

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, [1–3] affecting about 5% of schoolaged children and around 2.5% of adults worldwide.^[4,5] ADHD not only has an important impact on virtually every aspect of a individual's physical and mental health, daily functioning, and academic/occupational performance in the short and long run, but also entails a huge economic burden to patients, families, and broader society.^[6–8] Currently, several pharmacological and nonpharmacological options, such as behavioral interventions/parenting skills, dietetic changes, and cognitive training, have been proposed for the treatment of ADHD. [9–11] Psychostimulants, including methylphenidate (MPH), are recommended as a first-line pharmacological option in several guidelines for the treatment of ADHD.^[12–17] MPH, the most commonly used psychostimulant in many countries, inhibits the reuptake of dopamine and norepinephrine, increasing dopaminergic and noradrenergic activity in the prefrontal cortex, which may contribute its efficacy and effectiveness in ADHD.^[18,19] Despite evidence from short-term randomized controlled trials (RCTs) pointing to large effect size (ES) (among the largest not only in psychiatry but also in general medicine) for MPH (teacher-reported ADHD symptom ratings [SMD -0.83; 95% confidence interval, CI: -0.96, -0.70], general behavior [SMD -0.68; 95% CI: -0.78, -0.60], and quality of life [SMD 0.61; 95% CI: 0.48–0.80]),^[20] there are concerns over its tolerability and mixed evidence on its long-term effects.^[18] Storebo et al stated that MPH may improve symptoms of ADHD but is associated with a relatively high risk of nonserious adverse events.^[21,22]

Therefore, alternative nonpharmacological options directly targeting the pathophysiology of ADHD are currently being actively investigated. Among these, neurofeedback (NF) has been proposed by a number of research groups as an effective and safe option for ADHD.^[23,24] NF is a process of operant conditioning, which aims at improving self-regulation of brain activity.^[25,26] Meta-analytic evidence on the efficacy of NF for ADHD is currently mixed. Arns et al, 2014,^[27] pooled 15 studies (including 476 subjects from 11 prospective controlled studies and 718 subjects from 4 pre-post-test design studies) and concluded that NF treatment for ADHD can be considered “efficacious and specific,” with a large ES (0.8097 and 0.6862, respectively) for inattention and impulsivity and a medium ES (0.3962) for hyperactivity. By contrast, Cortese et al of the European ADHD Guidelines Group (EAGG), 2016, after pooling 13 RCTs (including 520 participants with ADHD), found that, although ratings from unblinded assessors show significant effects of NF in reducing ADHD core symptoms, ratings from probably blinded assessors fail to support NF as an effective treatment for ADHD core symptoms.^[28] Overall, we are not aware of any evidence suggesting that NF outperforms placebo-NF for ADHD.

Evidence on the comparative efficacy/effectiveness and tolerability of MPH and NF needs further investigation. Catala-Lopez et al, 2017 did a comprehensive network meta-analysis including, among other treatments, MPH and NF. MPH emerged as more efficacious than NF on ADHD symptoms and global functioning.^[29] However, the meta-analysis by Catala-Lopez et al, 2017, did not focused on the effects of MPH and NF on subdomains of ADHD separately (i.e., inattention and hyperactivity-impulsivity). This is of relevance given that previous studies have shown that inattention and hyperactivity/impulsivity symptoms may have different degrees of sensitivity to different treatments.^[27]

Additionally, Catala-Lopez et al, 2017,^[30] chose to use a dichotomous outcome (i.e., proportion of patients who displayed improvements in the symptoms of ADHD or global functioning on standardized rating scales), which may be less informative compared to continuous outcomes.

Furthermore, when considering the comparison between MPH and NF, a key aspect relates to sustained effects. A meta-analysis by Van Doren et al, 2018, focused on sustained effects (defined by these authors as follow-up at 2–12 months) of NF in ADHD. They found that, compared to nonactive control treatments, NF had significantly more durable treatment effects for at least 6 months following treatment, although the authors concluded that more studies are needed for a properly powered comparison of follow-up effects between NF and active treatments.^[31] Indeed, this meta-analysis could not inform on the sustained effect of NF and MPH directly because it combined MPH with other active treatments including attention training, cognitive training, physical activity training, and self-management.

