What influences the efficacy of NFB in ADHD?

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Abstract

Numerous trials and several meta-analysis have been published on the efficacy of Neurofeedback (NFB) applied to Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents with inconsistent findings. We decided to replicate the latest meta-analysis on that topic published in 2016, and by doing so, we benchmarked choices originally made by authors. Furthermore, we searched for new studies to add to the meta-analysis in order to update it. This job highlighted the heterogeneity of studies included in meta-analysis, which may question the reliability of the results. We thus extended the analysis with a novel method: the systematic analysis of biases (SAOB) that took advantage of studies technical and methodological high heterogeneity rather than suffering from it. The SAOB was performed on k = 31 studies and three different methods (a linear weighted, a linear allowing selection variable and a non-linear but hierarchical) were applied. The update of the most recent meta-analysis with two new publications confirmed the results originally obtained: effect sizes were significant when parents were raters (p-value = 0.0017) unlike when teachers (considered as probably blind) were (p-value = 0.14). However, when only selecting studies fitting with standard NFB protocols definition, significant improvements are observed on probably blind raters as well (p-value = 0.043, k = 4 studies). The SAOB identified 3 elements that might have an impact on NFB efficacy: first, a more intensive treatment was associated with higher efficacy, second, high-end EEG systems improved the effectiveness of NFB in ADHD, third, the person assessing the symptoms changes during trials had an impact on results: teachers seemed to score less improvement. In conclusion, more than replicating previous findings, we introduced here a new way to look into the heterogeneity of clinical trials.

keywords: ADHD, Neurofeedback, influencing factors, analysis of bias, linear regression, decision tree, meta-analysis.

1 Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common child psychiatric disorder characterized by impaired attention and/or hyperactivity/impulsivity, symptoms that may persist in adulthood with clinical significance, which makes ADHD a life-long problem for many patients [Faraone et al., 2006]. The prevalence of ADHD is about 5% in school-aged children yielding to an estimated 2.5 millions of children in Europe [The American Psychiatric Association, 2013]. ADHD has an impact on the children well being because many of them may have low self esteem [Shaw-Zirt et al., 2005] and underachieve at school [Barry et al., 2002] but parents are also affected by this situation [Harpin, 2005]. Besides ADHD has a financial impact: a survey of 2013 in the Netherlands estimated at between 9,860 and 14,483 the ADHD related costs per patient annually [Le et al., 2014].

The diagnosis of ADHD primarily relies on questionnaire-based clinical evaluation [The American Psychiatric Association, 2013], which can be supported with objective assessment metrics of executive function such as the Test of Variables of Attention (TOVA) [Forbes, 1998], the Continuous Performance Test (CPT) [Barkley, 1991] and the Sustained Attention to Response Task (SART) [Robertson et al., 1997]. At the opposite, objective markers of brain function using Electroencephalogram (EEG), functional Magnetic Resonance Imaging (fMRI), or Positron Emission Tomography (PET) could not successfully improve diagnosis (Neba) at the individual level but proved significantly heterogeneous on the population. More specifically, these studies allowed to identify specific neurophysiological phenotypes of ADHD: this was particularly reported with EEG recordings [Loo et al., 2017]. For instance, ADHD patients were found to show an increase in theta waves (4-8Hz) in the frontal area whereas there are less beta waves (12-32Hz) and Sensorimotor Rhythm (SMR) (13-15Hz) in the central area [Monastra, 2005; Matoušek et al., 1984; Janzen et al., 1995].

Among all existing treatments, the most widely used is psychostimulants, which have been proven to be efficacious [Taylor, 2014; Storebo et al., 2015]. However, the long-term effects when taking psychostimulants are not established [DuPaul, 1998; Swanson et al., 2001; Jensen, 1999]. Moreover, ADHD children under medication commonly suffer from side effects such as loss of appetite and sleep problems but no serious adverse events have been reported [Storebo et al., 2015; Cooper et al., 2011]. These drawbacks make some parents and clinicians reluctant to choose such medications, so they turn to drug-free treatment options such as dietary changes [Bélanger et al., 2009] and behavioral therapy, which have been proven in most of cases less efficient [Sonuga-Barke et al., 2013].

Neurofeedback (NFB) is a noninvasive technique that aims to reduce ADHD symptoms [Arns et al., 2015; Steffert and Steffert, 2010; Marzbani et al., 2016]. It is a self-paced brain neuromodulation technique that represents one's brain activity in real-time using auditory or visual modulations, on which learning paradigms can be applied such as operant conditioning [Reynolds, 1975] or voluntary control. To deliver this intervention, neurophysiological time series must be recorded and analyzed in real-time and implemented in serious games leveraging learning paradigms [Wang et al., 2010]. To that effect, recorded brain signals are analyzed to extract a real time representations of the activity of a population of neurons involved in attentional networks to which learning paradigms are applied, which is translated into a visual or auditory cues. The sensory feedback constitutes the rewards mechanism that promotes learning using a well-known operant conditioning protocol [Sherlin et al., 2011]. The operant conditioning principle will enable the child to repeat more and more easily this task [Skinner, 1961] and thanks to the natural neuronal plasticity, a neuronal reorganization is observed [Van Doren et al., 2017].

In case of ADHD, several NFB protocols have been proposed and investigated to decrease the symptoms:

- protocols based on frequency band training: a child can be asked to enhance his SMR while suppressing theta or beta [Lubar and Shouse, 1976], or he can have to enhance beta while suppressing theta (this scenario is known as Theta Beta Ratio (TBR)) [Arns et al., 2013];
- protocol based on the Slow Cortical Potentials (SCPs) training which consists in the regulation of cortical excitation thresholds by focusing on activity generated by external cues (similar to Event-Related Potentials (ERPs)) [Heinrich et al., 2004; Banaschewski and Brandeis, 2007];
- protocol based on ERPs (P300) [Fouillen et al., 2017]: children have to focus on external cues leading to a reduced P300 amplitude so it can be considered as a specific neurophysiological marker of selective attention.

Shortly after the discovery of the brain's electric activity by Berger [1929], Durup and Fessard [1935] proved it could be voluntarily modulated. The first indication of its therapeutic potential came forty years later when Sterman et al. [1974] serendipitously found the training of SMR activity to reduce the incidence of epileptic crisis in kerozen-exposed cats. The technique, then known as NFB quickly became investigated in various fields of neuropsychiatry including, most notably, ADHD and resulting in a relatively large body of scientific literature [Lubar and Shouse, 1976; Rossiter and La Vaque, 1995; Linden et al., 1996; Maurizio et al., 2014]. Subsequently, its efficacy on the core symptoms of ADHD (inattention, hyperactivity and impulsivity) has been subject to several meta-analytic studies [Loo and Barkley, 2005; Lofthouse et al., 2012; Arns et al., 2009; Micoulaud-Franchi et al., 2014; Sonuga-Barke et al., 2013].

