Supplemental material

1 Materials and methods

1.1 Perform a meta analysis

To conduct meta-analysis, different software exist: for instance Cortese et al. [2016] used RevMan 5.3 [Cochrane Collaboration, 2011] which computes the effect size (ES) and its variance of each included study by applying the formula presented in Morris [2008]. However, in order to compute the variance of the ES, the pooled within-group Pearson correlation ρ (i.e the pre-post correlation) was required [James et al., 2013]. In our case, this correlation was not known and the raw data were not available so we took an approximation: Balk et al. [2012] found that a value of 0.5 yields values closer to those computed with the right value of the correlation.

In this replication of the work of Cortese et al., the same formulas are used [Borenstein et al., 2009] but instead of using RevMan, a Python code was developed in order to perform the meta-analysis. To increase replicability and transparency and promote open science, we provide the full raw data used for this research as well as the Python code on a GitHub repository [put ref]; it is tested with Cortese et al. [2016] raw data to show that same results were found and could be used for replication and expansion of this work. The toolbox could also be used to run any similar meta-analysis.

To perform the meta-analysis several steps must be followed. First the choice of the model: this analysis is based on either one of the following statistical models [Borenstein et al., 2009]:

- *the fixed-effect model*: the true ES (i.e the ES that would be observed with an infinitely large sample size) is the same for all the studies in the analysis. The differences between the actually observed ESs are due to sampling errors;

- *the random-effects model*: the true ES could vary from study to study. The differences between the observed ESs are due to sampling errors but also to the various designs of the studies (for instance the number of participants or the implementation).

In the present case, although the studies included into the meta-analysis meet the same criteria, they remain different from each other on various points, so the random effects model is more appropriate than the fixed-effect model.

1.2 Compute the effect size of each study

First, the scores presented in the articles were extracted and the ES of each study as defined in Morris [2008] was computed

$$\mathsf{ES} = c_p \left[\frac{(M_{\mathsf{post},T} - M_{\mathsf{pre},T}) - (M_{\mathsf{post},C} - M_{\mathsf{pre},C})}{\sigma_{\mathsf{pre}}} \right]. \tag{1}$$

An ES is exactly equivalent to a z-score of a standard normal distribution, it is computed as mean pre- to post-treatment score change in the Neurofeedback (NFB) group ($M_{\mathsf{pre},T}$, $M_{\mathsf{post},T}$) minus the mean pre- to post- treatment score change in the control group ($M_{\mathsf{pre},C}$, $M_{\mathsf{post},C}$), divided by the pooled pre-test standard deviation (σ_{pre})

$$\sigma_{\mathsf{pre}} = \sqrt{\frac{(n_T - 1)\sigma^2_{\mathsf{pre},T} + (n_C - 1)\sigma^2_{\mathsf{pre},C}}{n_T + n_C - 2}}, \tag{2}$$

where $\sigma_{t,G}$ indicates the standard deviation for group G at time t and n_G defines the sample size of each group; c_p is a bias adjustment typically used for small sample sizes

$$c_p = 1 - \frac{3}{4(n_T + n_C - 2) - 1}. \tag{3}$$

1.3 Compute the variance of each effect size

Then, the variance of each ES was computed [Morris, 2008]

$$\sigma^2(\mathsf{ES}) = c_p^2 \left(\frac{n_T + n_C - 2}{n_T + n_C - 4} \right) \left[\frac{2(1-\rho)(n_T + n_C)}{n_T n_C} + \mathsf{ES}^2 \right] - \mathsf{ES}^2. \tag{4}$$

To compute the variance of the ES, the pooled within-group Pearson correlation ρ (i.e the pre-post correlation) was required [James et al., 2013]:

$$\rho = \frac{\sum_{i=1}^{n}(\mathsf{pre}_i - \mu_{\mathsf{pre}})(\mathsf{post}_i - \mu_{\mathsf{post}})}{\sqrt{\sum_{i=1}^{n}(\mathsf{pre}_i - \mu_{\mathsf{pre}})^2}\sqrt{\sum_{i=1}^{n}(\mathsf{post}_i - \mu_{\mathsf{post}})^2}}, \tag{5}$$

where n is the number of patients included in a study, pre_i, $post_i$ are score values for patient i at pre- and post-test respectively, and μ_{pre}, μ_{post} the mean scores over all patients. It is a measure of linear correlation between two variables. A value of 1 means that there is a positive correlation whereas a value of -1 means a negative correlation. When $\rho = 0$, there is no linear correlation. In our case, this correlation was not known and the raw data were not available so we took an approximation: Balk et al. [2012] found that a value of 0.5 yields values close to those computed with the right value of the correlation.

