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Neurofeedback for Attention Deficit Disorder in preschoolers (NeFAP): A randomized, sham-controlled, efficacy study protocol of a novel non-pharmacological therapy

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Abstract:

Introduction: *Attention Deficit Hyperactivity Disorder (ADHD) is an impairing condition that widely affects a child's life. Current treatment guidelines for preschool-aged children suggest prescribing evidence-based parent or teacher-administered behavior therapy (BT) as the first line of treatment. Psychostimulants can be prescribed for non-respondents and moderate-to-severe cases, but they have side effects. Alternative therapy is neurofeedback, which has already shown effectiveness in the older children population but not in preschoolers. Objective: To evaluate if neurofeedback associated with behavioral therapy is superior in efficacy compared to sham neurofeedback plus behavioral therapy for treating newly diagnosed ADHD in preschoolers.*

Methods: *This will be a multicenter, randomized, single-blinded, parallel-group, superiority phase III study including 274 patients in five sites. Participants are children aged 4 to 6 years old with a confirmed diagnosis of moderate-severe ADHD by a treating physician. Both groups will receive 48 neurofeedback or sham sessions in 24 weeks plus BT, with 6-month follow-up up to 36 months. The primary outcome is the improvement of ADHD symptoms measured by the ADHD Rating Scale-IV (ADHD-RS-IV). After six months, participants will be allowed to use medication if needed. Therefore, one of our secondary endpoints will be time-to-medication. Two hundred seventy-four participants will be enrolled.*

Discussion: *The NeFAP study is an innovative study of NF to treat symptoms of ADHD in preschoolers. If positive results are obtained, it may change the treatment landscape for preschoolers who typically have difficulty adhering to drug-based treatments.*

Keywords: *ADHD, Preschoolers, Neurofeedback, Child, Behavioural therapy*

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is an impairing condition that widely affects a child's life, impacting social areas and academic, cognitive, emotional, and behavioral fields (Brown et al., 2001). This condition creates a substantial burden for the individuals, their families, and the community.

The prevalence of ADHD worldwide in children 2-17 years of age is 9.4%. Approximately 129 million children worldwide have ADHD (Danielson et al., 2016), with very high annual medical costs (Matze et al., 2005).

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), ADHD symptoms begin as early as preschool. Early diagnosis

Abbreviations:
ADHD: Attention Deficit and Hyperactivity Disorder
ADHD-RS-IV: ADHD Rating Scale-IV
APA: American Psychological Association
BT: Behavioral Therapy
BPT: Behavioral Parent-Training
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG: Electroencephalogram
FDA: European equivalent of the Food and Drug Administration
ICH-GCP: International Conference on Harmonization - Good Clinical Practice (Food and Drug Administration guideline)
IRB: Institutional review board
ITT: Intention-to-Treat
PI: Principal investigator
PP: Per-Protocol
NF: Neurofeedback
NeFAP: Neurofeedback for Attention Hyperactivity Disorder (ADHD) in preschoolers
SCP: Slow Cortical Potential
SMR: Sensorimotor Rhythm
TBR: Theta / Beta ratio
AE: Adverse Events
DMCs: Data Monitoring Committees

and treatment of ADHD in preschoolers can minimize these problems (Geladé et al., 2017).

Current guidelines for preschool-aged children with ADHD (4-5 years old) (American Psychiatric Association, 2013) suggest prescribing evidence-based parent or teacher-administered behavior therapy as the first line of treatment. For non-respondents and moderate-to-severe cases, psychostimulants, such as methylphenidate, can be prescribed (Halperin et al, 2012). However, the use of psychostimulants in preschoolers and adolescents has shown difficulties like swallowing medications and intolerable adverse reactions such as anorexia, insomnia, abdominal pain, headache, nausea, and irritability. Therefore, the use of alternative therapies for pharmacological treatment may be beneficial.

Even for non-pharmacological treatments, the few conducted studies with preschool-aged children, compared with a drug treatment (Sonuga-Barke et al., 2013), have reported limited effects of isolated behavioral therapy, which seems insufficient for preschool-aged children with ADHD (Arns et al., 2020).