The most recent meta-analysis solely on the efficacy of NFB has been conducted by Cortese et al. [2016] where 13 studies are included. Although only Randomized Controlled Trials (RCTs) were selected, the authors of this meta-analysis made some choices that have been debated by the community in particular by Micoulaud-Franchi et al. [2016] who criticized the use of an uncommon behavioral scale provided by Steiner et al. [2014] for the teachers' assessments and the inclusion of a pilot study carried out by Arnold et al. [2014] in the meta-analysis.

Because of the publication of new RCTs meeting Cortese et al.'s inclusion criteria, it was decided to update his work and take the opportunity to investigate some choices that later proved controversial. Eventually, we extended the analysis with a novel method we introduced: the Systematic Analysis of Biases (SAOB) that takes advantage of studies technical and methodological high heterogeneity rather than suffering from it. Indeed, the NFB domain is characterized by a clinical literature that is tremendously heterogeneous: studies differ on a methodological point of view (randomization and presence of a blind assessor for instance), but also on the NFB implementation (number of sessions, session and treatment length and type of protocol for instance) and on the acquisition and pre-processing of the EEG. Since we supposed that the methodological and technical choices made by authors may lead to various NFB results, we propose here to identify which of the factors independently influence the reported Effect Size (ES) thanks to adequate statistical tools.

2 Materials and Methods

2.1 Studies selection

Search terms described in Supplemental Material were entered in Pubmed and studies included in previous meta-analysis were identified. Among these studies, those that satisfied each of these points were selected:

- studies have to assess NFB efficacy;
- subjects must be diagnosed ADHD based on DSM-IV [The American Psychiatric Association, 2000], DSM-V [The American Psychiatric Association, 2013], ICD-10 [World Health Organization, 1993] criteria or according to an expert psychiatrist;
- studies have to be written in English, German or French;
- studies have to include at least 8 subjects in each group;
- subjects must be younger than 25 years old;
- studies have to provide enough data to compute required metrics for the following analysis.

The studies satisfying all these points were included in the SAOB. To replicate and update Cortese et al.'s meta-analysis, we then applied the inclusion criteria of this meta-analysis to the selected studies.

2.2 Outcome definition

In included studies, the severity of ADHD symptoms have been assessed by parents and, when available, by teachers. Cortese et al. [2016] and Micoulaud-Franchi et al. [2014] defined parents as Most Proximal (MPROX) raters who were not blind to the treatment of their child, as opposed to teachers who were considered as Probably Blind (PBLIND) raters. This distinction is meant to assess the amplitude of the placebo effect where it is hypothesized that teachers who are presumed more blind to the intervention are less influenced in their assessment by their perception of it. Efficacy of NFB was given for the following outcomes on clinical scales when available: inattention, hyperactivity/impulsivity and total scores. The factors analysis was performed using the total score only.

2.3 Meta-analysis

Meta-analysis is typically used to aggregate results from different clinical investigations and offer a consolidated state of evidence. To aggregate results from different studies, it is necessary to assume some level of homogeneity in their design relative to the inclusion criteria, the specificity intervention, the presence and the type of control (active, semi-active or non-active). Because studies occasionally use slight variations of a clinical scales and because of the clinical heterogeneity of patients and control, the scores are standardized before being pooled. The between ES is one of such standardized metrics, which we implemented in this paper as described in the Supplemental Materials. The work was carried with an open-source Python package developed for this work that offers a more transparent approach to the choice or parameters and increases replicability. This package was benchmark against RevMan v5.3 [Cochrane Collaboration, 2011] by replicating Cortese et al. [2016]'s work and obtaining the same results. The code is made fully available on a GitHub repository [Bussalb, 2018] including raw data for everyone to review its implementation, update it, or use it for their own projects.

Before updating the Cortese et al. [2016]'s work with recently published studies fitting with their inclusion criteria [Strehl et al., 2017; Baumeister et al., 2016], we decided to run a sensitivity analysis investigating choices that later proved controversial [Micoulaud-Franchi et al., 2016]. Altogether, the changes investigated in our update included the following:

- the ES of Arnold et al.'s study was computed from the post-test clinical values taken after the completion of the 40 sessions at the opposite of Cortese et al. [2016]'s report which used the results after 12 sessions of NFB because the end point values were not available;

- the ES computed from teachers' assessments reported by Steiner et al. [2014] relied on the BOSS Classroom Observation [Shapiro, 2010]. This was an atypical scale to quantify ADHD symptoms since the ADHD-Rating scale [Pappas, 2006] or the Conners Rating Scale Revised [Conners et al., 1998] [Christiansen et al., 2014; Bluschke et al., 2016] whose metrics were well-defined [Collett et al., 2003; Epstein and Weiss, 2012], were more often used. Thus, we decided to compute the ES based on the results from the Conners-3, which was used in this study to compute the ES for the parents' ratings.

As initially suggested, we performed two subgroups analysis with the two choices described above: the Summary Effect (SE), the weighted average of all the ES, was calculated first with only studies following standard protocol as defined by Arns et al. [2014] and in a second time with studies whose participants took low-dose or no medication during the trial.

2.4 Detect factors influencing the Neurofeedback

While revisiting the work carried on meta-analysis, it became apparent that the studies pooled together where highly heterogeneous in terms of methodological and practical implementation as pointed out by Alkoby et al. [2017]. For instance, all NFB interventions were pooled together irrelevant to the quality of the acquisition, the level excreted on real time data quality, and the trained neuromarker. Likewise, the methodological implementations varied significantly, requiring the 'subgroup' analysis (low drug, standard protocols) that are somewhat arbitrary. To circumvent these limitations, we implemented a novel approach: the SAOB. In this setting, the within-ES of each intervention was considered as a dependent variable that methodological and technical biases tried to explain using standard statistical tools. The results of such analysis should enable us to identify known methodological biases (e.g. blind assessments negatively associated with ES) and possibly technical factors (e.g. a good control on real time data quality influences positively the treatment outcome).