Finally, another aspect that deserves further investigation relates to the comparative efficacy of MPH and NF on neuropsychological measures, such as working memory or sustained attention. This is of relevance because executive dysfunctions, albeit far from being universal in ADHD, affect a sizable portion of individuals with ADHD and impact on their academic and global functioning.^[32]

Therefore, a number of questions still need to be answered in relation to the comparative efficacy and tolerability of MPH and NF.

2. Objectives

Our study aimed to fill these gaps by means of a systematic review and meta-analysis of head-to-head RCTs comparing the effects (at trial end point and, if available, at follow-up) in terms of efficacy of MPH and NF on separate ADHD core symptoms (inattention and hyperactivity/impulsivity), using continuous measures as outcome. We will also explore the feasibility of assessing the comparative effects on neuropsychological variables. We also will assess the comparative tolerability of MPH and NF.

3. Methods

Methods for this systematic review/meta-analysis have been developed according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^[33]

3.1. Eligibility Criteria

3.1.1. Population. Individuals (children/adolescents [<18 years] and or adults [≥ 18 years]) with a categorical diagnosis of ADHD according to the DSM (III, III-R, IV, IV-TR or 5) or hyperkinetic disorder as per the ICD-10 or previous ICD versions or above cut point on any validated ADHD measure.^[34,35]

3.1.2. Intervention(s). We will include trials comparing NF and MPH. Both fixed-dose and flexible-dose designs (in relation to the MPH regime) will be allowed. Studies assessing the efficacy of multimodal treatments including the combination of NF plus other treatments will be excluded.

3.1.3. Comparator(s)/control. Studies including a nonactive comparator will be retained if they include at least 2 other active arms, that is, MPH and NF.

3.1.4. Types of outcome(s). The primary outcome will be the efficacy (as a continuous outcome) on the severity of ADHD core symptoms (at the end of the study and, if available, at follow-up, filled out by parents, teachers, patients or clinician(s). We will perform an analysis focusing on the total ADHD score, that is, inattentive plus hyperactive/impulsive symptoms, and another analysis focusing on ADHD subdomains, that is, analyzing separately inattention and hyperactivity/impulsivity. Validated ADHD rating scales that we will consider eligible for the measurement of the outcomes are reported in Table 1.^[36] As in previous studies,^[37] we will conduct separate analyses for measures rated by clinicians, parents, teachers, and patients

(self). Secondary outcomes will be the number of dropouts for any reasons at the end of the intervention (and, if available, at follow-up) and neuropsychological laboratory-based measures of working memory (e.g., The visual spatial working memory task,^[38] attention (e.g., Test of Variables of Attention,^[39,40] Attention Endurance Test (d2)^[41]), and inhibition (e.g., Integrated Visual and Auditory Continuous Performance Test).^[42]

Timing: the primary analysis will focus on endpoint- baseline changes; secondary analyses will focus on data, when available, at a follow-up (time point closest to 12 months after treatment as in Van Doren et al's, 2018, and other studies^[31,43], or longer follow-up, if available).

Table 1
Scales/subscales for ADHD considered for possible inclusion.