Neurofeedback is a type of brain-training therapy that relieves symptoms of some mental health conditions and improves self-regulation skills in daily life (Duric et al., 2012), acting on the most affected brain area (Danielson et al., 2016). In summary, neurofeedback is based on a brain-computer interface in which the participant's brain activity is measured. Afterward, selected brain parameters are fed back to the participant as perceivable signals. Through this feedback, the participant can self-regulate his brain activity to directly change the behavior mechanism (Enriquez-Geppert et al., 2019).

The use of neurofeedback as monotherapy has shown promising results compared to psychostimulant medication in older children (7 years of age or older) and adolescents with ADHD, achieving remission rates around 32-47% and sustained effects after 6-12 months (Brown et al., 2001). Although the benefits of neurofeedback have been shown in older children, this treatment modality has never been studied in preschoolers. As behavioral therapy is the first-line treatment in this age group, we considered neurofeedback as an add-on (combined) therapy for our target population (preschoolers).

Therefore, this study aims to determine if neurofeedback as an add-on intervention to BT is superior in efficacy to BT with a sham neurofeedback procedure for treating ADHD in preschoolers.

MATERIALS AND METHODS

Trial Design

This is a multicenter, randomized, single-blinded, parallel-group, superiority, phase III study to assess the efficacy of neurofeedback (NF) along with behavioral therapy (BT) compared with sham NF and behavioral therapy in preschoolers (aged 4 to 6) newly diagnosed with ADHD.

The main goal is to analyze the superiority effect of neurofeedback associated with behavioral therapy on preschoolers with ADHD by focusing on observed symptomatology.

Study Setting

Patients will be recruited from well-established Medical Centers and high-volume ADHD Pediatric Clinics in the United States of America according to recruitment yield. Neurofeedback and behavioral therapy sessions will be carried out by specialized local reference centers.

Children aged from 4 to 6 years old with a confirmed diagnosis of moderate to severe ADHD, according to the treating physician, following the DSM-5 criteria, will be included in this study.

Randomization

Participants will be randomly assigned in a 1:1 allocation ratio, with the allocation sequence to be generated through an online web-based randomization system (Sealed Envelope). Randomization will be done through blocked randomization with variable block sizes (4 or 8) associated with stratified randomization by sex and center.

Blinding

This is a single-blinded study. Although patients, caregivers, and data analyzers will be all unaware of group allocation, we cannot traditionally call this study double-blinded because technicians applying the intervention will not be blinded. Even though the technician applying the protocol will be aware of the allocation arm, it will not affect the unbiased collection of outcome data since technicians will be strictly instructed not to reveal group allocation to the participants.

We will include a sham neurofeedback procedure in the control group that will allow us to detect whether the benefits that have been described of neurofeedback are due to the intervention itself or if they are related to the nonspecific effects of the NF treatment package (supportive coaching, practice focusing on a screen, reinforcement for sitting still, placebo response). The experience during the intervention for both groups will be identical, making it unlikely for parents or children to guess the assigned intervention to prevent unblinding.

To control for possible biases in the interpretation of results, the risk of unblinding will be assessed in the last telephonic follow-up call by asking the participants to guess allocation.

Any code violation should be reported and explained, irrespective of the reason for its occurrence, and should be reported to the Institutional Review Board (IRB) in the next 24 hours.

Eligibility criteria

We will evaluate potential candidates according to the following criteria:

Inclusion criteria

To participate, a child must fit all the following criteria:
1. Age from 4 up to 6 years old.
2. Both genders.
3. Confirmed Diagnosis of ADHD from the ADHD center, as defined by the guidelines in the American Psychological Association (APA) Diagnostic and Statistical Manual, Fifth Edition (DSM-5) (American Psychiatric Association, 2013), without any previous ADHD treatment.
4. Ability to physically & intellectually collaborate with the interventions proposed.

Exclusion criteria

1. Absence of an adult tutor during sessions
2. Any history or current psychotic, neurological, or autism spectrum disorders (e.g., Schizophrenia, bipolar disorder, seizure disorder, degenerative disorders, Down's Syndrome), not including common ADHD comorbidities like learning disorders.
3. Any clinical change that the Principal Investigator (PI) considers a risk to the subject's enrollment in the study.

Recruitment Strategy

Participants will be enrolled through clinician invitation letters to physicians working in the participating centers and public awareness campaigns mediated by specialized medical societies. Each participant will have the written consent of their caregiver collected before randomization.