2.4.1 Identify and pre-process factors

We classified the factors influencing the efficacy of NFB in 5 categories: methodological, technical, characteristics of the included populations, representative of the quality of acquisition and of the signal. Factors were chosen based on what was typically reported in the literature and presumed to influence ES and categorized as follow:

- *the signal quality*: correction for the presence of ocular artifacts and correction for artifacts based on amplitude;

- *the population*: the psychostimulants intake during NFB treatment and the age bounds of children;
- *the methodological biases*: the presence of a control group, the blinding of assessors, the randomization of subjects, and the approval of the study by an Institutional Review Board (IRB);
- *the NFB implementation*: the protocol used (SCP, SMR, theta up, beta up in central areas, theta down), the presence of a transfer phase during NFB training, the possibility to train at home or at school with a transfer card reminding of the NFB session, the type of thresholding reward, the number of NFB sessions, the sessions frequency during a week, the session length and the treatment length;
- *the acquisition quality*: the presence of one or more active electrodes and the EEG quality. This last factor was an indicator between 1 and 3: if EEG was recorded and processed in poor conditions then the indicator was 1. Besides, if the article did not mention the recording conditions, the factor was set to 1. To get an indicator bigger than 1, several points had to be satisfied:
  - *the type of electrodes used*: Silver Chloride (AgCl)/Gel and Gold (Au)/Gel;
  - *a check of electrode contacts quality trough the amplifier impedance acquisition mode*: inter-electrode impedance should have to be smaller than $40k\Omega$;
  - *the type of amplifier used*: those that were in accordance with European standards (such as Thera Prax®, by NeuroConn©, Germany NeuroCare and Eemagine©, Germany Eemagine) were preferable or whose reliability is known.

  If at least one point was checked, the quality was set to 2. To get an indicator of 3, all these criteria had to be satisfied.

We provided in the Github repository [Bussalb, 2018] the raw data extracted from the publications. To prevent any bias, the names of these factors were hidden during the entire analysis so that the data scientist (AB) was fully blind to them. The variable names were only revealed once the data analysis and results were accepted as valid: this included choice of variable normalization and validation of model hypothesis as detailed below.

The pre-processing of factors for the analysis included the following steps: factors for which there were too many missing observations, arbitrarily set to more than 20% of the total of observations, were removed from the analysis. Furthermore, if a factor had more than 80% similar observations it was removed as well. Categorical variables were coded as dummies meaning that the presence of the factor was represented by a 1 and its absence by 0. All variables were standardized, except when the decision tree was performed.

2.4.2 Associate independent factors to effect sizes

To compute this ES, means of total ADHD scores given by parents and teachers were used. Besides, in case studies provided results for more than one behavioral scale, ES were computed for each one as

$$\text{ES} = \frac{M_{\text{post},T} - M_{\text{pre},T}}{\sqrt{\frac{\sigma^2_{\text{pre},T} + \sigma^2_{\text{post},T}}{2}}},$$

where $M_{t,T}$ is the mean of clinical scale taken at time t (pre-test or post-test) and for treatment T and σ similarly represents its standard deviation.

The ES computed in this analysis was different from the one used previously for the replication and updating of Cortese et al. [2016]. Indeed, here we focused on the effect of the treatment within a group as defined by Cohen [1988], definition of the ES that was already used in the literature [Arns et al., 2009; Maurizio et al., 2014; Strehl et al., 2017]. This ES enables to quantify the efficacy of NFB inside the treatment group

The ES was then considered as a dependent variable to be explained by the factors (the independent variables) identified using the following three methods, which were implemented in the Scikit-Learn Python [Pedregosa et al., 2011, 0.18.1] and the Statsmodels Python [Seabold and Perktold, 2010, 0.8.0] libraries:

- 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].

The most often used linear regression analysis is the Ordinary Least Squares (OLS) but here we applied the WLS: a weight was assigned to each observation in order to take into account the fact that some observations came from the same study because studies may provide several scales. Besides, the weight was a function of the sample size as well: due to their different sample sizes, studies were not equivalent and should be analyzed accordingly. That's why the weight corresponded to the ratio between the experiment group's sample size of the study and the number of behavioral scales available in the study. We also ran the analysis with OLS method to assess the impact of the weights on the results.

The aim of the WLS was to estimate the regression coefficients. A significant coefficient (meaning significantly different from 0) indicated that the associated factor had probably an influence on NFB efficacy and the sign of the coefficient indicated the direction of the effect.

The second linear method applied was the LASSO, that naturally incorporates variable selection in the linear model thanks to $\ell - 1$-norm applied on the coefficients. A coefficient not set at zero means that the associated factor may have had an influence on NFB and once again, the sign of the coefficient indicated the direction of the effect.

Eventually, the last method used to determine factors influencing NFB was the decision tree [Quinlan, 1986], a hierarchical and non linear method. It braked down a dataset into smaller and smaller subsets using at each iteration a variable and a threshold chosen to optimize a simple Mean Square Error (MSE) criteria [James et al., 2013]. A tree is composed of several nodes and leafs, the importance of which is decreasing from the top node called root node.

These methods are intrinsically different from each others, so we compared their results. They are more precisely described in the Supplemental Material.

3 Results

3.1 Studies selected

Search terms entered in Pubmed returned 152 results during the last check on December 14, 2017 and 28 articles included in previous meta-analysis on NFB were identified. After the selection process illustrated in fig. 1, 31 studies were included in the SAOB and 15 in the meta-analysis as summarized in table 1. The 31 studies selected for the SAOB followed the Cortese et al.'s criteria to the exception of the control group point. Indeed, since we computed the effect size within the NFB group, we did not need a control group.

3.2 Perform the meta-analysis

The Python module created in order to perform a meta-analysis was successfully validated as describes in the Supplemental Materials and made available online. So all the following results were computed with the Python code.

The replication and the update of Cortese et al.'s study was conducted by applying the choices described in the Materials and Methods part and the results obtained are presented in table 2:

- when computing the ES for Arnold et al. [2014] with the values after 40 sessions of NFB, we found smaller ES than Cortese et al. [2016];
- when relying on the teachers' ratings from the Conners-3 to compute the ES of Steiner et al. [2014], we found higher SE in attention but not in total and hyperactivity. Moreover, this different choice of scale did not affect the significance of the SEs.

The next step consisted in extend Cortese et al. meta-analysis by adding the two new articles [Strehl et al., 2017; Baumeister et al., 2016] found during the systematic review. Baumeister et al. [2016] provided results only for parents total outcome whereas Strehl et al. [2017] gave teachers and parents' assessments for all outcomes. In spite of favorable results for NFB, particularly on parents' assessments, adding these two new studies did not change either the magnitude or the significance of the SE for any outcome whatever the raters as illustrated in fig. 2.

We then ran the analysis on two specific subgroups: one gathering studies following the standard protocol defined by Arns et al. [2014] and a second one only studies including participants without drug during the clinical trial.

Regarding the standard protocol subgroup, Cortese et al. [2016] found all the outcomes significant except for the hyperactivity symptoms rated by teachers (p-value = 0.11). However, when adding [Strehl et al., 2017] results, we found no significance for the inattention symptoms assessed by teachers as well (p-value = 0.11). The SE for the total outcome assessed by teachers remained significant even with the addition of the two new RCTs (p-value = 0.043).

As for the no drug subgroup, SEs were not significant except for the inattention symptoms assessed by parents (p-value = 0.013). Besides, the differences in Arnold et al. [2014] values caused a loss of significance in hyperactivity outcome for parents (p-value = 0.066) compared to Cortese et al. [2016] (p-value = 0.016). The two new studies were not included in this subgroup because subjects were taking psychostimulants during the trial.