Once variances were obtained with eq. (4), we could compute the standard error and the 95% confidence interval of each ES.

1.4 Compute the weight of each study

To compute the summary effect (SE) a weight must be assigned to each study. To obtain them several steps must be followed. At first, the fixed-effects model weight w_{fixed} of each study k was computed as defined in Borenstein et al. [2009]:

$$w_{\mathsf{fixed}_k} = \frac{1}{\sigma^2(\mathsf{ES}_k)}. \tag{6}$$

Nevertheless, we chose to use the random effects model, so the weights associated to this model are different. To compute them, the between-studies variance τ^2 is required. It was calculated in three steps described in eq. (7), eq. (8) and eq. (9) [Borenstein et al., 2009]:

$$Q = \sum_{k=1}^{K} (w_{\mathsf{fixed}_k} \mathsf{ES}_k^2), \tag{7}$$

$$C = \sum_{k=1}^{K} (w_{\mathsf{fixed}_k} - \frac{\sum_{k=1}^{K} (w_{\mathsf{fixed}_k})^2}{\sum_{k=1}^{K} (w_{\mathsf{fixed}_k})}, \tag{8}$$

with K the total number of included studies.

$$\tau^2 = \frac{Q - \mathsf{df}}{C}, \tag{9}$$

with $\mathsf{df} = K - 1$ the degrees of freedom.

The random-effects model takes into account the differences between the studies, so the weights are equal to the inverse of the addition between the within-study variance (the variance of the ES) and the between-studies variance

$$w_k = \frac{1}{\sigma^2(\mathsf{ES}_k) + \tau^2}. \tag{10}$$

1.5 Compute the summary effect

Eventually, the weighted average of the K ES was computed to obtain the SE as described in eq. (11) [Borenstein et al., 2009]:

$$\mathsf{SE} = \frac{\sum_{k=1}^{K} w_k \mathsf{ES}_k}{\sum_{k=1}^{K} w_k}. \tag{11}$$

Once the SE is obtained, we can compute its variance, its standard error, its 95% confidence interval, its p-value, and I^2 estimating effects size's between studies heterogeneity.

1.6 Scales used for the meta-analysis

All scales used for the meta-analysis are summarized here in order to facilitate the replication of this work.

Table 1: Clinical scales used to update Cortese et al. [2016] with our choices and the two new articles.

Study	Outcome	Score Names - Parents ratings	Score Names - Teachers ratings
Arnold et al.	Total Inattention Hyperactivity	SNAP IV SNAP IV SNAP IV	SNAP IV SNAP IV SNAP IV
Bakhshayesh et al.	Total Inattention Hyperactivity	German ADHD-RS German ADHD-RS German ADHD-RS	German ADHD-RS German ADHD-RS German ADHD-RS
Baumeister et al.	Total	DISYPS	-
Beauregard and Levesque	Total Inattention Hyperactivity	CPRS CPRS CPRS	- - -
Bink et al.	Total Inattention Hyperactivity	ADHD-RS self report ADHD-RS self report ADHD-RS self report	- - -
Christiansen et al.	Total	Conners-3 Parents	Conners-3 Teachers
Gevensleben et al.	Total Inattention Hyperactivity	German ADHD-RS German ADHD-RS German ADHD-RS	German ADHD-RS German ADHD-RS German ADHD-RS
Heinrich et al.	Total	German ADHD-RS	-
Holtmann et al.	Total Inattention Hyperactivity	German ADHD-RS German ADHD-RS German ADHD-RS	- - -
Linden et al.	Total Inattention	IOWA Conners IOWA Conners	- -
Maurizio et al.	Total Inattention Hyperactivity	CPRS CPRS CPRS	CTRS CTRS CTRS
Steiner et al.	Total Inattention Hyperactivity	Conners Rating Scales Revised Conners Rating Scales Revised Conners Rating Scales Revised	Conners Rating Scales Revised Conners Rating Scales Revised Conners Rating Scales Revised
Steiner et al.	Total Inattention Hyperactivity	Conners-3 Parents Conners-3 Parents Conners-3 Parents	Conners-3 Teachers Conners-3 Teachers Conners-3 Teachers
Strehl et al.	Total Inattention Hyperactivity	German ADHD-RS German ADHD-RS German ADHD-RS	German ADHD-RS German ADHD-RS German ADHD-RS
van Dongen-Boomsma et al.	Total Inattention Hyperactivity	ADHD RS ADHD RS ADHD RS	ADHD RS ADHD RS ADHD RS