Adherence

Trained health coaches will implement adherence-enhancing strategies. They will include two webinars (a week prior and at six months) to address the use of the platforms, constant technical support, and reminders before the follow-up visits at 6 and 12 months via the DPP platforms. Adherence will be assessed by tracking the DPP mobile platform for participants' self-recorded information. At 4, 6, and 12 months within the study, participants will rate their compliance to the intervention and mention possible barriers to non-compliance through questionnaires delivered via the DPP platform.

Adherence

We will assess protocol adherence by the count of participation in each visit for therapy (session). Unattended sessions will be counted and recorded on the appropriate Case Report Form.

Weekly assessments during intervention time will be done through face-to-face meetings and monthly phone calls after the intervention period with patients and caregivers to evaluate patients' experience and satisfaction, promote adherence and check for reported side effects during, before, or after the previous therapy sessions. The face-to-face meetings will be held during the sessions of neurofeedback. As we plan to complete 48 sessions in 24 weeks, there would be two sessions per week. Providers will be submitted monthly for quality control of the procedures by third-party assessors to certify that the NF and BT are optimal. Incentives for adherence of patients and caregivers will include complimentary parking, food, and beverages offered during the treatment sessions, transportation reimbursement, and prizes for children (e.g., toys) after the completion of each NF session. Flexible appointments will be scheduled in order to increase adherence.

Intervention

The intervention group will receive up to 48 neurofeedback sessions in 24 weeks, with 6-12-24-36-month follow-up (dated from baseline) (Halperin et al., 2012) (Arnold et al., 2020). (**Figure 1**)

The treatment will be done with a standard neurofeedback protocol, being one of the following: Theta/Beta ratio (TBR) or slow cortical potential (SCP) (Arns et al.,2020). The protocol will be chosen according to the expert's assessment in the first week of intervention with neurofeedback and will remain until the last session. The goal is to individualize the best therapy for each subject.

TBR represents the ratio of the quantity of theta activity divided by the amount of beta activity, with both being measured at the scalp vertex site Cz. This protocol consists of down-training theta and up-training beta power at the central location, Cz. SCPs, on the other hand, aim to evaluate the underlying cortical area by