All the scales used to compute the ES following our choices are summarized in the Supplemental Materials.

3.3 Detect factors influencing the Neurofeedback

The analysis was performed on 31 trials assessing the efficacy of NFB as presented in table 1. Among the 25 factors selected, 6 were removed for too many missing or too homogeneous observations:

beta up in frontal areas, the use of a transfer card, the type of threshold for the rewards (incremental or fixed), the EEG quality equal to 3 and the presence of a control group.

The ES within subjects was computed for all available clinical scales of each study and then factors were associated with the computed ES thanks to three different methods: the WLS, the LASSO and the decision tree. The global results were presented in table 3, which highlighted the fact that the techniques used did not select similar factors. Thus, the more methods identified a factor, the more confident we could be in the results.

With the WLS, we found that 8 factors were significantly different from zero for an adjusted R-squared of 0.74. When applying the OLS, the same factors were significant except the transfer phase, the protocol theta down and the artifact correction based on amplitude with an adjusted R-squared of 0.42. The LASSO regression selected significant factors by setting to 0 the factors that did not explain the model, here 12 factors better predicted the model. With these two methods, a negative coefficient meant that the factor was in favor of the NFB.

Eventually, the decision tree presented in fig. 3 split the dataset based on the factor leading to the smallest MSE. The best predictor was the one at the top of the tree: in our case it was the PBLIND. Five other factors also split the subsets, however, the lower we got into the tree, the less samples were available, so results were less and less reliable.

Several factors were common to the three methods we used, in particular the treatment length, the assessment by a blind rater and EEG quality of 2 that were all three returned by the three methods. Besides, the methods agreed on the direction of the influence of these factors. So, a shorter treatment and recording the EEG with a good system seemed preferable, whereas teachers' assessment appeared less favorable.

It was more difficult to interpret the influence of the factors returned by only one or two methods. Indeed, it was not clear if they were selected due to an imprecision of the method or if they really had an impact on NFB efficacy. For instance, both WLS and LASSO found that relying on the amplitude of the signal to correct artifacts, and including a transfer phase seemed not to improve ADHD symptoms. Conversely, the IRB approval, a theta down protocol, and a high number of sessions per week appeared to positively influence the results. The decision tree and LASSO had in common the protocol SMR: it was associated with lower ES. Five factors were returned by only one of the methods: the minimal age of the children, being on drugs during NFB treatment, randomizing the groups and the SCPs protocol. So it was complicated to conclude if they had an influence or not on the NFB efficacy.

Eventually, five factors were selected by no method: the correction for the ocular artifact, the children maximum age, the number of sessions, the protocol beta up in central areas and the presence of more than one active electrode. Thus, these factors appeared not to have an influence on NFB efficacy.

4 Discussion

4.1 Perform the meta-analysis

In the meta-analysis performed here, we challenged some choices made by Cortese et al., which proved controversial: the computation of ES based on an unusual scale [Steiner et al., 2014] and the inclusion of a pilot study [Arnold et al., 2014] whose end point values were not available at the time Cortese et al. conducted his meta-analysis. We review here the list of changes, their justification, and their impact on the analysis.

First, relying on the Conners-3 [Conners, 2008] instead of the BOSS Classroom Observation [Shapiro, 2010] for teachers ratings seemed preferable because this scale is more often used [Christiansen et al., 2014; Bluschke et al., 2016] and is the revision of the Conners Rating Scale Revised [Conners et al., 1998] whose reliability has been studied [Collett et al., 2003]. However, relying on one or the other scale did not change the significance of the ES whatever the outcome studied.

Second, to compute the ES of Arnold et al. [2014] we used the values at post-test that is to say when all sessions were completed. Some studies suggested that the number of sessions positively correlates with the changes in the EEG [Vernon et al., 2004] so a lower number of sessions would lead to artificially smaller ES. Here, the ES computed with the values at post test of Arnold et al. [2014] were smaller than those obtained after 12 sessions but these differences did not lead to a change of significance of the SE.

To conclude on that meta-analysis, though some points from the original were controversial and the fact that - for the reasons mentioned earlier - different choices could reasonably be made, it turned out that the impact on the meta-analysis results were minimal and did not change the statistical significance of any outcome. Consequently, the completion of the meta-analysis with studies published since the publication of his work were done with the choices:

- to compute the ES of Arnold et al. [2014] the end point values at were used;
- the scores reported by teachers on the Conners-3 in Steiner et al.'s study were taken into account instead of these of the BOSS Classroom Observation.

The addition of the two new studies [Strehl et al., 2017; Baumeister et al., 2016] further confirmed original results. Indeed, the significance did not change for any outcome: SE found remained significant for MPROX raters and non-significant for PBLIND.

Adding two more studies increased the significance of the sensitivity analysis ran by Cortese et al., most interestingly, the SE from the subset of studies corresponding to NFB standard protocols as defined by Arns et al. [2014]. While Cortese et al. found that this subset tended to perform better, particularly on the PBLIND outcome, adding two studies confirmed this result on the total clinical score (p-value < 0.05). Despite the obvious heterogeneity of the studies included in this subset (particularly in terms of protocol used), this result suggests a positive relation between the features of this *standard* design and NFB performance.

Eventually, concerning the raters, we considered teachers as PBLIND raters as Cortese et al. and Micoulaud-Franchi et al. did although they may be aware of the treatment followed thanks to the parents. Besides, the amplitude of the clinical scale at baseline suggested that teachers did not capture the full picture of the condition or saw it differently and were therefore less likely to see a change (prone to type II error) [Sollie et al., 2013; Narad et al., 2015; Minder et al., 2018]. So using PBLIND as an estimate for placebo amplitude assessment might be wrong.

Along with this article, the Python code and raw data are provided in order to facilitate a potential replication of this work (available on the GitHub repository).

4.2 Identify factors influencing the Neurofeedback

Description and analysis of NFB implementation was subject to several studies [Arns et al., 2014; Enriquez-Geppert et al., 2017; Vernon et al., 2004; Jeunet et al., 2018] but to our knowledge none used statistical tools to detect the influence of methodological, clinical and technical factors on such a wide range of studies.

A somewhat puzzling result was the fact that the three methods which offered to identify factors contributing to the NFB performance did not lead to the exact same results. These discrepancies were clearly explained by the varying hypothesis of these models and actually offered interesting insight into the results and their significance. For instance, the decision tree method was non linear and accounted for variables interaction which was not the case for the two others methods. Moreover, the decision tree was more unstable [Dwyer and Holte, 2007], meaning that a small change in the data could cause an important change in the structure of the optimal decision tree.