SNAP: Wanson, Nolan and Pelham Questionnaire, ADHD-RS: ADHD Rating Scale, CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, BOSS Classroom Observation: Behavioral Observation of Students in Schools, DISYPS: Diagnostic System of Mental Disorders in Children and Adolescents

1.7 Associate independent factors to effect sizes

Three different methods were used to perform the systematic analysis of biases (SAOB):

- weighted multiple linear regression (Weighted Least Squares (WLS)) [Montgomery et al., 2012];

- sparsity-regularized linear regression with Least Absolute Shrinkage and Selection Operator (LASSO) [Tibshirani, 1996];

- decision tree [Quinlan, 1986].

However, before interpreting the results of the WLS, the assumptions of this model had to be checked (distribution of the residuals was normal, the moment matrix was full rank, the fit was significant and the independent variables were uncorrelated).

To perform the LASSO, the tuning parameter λ has to be determined. To do so, we used the leave-one-out cross validation method. This method retains 1 observation as the validation data for testing the model and the remaining n - 1 observations are used as training data. The cross-validation process is then repeated n times with each of the observation used exactly once as the testing data. For each fold, the Mean Square Error (MSE) on the test set was computed and eventually, the n results can be averaged to produce a single observation that enables to find the optimal λ: it corresponds to the abscissa of the minimum value of the MSE on the mean fold computed for a large range of λ [James et al., 2013].

No weights are applied when running the LASSO and the decision tree because the frameworks don't easily account for this.

2 Results

2.1 Perform a meta-analysis

First, when using the ES found by Cortese et al. [2016] thanks to RevMan [Cochrane Collaboration, 2011], and then performed the following steps of meta-analysis with the Python code, we observe no major differences between these results and those obtained with RevMan [Cochrane Collaboration, 2011] as listed in table 2. The minor discrepancies, especially observed at the p-values level, are due to our choice to always use a pre-post correlation of 0.5 when computing the variance of each ES. Moreover, a sensitivity analysis was conducted to ensure the minor impact of the pre-post correlation value: when it varies between 0.2 and 0.8 the significance of the SE does not change.

Table 2: Comparison between Cortese et al. [2016] results obtained with RevMan [Cochrane Collaboration, 2011] and those obtained with the Python code. Summary effects and their corresponding p-value in parenthesis are presented. With the Python program, a negative summary effect is in favor of NFB.

Input data		Results from Cortese et al. [2016]	Effect sizes from Cortese et al. [2016]
Implementation		RevMan Cochrane Collaboration [2011]	Python program
	Total	$0.35\ (0.004)$	$-0.34\ (0.004)$
Parents	Inattention	$0.36\ (0.009)$	$-0.35\ (0.011)$
	Hyperactivity	$0.26\ (0.004)$	$-0.24\ (0.02)$
	Total	$0.15\ (0.20)$	$-0.13\ (0.25)$
Teachers	Inattention	$0.06\ (0.70)$	$-0.09\ (0.50)$
	Hyperactivity	$0.17\ (0.13)$	$-0.15\ (0.21)$

Thanks to the previous step, we can conclude that the Python code yields results close to those returned by RevMan Cochrane Collaboration [2011], so we decide to use this code to perform our meta-analysis.

2.2 Detect factors influencing the Neurofeedback

To assess the variability of each factor, box plots of their standardized values were displayed in fig. 1: treatment length, session length and number of sessions are more variable across studies than session pace, minimum and maximum age.