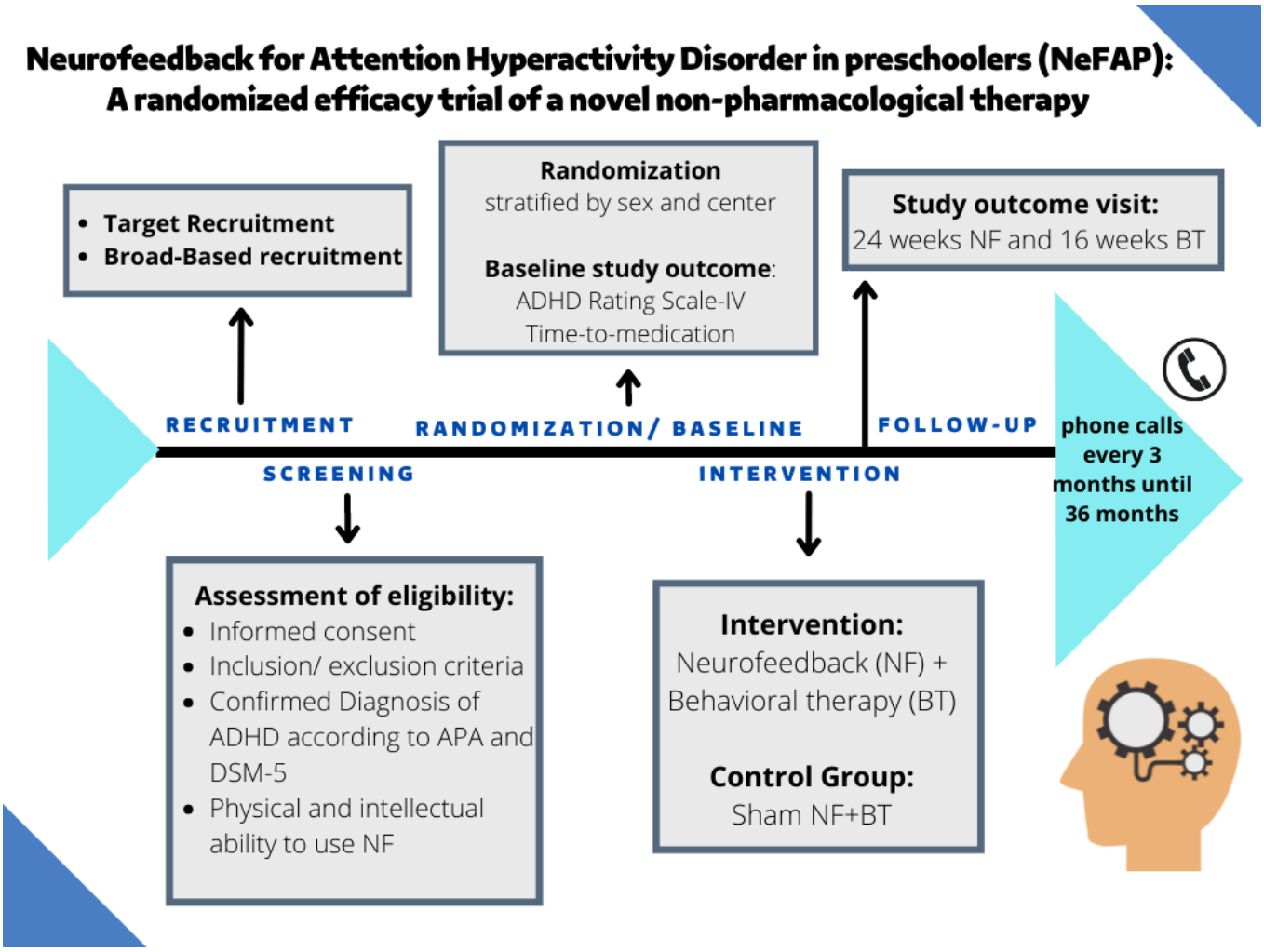

Figure 1. Study Timeline

reflecting its excitability. This protocol consists of training voluntary control of SCPs with a neurofeedback procedure (Arns et al., 2020).

Compliance to a mean of 35 sessions is assumed, given particular aspects of a child's daily life (Geladé et al., 2017), (Meisel et al., 2013).

The control group will receive sham neurofeedback therapy associated with BT. The sham procedure will be equal to the EEG-neurofeedback training, except that the feedback will be based on a simulated EEG signal instead of actual brain activity.

BT will be offered to both groups through behavioral parent training (BPT) (Jensen et al., 1999). This parent training program will contain 8-16 weekly sessions, or 27 group sessions, eight individuals per family and six families per group (Barkley et al., 2000). We will offer combined schedules where children have the neurofeedback sessions while parents are at BPT. These sessions will aim to teach parents about the causes of defiant behavior, positive attendance skills and praising, rewarding children for non-disruptive behavior, and dealing with children in public places with "think aloud - think ahead" strategies, among other skills (Arns et al., 2014).

Modification/Discontinuation

Subjects are free to withdraw their consent or stop their participation in the study at any time without prejudice to additional treatment, penalties, or loss of benefits. Additionally, study subjects may be discontinued from the study by trial investigators for various reasons, including harm, deterioration of health status or death, dropouts or loss to follow-up, protocol violation at the investigator or sponsor's discretion; less than 65% attendance of therapy sessions (Geladé et al., 2017) (Meisel et al., 2013).

The procedure of discontinuation must be recorded in the protocol documents. The research site must send a telegram requesting an urgent contact if not contacted via telephone. After two telegrams with an interval of 5 business days, the subject will be classified as a dropout.

Outcomes

The primary outcome includes the improvement of ADHD symptoms in preschoolers, measured by the ADHD Rating Scale-IV (ADHD-RS-IV), based on a semi-structured interview with the patient's parent (or primary caretaker) performed by a clinician experienced in working with children with ADHD. The assessment of the primary outcome will occur after 12 months of follow-up.

The scale consists of 18 ADHD symptoms as defined in the DSM-IV, to be rated on a four-point Likert scale ranging from 0 (the symptom is "never/rarely" present) to 3 (the symptom is "very often" present).

This instrument provides specific inattention and hyperactivity/impulsivity scores (odd and even-numbered items, respectively) for a total score ranging from 0-54 (27 points each) (Mcgoey et al., 2007).

The ADHD Rating Scale-IV Preschool version of this scale is a modified version of the ADHD Rating Scale-IV with developmentally appropriate examples of preschool activities and play (Barkley et al., 1991). The cut-off for the ADHD rating scale is a score above the 93 percentiles of the scale. A Scoring Sheet determines the percentile for girls and boys. Training on administering this instrument will be conducted for all efficacy raters at the study startup time (Barkley et al., 1991).