Surprisingly, the number of sessions was not found as a significant influencing factor by any method, which was somewhat in contradiction with existing literature. For instance, Enriquez-Geppert et al. [2017] insisted on the fact that the number of sessions should be chosen carefully to avoid "overtraining". Moreover, Arns et al. [2014] stated that performing less than 20 NFB sessions led to smaller effects. Indeed Vernon et al. [2004] observed that positive changes in the EEG and behavioral performance occurred after a minimum of 20 sessions, but he also pointed out the fact that the location of the NFB training may had an important influence. Nevertheless, a recent study investigated that last point by performing NFB at school or at the clinic [Minder et al., 2018] and they found that the setting has no significant impact on treatment response. The number of sessions found as a non-significant factor might be explained by the fact that, in the trials included in the SAOB, only one proposed less than 20 sessions. So maybe the efficacy threshold was reached and adding sessions above it might not lead to significant symptoms improvement. However, regardless of the significance of the number of sessions, the coefficient found by the WLS was negative, meaning that as expected, the more sessions performed the more efficient the NFB seemed to be.

The type of protocol was not identified by all the three methods but it seemed to influence the NFB results according to 2 methods, in particular the theta down protocol that appeared more efficient and SMR protocol that conversely seemed associated with lower ES. We expected more precised results on the protocols criteria because this point is central in NFB as pointed out by Vernon et al. [2004]. A possible explanation was that all these protocols were equally efficacious to the populations they were offered to and thereby did not constitute a significant explanatory factor. This result, however, did not preclude a combined and personalized strategy (offer the right protocol to the right kid) to further improve performance as mentioned by Alkoby et al. [2017].

Nevertheless, despite the differences between the methods, several factors were selected by at least two methods and among them 3 were consistently identified by all the methods with the same direction of influence: if the rater was probably blind to the treatment, the treatment length, and the EEG quality.

First, this analysis pointed out the fact that recording EEG in good conditions seemed to lead to better results, which could be explained by the fact that better signal quality enabled to extract more correctly the EEG patterns linked to ADHD and henceforth led to better learning and therapeutic efficacy. However, it remained difficult to really assess the quality of the hardware because little information was provided in the studies.

Next, it appeared here that the longer the treatment the less efficient it became. Arguably, the treatment length was a proxy for treatment intensity, which meant that a treatment that was short in length (and consequently intense in pace) was more likely to succeed. This hypothesis was back-up by the fact that the variable *session pace* (number of sessions per week) was also associated with larger ES according to the WLS and LASSO. Impact of the intensity of treatment have been investigated by [Rogala et al., 2016] on healthy adults: it was observed that studies with at least four training sessions completed on consecutive days were all successful.

As expected, the assessment of symptoms by non-blind raters led to more favorable results than by PBLIND raters - result in compliance with several meta-analysis [Cortese et al., 2016; Micoulaud-Franchi et al., 2014].

We decided to investigate more precisely this factor, in order to determine if this observation could be solely explained by the placebo effect. First, to assess the impact of the placebo effect, we relied on the results of the decision tree presented in fig. 3 that split the dataset in two subsets: on one hand 43 observations corresponding to MPROX raters assessments and on the other hand 19 observations corresponding to PBLIND. If the differences observed between PBLIND and MPROX raters were due to the placebo effect, we could expect to find in the MPROX part of the decision tree factors linked to the perception of the treatment. It was, indeed the case: session and treatment length were returned but if these factors were really linked to the placebo effect, we could expect that the longer the session and the treatment, the higher the ES. Yet, we observed the opposite: it was not in favor of the presence of the placebo effect.

Another way to highlight a possible placebo effect, was to focus on the difference between PBLIND and MPROX raters first at pre-test and then at post-test. The differences of ratings between teachers and parents have been prone to different studies [Sollie et al., 2013; Narad et al., 2015; Minder et al., 2018] that noted that teachers were more susceptible to give lower scores especially on younger children. We also observed that fact on most of the studies included in our analysis as illustrated in fig. 4.

Thus, these results suggested that PBLIND assessments could hardly be used to assess placebo effect as they seemed to be more blind to symptoms rather than to intervention. Besides, we noticed that there was more variability in teachers' scores compared to parents', which could partly explained the lower ES obtained for PBLIND raters. In the absence of ethically and technically feasible sham NFB protocols [World Medical Association, 2000], it seemed preferable that evidence of control, learning, and specific changes (correlation with symptoms) were used to determine the mode of action further (neuromarker analysis).

It would have been interesting to study the influence of some other factors such as the delay between brain state and feedback signal as well as the type of NFB metaphor and feedback used as pointed out by Alkoby et al. [2017], but these information were rarely available in studies. Besides, to add more reliability to these results it should be preferable to add more studies, particularly studies with teachers assessments (considered as PBLIND).

5 Conclusion

This work offers an open source tool for running meta-analysis and SAOB: the code and data used are available, assuring the transparency and replicability of these analysis.

The results of the first part of the work confirm Cortese et al. [2016]'s findings in the light of recent published clinical work. In particular, studies following a standard protocol as defined by Arns et al. [2014] show significant improvements on PBLIND raters ($k = 4$ studies instead of 3 Cortese et al. [2016]).

Besides this meta-analysis, we propose here a new method for tackling the heterogeneity of clinical data on NFB. This method aims at identify factors as positively or negatively contributing to NFB efficacy.

Among the probable influencing factors, one of them is linked to the quality of acquisition of the EEG. This result indirectly confirms a mode of action through specific EEG training. Likewise, treatment intensity corroborates what is known of learning theory (memory consolidation) [Mowrer, 1960] and indirectly validates it as part of the mode of action. Eventually, our results show that therapeutic efficacy measured by teachers is reduced compared to parents. However, this result does not seem to be fully explained by the placebo effect. To estimate the placebo effect, it may be preferable to compare NFB to some biofeedback (for instance Electromyogram (EMG)-biofeedback). However in Europe, since an efficient treatment exists for ADHD, comparing NFB to sham-NFB raises an ethical problem, so implementing a single blind study is complex.

These elements converge to the conclusion that existing methodologies traditionally used to assess pills seem not adapted to the evaluation of medical devices. Consequently, NFB is probably efficacious and the risk/benefit ratio is certainly in favor of its use as the clinical evidence stands today.

6 Conflict of Interest Statement

Four authors, A. Bussalb, PhD student, Q. Barthelemy, D. Ojeda, PhD and L. Mayaud, PhD of this publication work for Mensia Technologies, which is developing products related to the research being reported. An other author, M. Congedo, PhD, served as an advisor for Mensia Technologies when this work was conducted.

7 Author Contributions

A.B. extracted all data from articles and performed the analysis, M.C. provided useful advice concerning statistics and methods used, R.D. and E.A. followed closely the evolution of the work and provided good ideas especially on the clinical level. Q.B. and D.O. gave useful ideas to optimally apply methods used in the SAOB and helped in the interpretation of the results. L.M. oversaw all this work.