Questionnaire/scale	Abbreviation	Subscales	Scales/subscales on ADHD core symptoms considered for the present meta-analysis
ADHD Rating Scale (including parent and teacher version)	ADHD-RS	Inattention; impulsivity/hyperactivity; total	Total; if not available, inattention and/or impulsivity/hyperactivity
ADHD Symptoms Rating Scale	ADHD-SRS	Inattention; impulsivity/hyperactivity; total	Total; if not available, inattention and/or impulsivity/hyperactivity
Swanson, Nolan, and Pelham-IV (teaching and parent rating scales), 90 items	SNAP-IV	Inattention; hyperactivity/impulsivity; ODD; inattention/overactivity; aggression/ defiance; Conners Index	Inattention/overactivity; if not available, inattention and/or impulsivity/hyperactivity
Swanson, Nolan, and Pelham-IV, 26 items	SNAP-IV, 26-item	Inattention; hyperactivity/impulsivity; ODD; total	Inattention and/or impulsivity/hyperactivity
Swanson, Nolan, and Pelham-IV, 18 items	SNAP-IV, 18-item	Inattention; hyperactivity/impulsivity; combined	Combined; if not available: inattention and/or impulsivity/hyperactivity
Conners Parent Rating Scale-Revised, long version and Conners Teacher Rating Scale-Revised, long version	CPRS-R:L and CTRS-R:L	Oppositional; cognitive problems/inattention; hyperactivity; anxious-shy; perfectionism; social problems; psychosomatic (for parent version); ADHD Index; CGI restless-impulsive; CGI, emotional lability; CGI, total; DSM-IV inattentive, DSM-IV hyperactive impulsive, DSM-IV total	ADHD index, DSM-IV total; if not available, cognitive problems/inattention and/or hyperactivity or DSM-IV inattentive, DSM-IV and/or hyperactive impulsive
Conners Parent Rating Scale-Revised, short version and Conners Teacher Rating Scale-Revised, short version	CPRS-R:S and CTRS-R:S	Oppositional cognitive problems, hyperactive-impulsive ADHD Index	ADHD index; if not available: cognitive problems and/or hyperactive-impulsive
Conners- Wells Adolescent Self Report Scale, long version	CASS-L	Family problems, conduct problems, anger control, problems emotional, problems cognitive, problems hyperactive-impulsive, DSM-IV symptoms ADHD Index	ADHD index; if not available: cognitive problems and/or hyperactive-impulsive
Conners- Wells Adolescent Self-report Scale, short version	CASS-S	Conduct Cognitive Hyperactivity ADHD index	ADHD index; if not available: cognitive and/or Hyperactivity
Conner 3- Parent and Conners 3- teachers	Conners 3-P and Conners 3-T	Inattention; hyperactivity-impulsivity; learning problems; executive function; aggression; peer relations	Inattention and/or impulsivity-hyperactivity
IOWA Conners Parent Rating Scale and IOWA Conners Teacher Rating Scale; adolescent form also available	IOWA CPRS and IOWA CTRS	Inattentive/overactive Oppositional-defiant; total	Inattentive/overactive
Swanson, Kotkin, Atkins, M-Flynn, Pelham Scale	SKAMP	Inattention, department (behavior); total (combined)	Total; if not available, inattention and/or department
Vanderbilt ADHD teacher report	VADTRS	inattention; hyperactivity/impulsivity; ADHD combined; oppositional defiant/conduct; anxiety depression; academic performance; classroom behavioral performance	ADHD combined; if not available, inattention and/or hyperactivity/impulsivity
Vanderbilt ADHD parent report	VADPRS	Inattention; hyperactivity/impulsivity; ADHD combined; oppositional defiant/conduct; anxiety depression	ADHD combined; if not available, inattention and/or hyperactivity/impulsivity