The effect size calculation to establish the difference between the two treatment arms was based on a study that demonstrated that a change of 10 to 15 points in the ADHD-Rating Scale-IV total corresponded to a change of one level in Clinical Global Impression–Improvement (CGI-I) scale (Goodman et al., 2010).

The CGI-I is a clinician-rated scale that allows assessment of improvement/deterioration of symptoms compared to baseline (Busner et al., 2007). It has not been validated in preschoolers, so it will not be used as a primary outcome in our study (Wolraich et al., 2019).

After six months, subjects will be allowed to use the medication if needed.

As a secondary outcome, time-to-medication will be assessed using a Kaplan-Meier analysis through telephone calls after six months of randomization and then every three months until the end of the follow-up at 36 months. Repeated measures using linear mixed models will require ADHD scale assessment at baseline, 12 months, and 24 months for the secondary outcome of within-group improvement.

The scales will be applied at 12 months for between-group differences, according to the primary outcome. For the secondary outcome, for within-group differences, we will apply the scales at baseline, 12, and 24 months (using a linear mixed models approach). The parents will apply them to their children.

Data Monitoring

The Neurofeedback for ADHD in Preschoolers (NeFAP) participants' files will be entered in numerical order

electronically or saved in the study database in a secure/accessible manner and maintained in storage for ten years after the completion of the study. This may be done at a Coordination Center (CC) or the participating site where the data originated. A subset will be requested later for quality control; when a form is selected, the participating site staff will pull that form, copy it, and send the copy to the NeFAP CC for re-entry.

Data integrity will be enforced by various mechanisms, such as referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks). Discrepancies or resolutions will be updated in the database.

Access to the study data will be restricted by personal logging into the system data. All paper forms or electronic devices (such as pen drives) will be kept in locked cabinets. Passwords to access will be changed regularly.

All reports prepared by the NeFAP coordinator center will be prepared such that no individual subject can be identified. A complete backup will be regularly provided.

All adverse events will be reported to a monitoring committee (Food and Drug Administration, 2006). Likewise, Data Monitoring Committee (DMC) is not needed for studies that address minor outcomes, such as symptom relief, without increasing risk to the study population for more severe outcomes.

Sample Size Calculation

The sample size was calculated based on the primary outcome, the difference between the mean scores on the ADHD Rating Scale-IV between the intervention and control groups. Because there had been no previous studies that assessed the same intervention (neurofeedback vs. behavioral therapy) with the improvement of the overall score on the ADHD Rating Scale-IV, we considered a minimal clinically significant difference of 5 points and accounting for a dropout rate of 25% and a standard deviation of 11. The minimal clinically significant difference is the difference we will consider as valid and, therefore, superior clinically.

We expect to include 137 participants in each arm of the study (a total of 274 patients) to obtain a statistical power of 90% with a two-sided significance level of 5%.

Primary and Secondary Outcome Measurement

For the evaluation of the best response, the score obtained from the ADHD-RS-IV was defined as the primary endpoint. Parents are asked to determine the symptomatic frequency that describes the child's home behavior over the previous six months. The ADHD-RS-IV is completed independently by the parent and scored by a clinician. It consists of 2 subscales: inattention (9 items) and hyperactivity-impulsivity (9 items). The clinician should interpret the scale with extreme caution, if three or more items are skipped.

We will compare the intervention and the control arms to each other regarding all primary analyses. The main outcome will be measured as a continuous variable, and a two-sided, unpaired T-test will be used to assess for between-group differences in the ADHD-RS-IV (Preschool version) score at 12 months if parametric assumptions are met. Otherwise, the Mann-Whitney U test will be used.

Normality will be assessed a priori by visual inspection of histograms and specific statistical tests, like Shapiro-Wilk and Kolmogorov-Smirnov. We will use the chi-square or Fisher's exact test for binary variables and the unpaired T-test or Mann-Whitney U test for continuous variables.

Patients will be followed-up for 24 months, and we will test the between-group difference on the ADHD-RS-IV scale at 12 months and 24 months. A linear mixed model for repeated measures will include treatment (NF, Control), time (baseline, 12 months, and 24 months), sex (male, female), and participating site. We predict that sham neurofeedback's placebo effect may appear soon after the beginning of treatment, and as time goes by, this placebo effect will wane.