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Figure captions

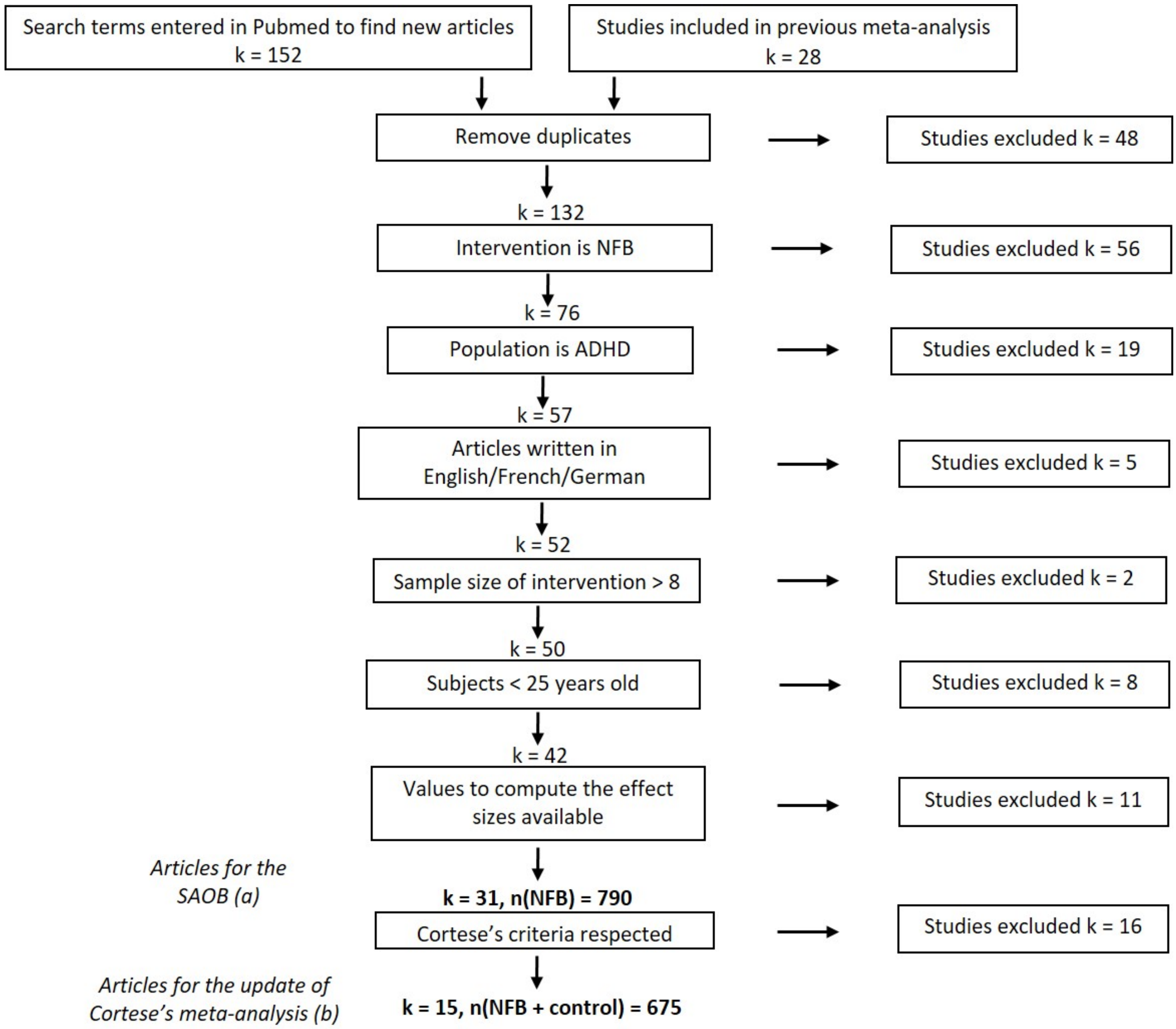

Figure 1: Flow diagram of selection of studies (last search on December 14, 2017). The subset (a) corresponds to the Cortese et al.'s inclusion criteria without the requirement for the presence of a control group. The number of patients is only equal to the subjects in the NFB groups. The subset (b) exactly corresponds to the studies included in Cortese et al. [2016] and more recent work meeting the same criteria. Here, the number of patients includes all patients whatever their treatment group.