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Questionnaire/scale	Abbreviation	Subscales	Scales/subscales on ADHD core symptoms considered for the present meta-analysis
Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale, teacher and parent version	SWAN	Inattention, hyperactivity-impulsivity, ADHD, ODD	ADHD; if not available, inattention and/or hyperactivity-impulsivity
Attention Deficit Disorder Evaluation Scale-second edition, parent (home) and teacher version, (short version)	ADDES-1 (S)	Inattention; hyperactivity/impulsivity Total	Total; if not available, inattention and/or hyperactivity-impulsivity
ACTeRS-second edition, parent and teacher version	ACTeR-second edition	Attention, hyperactivity, social skills, oppositional behaviors; early childhood problems (only in parent version)	Inattention and/or hyperactivity
ACTeRS-second edition Adolescent Self-report	ACTeRS-second edition	Inattention, hyperactivity/impulsivity, social adjustment	Inattention and/or hyperactivity
Adult ADHD Investigator System Report Scale	AISRS	Inattention; hyperactivity/impulsivity Total	Total; if not available, inattention and/or hyperactivity-impulsivity
Adult ADHD Self-report Scale	ASRS-v1.1	Inattention; hyperactivity/impulsivity Total	Total; if not available, inattention and/or hyperactivity-impulsivity
Adult ADHD Self-report Scale-screening	ASRS-S	Inattention; hyperactivity/impulsivity Total	Total; if not available, inattention and/or hyperactivity-impulsivity
Wender-Reimherr Adult Attention Deficit Disorder Scale	WRAADDS	attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional over-reactivity, disorganization, impulsivity and total	Total; if not available, Inattention = attention + disorganization impulsivity/hyperactivity = hyperactivity + impulsivity

Plus any other scale including ADHD core symptoms. ADHD = attention-deficit/hyperactivity disorder, CGI = Conners Global Index, ODD = oppositional defiant disorder.

3.1.5. Types of Study. RCTs will be included, regardless the level of blinding. Parallel-group RCTs, cross-over trials, and, if available, cluster trials will be considered. For cross-over studies, owing to concerns on possible “carry-over” effects,^[44] we will use data from the precross-over phase, whenever this is reported in the study report. When data for the precross-over phase are not reported, we will contact study authors to obtain them.

3.2. Search strategy

We will include published and unpublished studies pertinent to our criteria. An electronic literature search will be conducted independently by 2 authors. The following electronic databases will be searched with no language, date, and type of document restrictions: PubMed, OVID, ERIC, and Web of Science (including Science Citation Index Expanded (SCI-EXPANDED)). Chinese databases, including China National Knowledge Infrastructure (CNKI), CQVIP, and WanFang data, will also be searched with the translated searching strategy. We will also search Clinicaltrials.gov, clinicaltrialsregister.eu, and osf.io for additional reports not published in peer-reviewed journals.

The search terms/syntax in PubMed will be as follows:

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR minimal brain disorder OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND (neurofeedback OR neuro feedback OR “EEG biofeedback”

OR neuro therapy OR neurotherapy OR SCP OR “slow cortical potentials”) AND (Methylphenidate* OR methylphenidate* OR Ritalin OR ritalin)

The search strategy/syntax will be adapted for each database. The references of all selected studies will be hand searched for other published reports and citations of unpublished studies. Finally, we will contact experts in the field to query about any completed study not yet published.

3.3. Data extraction

Studies identified through electronic and manual searches will be listed with citation, titles, and abstracts in EndNote; duplicates will be excluded using the EndNote function “remove duplicates.” The eligibility for inclusion process will be conducted in 2 separate stages:

1. Two authors will independently screen title and abstracts of all nonduplicated articles and will exclude those not pertinent to the criterion. A final list will be agreed with discrepancies resolved by consensus between the 2 authors. When consensus is not reached, a third senior author will act as arbitrator. If any doubt about inclusion exists, the article will proceed to the next stage.
2. The full-text version of the articles passing stage 1 screening will be downloaded and assessed for eligibility by two authors, independently. We will provide a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Discrepancies will be resolved by consensus between the 2 authors and, if needed, a third senior author will act as arbitrator. Data from multiple reports of the same study will be linked together. Where required, we will contact the corresponding author to inquire about study eligibility.