For the time-to-event analysis of the secondary outcome (time-to-medication), we will use the Kaplan-Meier method to describe the data, followed by the log-rank test to compare the groups six months after randomization, and then every three months until 36 months of follow-up.

For all tests, 2-sided p-values will be used with a level of significance of alpha $\leqslant 0.05$. Data will be analyzed with the software STATA 17.0 Basic Edition.

Safety Variable Measurement

Adverse Events (AE) will be monitored and reported in the clinical record of the study from the signing of the consent form, including type, frequency, intensity, severity, action taken, and relationship with the investigational product of the study. Adverse events may be reported by the research participant or observed by the investigator.

Statistical Analysis

We will start with Intention-To-Treat followed by Per-Protocol Analysis.

All the intention-to-treat (ITT) will be performed for subjects with at least one efficacy evaluation to preserve the original randomization and avoid possible biases due to the exclusion of patients. Summary tables of protocol deviation type by treatment group will be provided for the ITT Population.

According to the protocol guidelines, all subjects who do not present major deviations will be part of the per-protocol (PP) population. The major protocol violations will be reviewed before the data analysis begins. All violations will be listed.

All the subjects who received at least one treatment in the study will be part of the safety analysis population: identical to the ITT population.

Missing Data

Missing data is expected at various trial stages. Safety will be analyzed using the observed dataset, and no data imputation techniques will be used. The efficacy evaluation will be adjusted using a Multiple Imputation technique to account for post-baseline missing data in the Intention-to-treat analysis.

Ethical Considerations

The study protocol has to be approved by each Institutional Review Board. Each participant will have the written consent of their caregiver collected before randomization. Once the Institutional Review Board approves the study protocol, it will be registered at clinicaltrials.gov.

DISCUSSION

This study aims to evaluate the efficacy and superiority of behavioral therapy associated with neurofeedback compared to sham neurofeedback with behavioral therapy for preschoolers between 4 to 6 years old diagnosed with ADHD.

Although the American Psychological Association (APA) guidelines rated neurofeedback as a well-established treatment in ADHD children, with a 32–47% remission rate and sustained effects after 6–12 months (Arns et al.,2020), there is a lack of previous studies comparing the combination of behavioral therapy with neurofeedback (Moreno-García et al., 2015) and there are still no established neurofeedback protocols.

The use of "commercially advertised methods" like 3-D LORETA neurofeedback (with or without Z-scores; LNFB) and the 19-channel Z-score neurofeedback (ZNFB) appeared to have conflicting and inconclusive results (Coben et al., 2019).

Instead, consistent benefits have been shown by using the standard, intensely studied protocols theta/beta (TBR), sensorimotor ng rhythm (SMR), and slow cortical potential (SCP) (Enriquez-Geppert et al., 2019).

Because of some reported side effects of using the SMR protocol (Rogel et al.,2015), our study only accepted the theta/beta (TBR) and slow cortical potential (SCP) neurofeedback protocols.

As the "neurofeedback package" can impact the results, using a sham is necessary to isolate the actual effect of the neurofeedback.

Thus, the study was designed as multicentric to ensure a meaningful and significant sample size to give power, applicability, and relevance to the trial results with random equal allocation by a central online service to produce comparable groups and to minimize potential sampling bias. The establishment of the blinding strategy aims to minimize bias, especially performance and attrition bias, and guarantee as much as possible the blindness of the study.

By using a non-pharmacological treatment like neurofeedback, our study will yield relevant data for ADHD treatment in preschoolers between 4 to 6 years old to enlarge the horizon of ADHD treatment for this population.

The main limitation of this study protocol is the difficulty in isolating the actual effect of neurofeedback in improving ADHD symptoms. Because there could be an effect using the sham neurofeedback, this "placebo effect" would decrease in efficacy as time goes by. Therefore, to address this issue, we decided to follow up the patients for as long as 24 months (for within-group improvement) and for 36 months (time-to-medication Kaplan-Meier analysis). Another limitation is using two standard neurofeedback protocols, which may result in variable efficacy. However, we decided to use the standard protocol, which the physician judged as the "best fit" for the specific patient (before randomization).

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Conflicts of interest

The authors have no personal or financial conflicts of interest related to this study protocol.

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