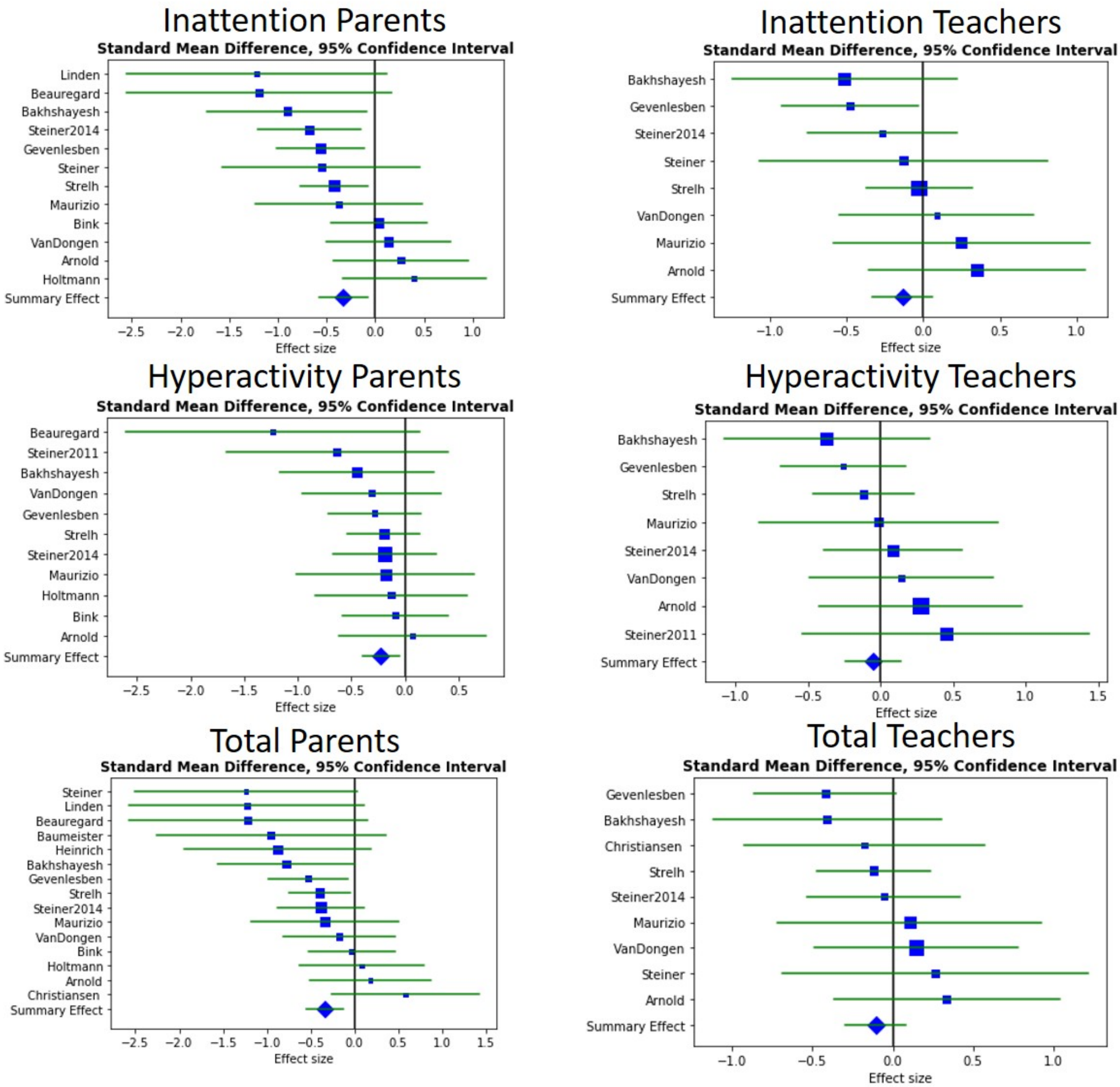

Figure 2: Forest plots obtained on the dataset "Update meta-analysis" with the Python code. The ES presented here correspond to the between subject effect size. A negative ES is in favor of NFB. The blue squares correspond to the ES, the blue diamond to the SE and the green line to the 95% confidence interval.

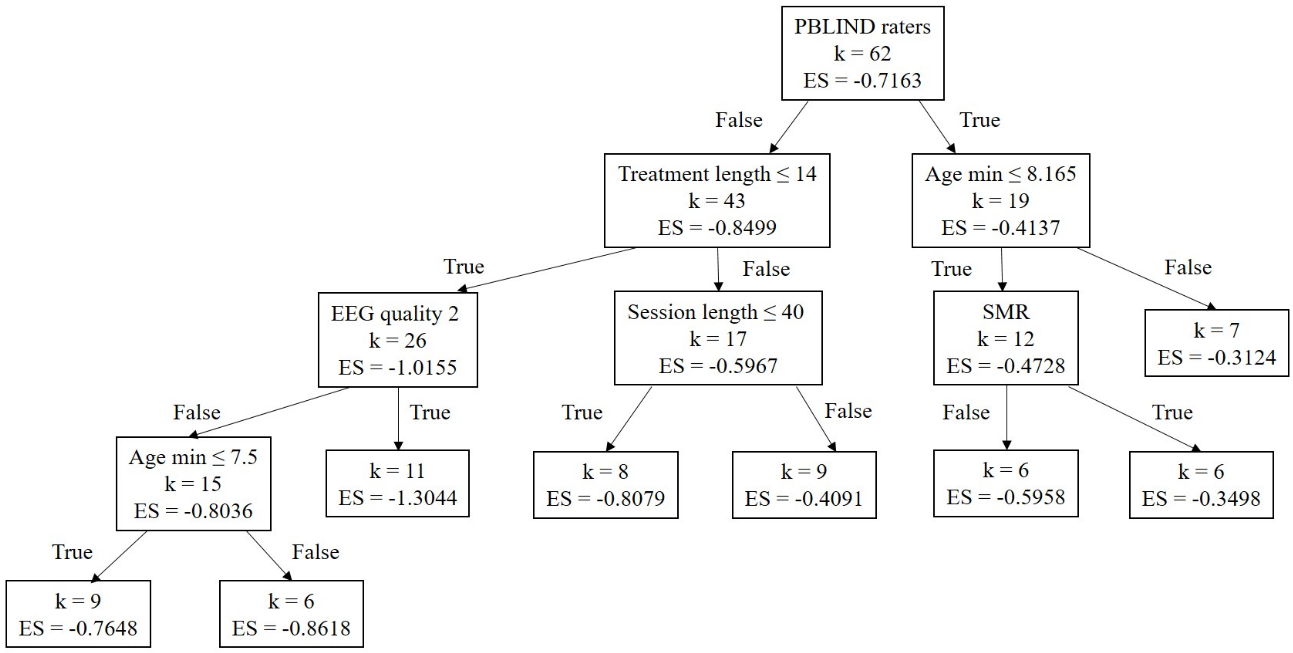

Figure 3: Decision Tree obtained: ES corresponds to the within subject effect size and k to the number of studies. The criteria to minimize was the MSE. The importance of nodes and leafs is decreasing from the root node.