One reviewer will input outcome data from studies included in previous systematic reviews into Excel. This will be independent-

ly cross-checked by another reviewer. The following data will be collected from each included study:

- Study details: first author/study ID, year(s) of study or publication, location (country or continent), setting, diagnostic criteria, funding/sponsor (industry or academic);
- Participants details, including sex distribution, mean and range of age, presence, and type of co-morbid (neuro) psychiatric conditions, mean (and SD) IQ, numbers in each group, and a number of dropouts for side effects in both groups.
- Interventions details, including mean and maximum doses of MPH, type of NF, the duration of interventions, and whether forced dose or optimized treatment with MPH; time(s) of outcome measurement
- Outcomes: mean, SD, or percentage in both groups at pre-test, post-test, and follow-up (any time point reported).
- Effect size, statistical power, and the original researcher's hypothesis for each study.
- Information as to whether participants in the NF studies learn to regulate the feedback.

3.4. Risk of bias (quality) assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration risk of bias tool, as a reference.^[45] The risk of bias domains include selection bias, performance bias, detection bias, attrition bias, and other bias. Two independent review authors will assess the risk of bias in selected studies. The degree of agreement between the two independent raters will be reported. Any disagreement will be resolved through discussion and in consultation with the principal investigators. Where necessary (i.e., unclear information for the published report), the authors of the studies will be contacted for further information. As in Cortese et al,^[46] the overall rating of risk of bias for each study will be the lowest rating for any of the criteria (e.g., if any domain is scored high risk of bias, the study will be considered high risk of bias).

3.5. Data synthesis

Meta-analyses will be performed by means of Comprehensive Meta-Analysis Software (CMA) (<http://www.meta-analysis.com/index.php>) using the option "standardized by post score SD." Additionally, we will use the appropriate function in CMA, to combine outcomes within study from the same subjects (<https://www.meta-analysis.com/downloads/Multiple%20outcomes.pdf>). Heterogeneity will be assessed and measured with Cochran's Q and I^2 statistics, which estimates the percentage of variation among ES that can be attributed to heterogeneity.^[47] $I^2 > 0$ indicates that the degree of heterogeneity is greater than would be expected by chance. Clinically significant values will be indicated by $SMD > 0.4$.^[48]

3.6. Subgroup and meta-regression analyses

We will explore the feasibility of conducting subgroup analyses to assess the impact of the following variables: age of population; the language in which studies were published; comorbidities. Additionally, we will carry out meta-regression analyses to investigate the effect of sponsorship, year of publication, duration of intervention, age of participants.

3.7. Publication bias

Publication bias will be assessed via funnel plots and Eggers test.^[49]

3.8. Sensitivity analyses

We will perform the following sensitivity analyses by: removing studies rated at overall high risk of bias; excluding studies with small sample size trials (at least 30 children per arm); excluding studies where the diagnosis was not made according to standardized DSM/ICD criteria; excluding unpublished data; removing studies on nonstandard NF (i.e., theta/beta EEG ratio, sensorimotor rhythm, and slow cortical potentials) as per Arns et al, 2014.^[26] We will also explore the feasibility of conducting sensitivity analyses by: (1) excluding studies not using the Conners' scale; (2) excluding studies without teachers' rating.

3.9. Ethics and dissemination

This systematic review and meta-analysis will not undertake any primary data collection, so no ethical approval is required. The findings of this study will be published in a peer-reviewed journal.

4. Conclusion

This is a comprehensive meta-analysis of head-to-head trials of MPH versus NF using published and unpublished data. ADHD subdomains as well as neuropsychological measures will be considered separately. Comparative effects of MPH and NF on ADHD will be assessed not only at study endpoint but also at follow-up. A possible limitation is the inclusion of different rating scales to assess the core symptoms of ADHD. However, we will select only validated scales that measure exclusively the same triad of symptoms, that is, inattention, hyperactivity, and impulsivity.

Author contributions

LY and JZ conceived the study and drafted the protocol. SC supervised the study design and edited the first draft of the protocol. SC and JZ designed the search strategy. LY and YY reviewed and commented on the protocol in PROSPERO. All authors (JZ, LY, YY, SC) contributed to the development of inclusion and exclusion criteria. All authors (JZ, LY, YY, SC) read, contributed, and approved the final manuscript.

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