2.3 Assumptions for applying linear regression

The first method used to detect the influencing factors was the WLS. The assumptions inherent to this method are checked:

- the moment matrix $\mathbf{X^TW^TWX}$ was invertible;
- no apparent correlation between the continuous independent variables was found;

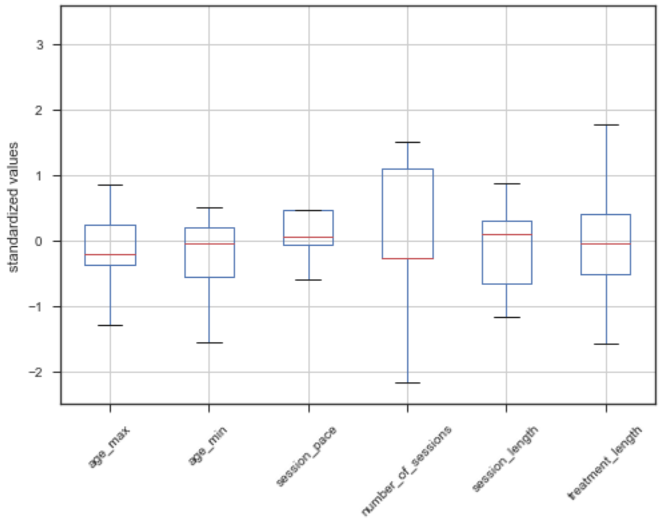

Figure 1: Boxplots of the standardized values of each continuous factor.

- the fit was significant as shown by the F-statistic (prob(F-statistic) = 2.81e-10);
- the residuals were normally distributed as demonstrated by the skew (-0.15), kurtosis (2.81) and the Omnibus test (prob(Omnibus) = 0.87).

These assumptions are also satisfied for the Ordinary Least Squares (OLS).

References

L. E. Arnold, N. Lofthouse, S. Hersch, X. Pan, E. Hurt, B. Bates, K. Kassouf, S. Moone, and C. Grantier. Eeg neurofeedback for attention-deficit/hyperactivity disorder: Double-blind sham-controlled randomized pilot feasibility trial. *Journal of Atention Disorder*, 2014. doi: https://doi.org/10.1177/1087054712446173.

A. R. Bakhshayesh, S. Hänsch, A. Wyschkon, M. J. Rezai, and G. Esser. Neurofeedback in adhd: a single-blind randomized controlled trial. *European child & adolescent psychiatry*, 20(9):481, 2011. doi: https://doi.org/10.1007/s00787-011-0208-y.

E. M. Balk, A. Earley, K. Patel, T. A. Trikalinos, and I. J. Dahabreh. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. 2012.

S. Baumeister, I. Wolf, N. Holz, R. Boecker-Schlier, N. Adamo, M. Holtmann, M. Ruf, T. Banaschewski, S. Hohmann, and D. Brandeis. Neurofeedback training effects on inhibitory brain activation in adhd: A matter of learning? *Neuroscience*, 2016. doi: https://doi.org/10.1016/j.neuroscience.2016.09.025.

M. Beauregard and J. Levesque. Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Applied psychophysiology and biofeedback*, 31(1):3–20, 2006. doi: https://doi.org/10.1007/s10484-006-9001-y.

M. Bink, C. van Nieuwenhuizen, A. Popma, I. L. Bongers, and G. J. M. van Boxtel. Behavioral effects of neurofeedback in adolescents with adhd: a randomized controlled trial. *European Child and Adolescent Psychiatry*, 2014. doi: https://doi.org/10.1007/s00787-014-0655-3.

M. Borenstein, L. V. Hedges, J. Higgins, and H. R. Rothstein. *Introduction to meta-analysis*. Wiley, 2009.

H. Christiansen, V. Reh, M. H. Schmidt, and W. Rief. Slow cortical potential neurofeedback and self-management training in outpatient care for children with adhd: study protocol and first preliminary results of a randomized controlled trial. *Frontiers in human neuroscience*, 8, 2014. doi: https://doi.org/10.3389/fnhum.2014.00943.