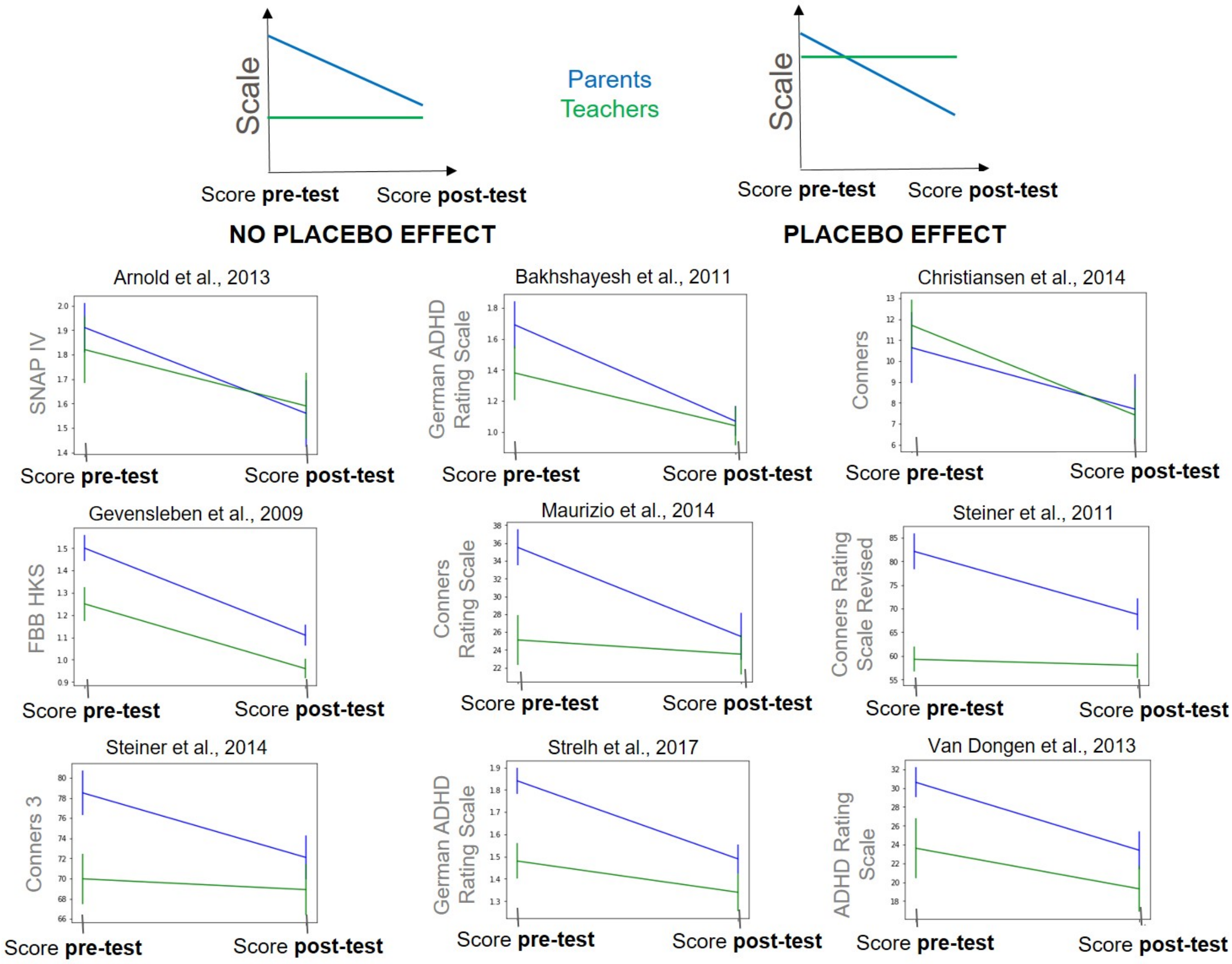

Figure 4: Pre-test and post-test scores ($\pm$ standard error) given by Parents (MPROX) in blue and teachers (PBLIND) in green. Two configurations: **(A)** teachers don't see the symptoms at pre-test so they can't see any improvement at post-test, **(B)** teachers see the symptoms at pre-test and don't see any improvement at post-test. **(C)** Evolution of parents and teachers' scores between pre and post-test on studies that satisfy Cortese et al.'s inclusion criteria and that provide teachers and parents scores on the same scale.

Table captions

Table 1: List of all studies included in the three different analysis. [a] Studies originally included in Cortese et al. [2016] (search on August 30, 2015), [b] studies satisfying Cortese et al. [2016]'s criteria (search on December 14, 2017), [c] studies satisfying Cortese et al. [2016]'s criteria to the exception of the part relative to the control group (search on December 14, 2017).

Dataset		Study	Year	Size of the NFB group
		Arnold et al.	2014	26
		Bakhshayesh et al.	2011	18
		Beauregard and Levesque	2006	15
		Bink et al.	2014	45
		Christiansen et al.	2014	14
		Gevensleben et al.	2009	59
		Heinrich et al.	2004	13
		Holtmann et al.	2009	20
		Linden et al.	1996	9
		Maurizio et al.	2014	13
		Steiner et al.	2011	9
		Steiner et al.	2014	34
		van Dongen-Boomsma et al.	2013	22
	Replicate Cortese et al.[a]	13 studies		297
		Baumeister et al.	2016	8
		Strehl et al.	2017	72
Update Cortese et al.[b]		15 studies		377
		Bluschke et al.	2016	19
		Deilami et al.	2016	12
		Drechsler et al.	2007	17
		Duric et al.	2012	23
		Escolano et al.	2014	20
		Fuchs et al.	2003	22
		Kropotov et al.	2005	86
		Lee and Jung	2017	18
		Leins et al.	2007	19
		Li et al.	2013	32
		Meisel et al.	2014	12
		Mohagheghi et al.	2017	30
		Mohammadi et al.	2015	16
		Monastra et al.	2002	51
		Ogrim and Hestad	2013	13
		Strehl et al.	2006	23
SAOB[c]		31 studies		790

Table 2: Comparison between Cortese et al. [2016] results obtained with RevMan [Cochrane Collaboration, 2011] and those obtained with the Python code with our choices applied ([a] post-test values for Arnold et al. are obtained after 40 sessions of NFB and Conners scale is used for Steiner et al. teachers' outcomes). SEs and their corresponding p-value (in parenthesis) are presented. With the Python program, a negative SE is in favor of NFB unlike Cortese et al..

Working hsypothesis		Same as Cortese et al. [2016]	Our choices[a]
	Total	0.35 (0.004)	-0.32 (0.013)
Parents	Inattention	0.36 (0.009)	-0.31 (0.036)
	Hyperactivity	0.26 (0.004)	-0.24 (0.02)
	Total	0.15 (0.20)	-0.11 (0.37)
Teachers	Inattention	0.06 (0.70)	-0.17 (0.16)
	Hyperactivity	0.17 (0.13)	-0.022 (0.85)

Table 3: Results of the WLS, LASSO and decision tree. For the WLS, a p-value < 0.05 (in bold) means that the coefficient of the corresponding factor is significantly different from 0. For the LASSO, factors not set to 0 (in bold) are selected. For the decision tree, the place of the factor in the tree is precised. When the value of the coefficient is negative, the corresponding factor may lead to better NFB results.

Independent variables (factors)		Coefficients found by WLS (p-value)	Coefficients found by LASSO	Place on the Decision Tree
Signal quality	Electro-Oculogram (EOG) correction	-0.078 (0.42)	0.00	/
	artifact correction based on amplitude	**0.15(0.040)**	**0.049**	/
Methodological	PBLIND	**0.10 (0.043)**	**0.11**	**root node**
	randomization	0.0069 (0.92)	**0.033**	/
	IRB	**-0.29 (0.00)**	**-0.15**	/
Population	age max	-0.090 (0.16)	0.00	/
	age min	-0.055 (0.37)	0.00	**2nd and 4th nodes**
	on drugs	0.069 (0.42)	**0.033**	/
NFB implementation	number of sessions	-0.0075 (0.92)	0.00	/
	session length	0.17 (0.17)	0.00	**3rd node**
	treatment length	**0.57 (0.00)**	**0.34**	**2nd node**
	session pace	**-0.25 (0.00)**	**-0.14**	/
	SMR	-0.063 (0.41)	**0.063**	**3rd node**
	beta up central	-0.027 (0.72)	0.00	/
	theta down	**-0.29 (0.014)**	**-0.055**	/
	SCP	-0.099 (0.50)	**0.10**	/
	transfer phase	**0.27 (0.032)**	**0.12**	/
Quality of acquisition	more than one active electrode	0.064 (0.37)	0.00	/
	EEG quality 2	**-0.36 (0.00)**	**-0.24**	**3rd node**