heterogeneity of effect sizes. This can probably be explained by the fact that this study was a naturalistic study and can hence methodologically be considered the weakest study included in the meta-analysis.

Finally, the current meta-analysis also addresses the issue of small-sample size by combining all studies into a meta-analysis, thereby further addressing the sample size concern.

Adequate control groups
In the past it has been suggested by many authors that a potential explanation of the effects of Neurofeedback could stem from 'cognitive training' since children are engaging in a feedback task for often 30-50 sessions. Furthermore, it has been suggested that the time spent with a therapist could be an explanation for the treatment effects. Such concerns could be addressed by double-blind controlled studies.

Four *'(double-blind) placebo-controlled'* studies have been conducted in the past demonstrating that Neurofeedback is superior to placebo. However, these studies have not been published and did hence not meet the criteria for inclusion in the meta-analysis. It is to be asked why 4 studies like these have been completed, but have not been published yet. Especially as these data have been collected more than 4 years ago for all studies. Therefore publication of these studies is warranted to judge their quality and implications.

Given the difficulty of conducting a double-blind placebo controlled study in Neurofeedback, which is likely to be associated with high drop-out rates in the control group [37] several groups have still addressed these concerns. For instance, Gevensleben et al [13] and Holtmann et al [14] have used control groups who were intensively and equally trained on an attention

demanding task (computerized cognitive training) to control for these unspecific effects. Furthermore, Drechsler et al [11] used a control group undergoing group-therapy and Bakshayesh [10] used an EMG Biofeedback group as a control group. In all these studies Neurofeedback in comparison to this semi-active control group still had medium to large ES for Inattention and Impulsivity, and small to medium ES for Hyperactivity. Especially the control groups used by Gevensleben et al [13], Holtmann et al [14] and Bakshayesh [10] can be considered a credible sham control, with even 'active' properties expected to show improvements on symptoms such as working memory, inattention and hyperactivity/impulsivity [35, 36].

None of the studies comparing Neurofeedback with stimulant medication used random assignment. Participants self-selected the treatment of their preference. This may bias these results, however self selection potentially maximizes the effects of expectancy in both groups. In addition, it has to be stressed that the ES for comparison of Neurofeedback to stimulant medication was 0, indicating the efficacy of Neurofeedback is equal to medication for at least Impulsivity. Unfortunately there were not enough data available to investigate the ES for Inattention and Hyperactivity.

Finally, many studies in the past have only been published in Neurofeedback specific journals such as the Journal of Neurotherapy (which is not indexed by Medline) and Applied Psychophysiology and Biofeedback. As can be seen from the studies in Table 1 most of the recent studies have been published in journals with higher impact factors which are indexed in Medline such as Biological Psychiatry, Neuroscience Letters and Pediatrics.

Long term effects

Long-term effects could not be addressed in this meta analysis. However, several studies did report follow-up results. Heinrich et al [4] performed 3 months follow-up for the SCP group and found all measures improving further (Heinrich, personal communication: Unpublished results). For the study of Strehl and colleagues 6 months follow-up scores in Impulsivity, Inattention and Hyperactivity were shown to improve even further as compared to the end of treatment [9, 12]. A 2-year follow-up for this study [43] showed that all improvements in behaviour and attention turned out to be stable. Test results for attention and some of the parents' ratings once more improved significantly. In addition, EEG-self regulation skills turned out to be still preserved, indicating that these children were still able to successfully regulate their EEG.

Taken together, it can be concluded that the clinical effects of Neurofeedback are stable and might even improve further with time. This, in contrast to stimulant medication where it is known that when the medication is stopped often the initial complaints will come back again, as is also clearly shown in the study from Monastra et al [2].

Pre- and post-QEEG differences

Finally, it is often stated that studies do not - or fail to report pre- and post-QEEG differences since the EEG is the basis of treatment in Neurofeedback (for example see Loo & Barkley [25]). However, this is not a credible reason to criticize the clinical efficacy of Neurofeedback or any other treatment. The primary question is 'does it work?', and a secondary question which is not addressed in this paper is 'how does it work?'. Other clinical trials into psychoactive medication or other neuromodulation techniques also do not demonstrate this. For example, a study investigating pre- and post QEEG en ERP (Event Related Potential) data after 20 sessions of rapid Transcranial Magnetic Stimulation (rTMS) in depressed patients also failed to find any pre- and post-QEEG differences, but did find localized changes in ERP's [44]. rTMS treatment is also based on the assumption of frontal-asymmetry, often reported in EEG studies as well [45, 46]. Interestingly, several studies did find a normalization of ERP's as a result of Neurofeedback [4, 6, 14] as can be seen in table 1 suggesting that rather task-related EEG (or ERP's) but not passive Eyes Open and Eyes Closed EEG should be further investigated. In our opinion, passive EEG such as Eyes Open and Eyes Closed EEG should be seen as a stable trait marker or Phenotype [47, 48, 49] and should hence not be considered a valid treatment end-point, whereas disorder specific behavioural questionnaires and/or event related EEG or ERP's should be the primary treatment end-points.

Conclusion

Due to the inclusion of some very recent and sound methodological studies in this meta-analysis many potential confounding factors have been addressed and the clinical effects of Neurofeedback in the treatment of ADHD can be regarded as clinically meaningful with large effect sizes for Inattention and Impulsivity and a medium ES for Hyperactivity.

The four randomized controlled trials from Levesque et al. [8]; Bakshayesh [10], Gevensleben et al. [13] and Holtmann et al. [14] have shown Neurofeedback to be superior to a (semi-active) control group, whereby the requirements for Level 4: Efficacious are fulfilled [24]. The semi-active control group in these studies can be regarded as a credible sham control providing an equal level of cognitive training and client-therapist interaction. Therefore, in line with the guidelines for rating clinical efficacy, we conclude that Neurofeedback treatment for ADHD can be considered 'Efficacious and Specific' with a high ES for inattention and impulsivity and a medium ES for hyperactivity.

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