Cochrane Collaboration. Revman 5.1, 2011.

S. Cortese, M. Ferrin, D. Brandeis, M. Holtmann, P. Aggensteiner, D. Daley, P. Santosh, E. Simonoff, J. Stevenson, A. Stringaris, et al. Neurofeedback for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(6):444–455, 2016. doi: https://doi.org/10.1016/j.jaac.2016.03.007.

H. Gevensleben, B. Holl, B. Albrecht, C. Vogel, D. Schlamp, O. Kratz, P. Studer, A. Rothenberger, G. H. Moll, and H. Heinrich. Is neurofeedback an efficacious treatment for adhd? a randomised controlled clinical trial. *Journal of Child Psychology and Psychiatry*, 50(7):780–789, 2009. doi: https://doi.org/10.1111/j.1469-7610.2008.02033.x.

H. Heinrich, H. Gevensleben, F. J. Freisleder, G. H. Moll, and A. Rothenberger. Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. *Biological psychiatry*, 55(7):772–775, 2004. doi: https://doi.org/10.1016/j.biopsych.2003.11.013.

M. Holtmann, D. Grasmann, E. Cionek-Szpak, V. Hager, N. Panzner, A. Beyer, F. Poustka, and C. Stadler. Spezifische wirksamkeit von neurofeedback auf die impulsivität bei adhs. *Kindheit und Entwicklung*, 18(2):95–104, 2009. doi: https://doi.org/10.1026/0942-5403.18.2.95.

G. James, D. Witten, T. Hastie, and R. Tibshirani. *An introduction to statistical learning*, volume 112. Springer, 2013.

M. Linden, T. Habib, and V. Radojevic. A controlled study of the effects of eeg biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Applied Psychophysiology and Biofeedback*, 21(1):35–49, 1996.

S. Maurizio, M. D. Liechti, H. Heinrich, L. Jäncke, H.-C. Steinhausen, S. Walitza, D. Brandeis, and R. Drechsler. Comparing tomographic eeg neurofeedback and emg biofeedback in children with attention-deficit/hyperactivity disorder. *Biological psychology*, 95:31–44, 2014. doi: https://doi.org/10.1016/j.biopsycho.2013.10.008.

D. C. Montgomery, E. A. Peck, and G. G. Vining. *Introduction to linear regression analysis*, volume 821. John Wiley & Sons, 2012.

S. B. Morris. Estimating effect sizes from pretest-posttest-control group designs. *Organizational Research Methods*, 11(2):364–386, 2008. doi: https://doi.org/10.1177/1094428106291059.

J. R. Quinlan. Induction of decision trees. *Machine learning*, 1(1):81–106, 1986.

N. J. Steiner, R. C. Sheldrick, D. Gotthelf, and E. C. Perrin. Computer-based attention training in the schools for children with attention deficit/hyperactivity disorder: a preliminary trial. *Clinical pediatrics*, 50(7):615–622, 2011. doi: https://doi.org/10.1177/0009922810397887.

N. J. Steiner, E. C. Frenette, K. M. Rene, R. T. Brennan, and E. C. Perrin. Neurofeedback and cognitive attention training for children with attention-deficit hyperactivity disorder in schools. *Journal of Developmental & Behavioral Pediatrics*, 35(1):18–27, 2014. doi: https://doi.org/10.1097/DBP.0000000000000009.

U. Strehl, P. Aggensteiner, D. Wachtlin, D. Brandeis, B. Albrecht, M. Arana, C. Bach, T. Banaschewski, T. Bogen, A. Flaig-Rohr, et al. Neurofeedback of slow cortical potentials in children with attention-deficit/hyperactivity disorder: A multicenter randomized trial controlling for unspecific effects. *Frontiers in human neuroscience*, 11, 2017. doi: https://doi.org/10.3389/fnhum.2017.00135.

R. Tibshirani. Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 267–288, 1996.

M. van Dongen-Boomsma, M. A. Vollebregt, D. Slaats-Willemse, and J. K. Buitelaar. A randomized placebo-controlled trial of electroencephalographic (eeg) neurofeedback in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*, 74(8): 821–827, 2013. doi: https://doi.org/10.4088/JCP.12m08321.