Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials

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Objective: We performed meta-analyses of randomized controlled trials to examine the effects of neurofeedback on attention-deficit/hyperactivity disorder (ADHD) symptoms and neuropsychological deficits in children and adolescents with ADHD.

Method: We searched PubMed, Ovid, Web of Science, ERIC, and CINAHAL through August 30, 2015. Random-effects models were employed. Studies were evaluated with the Cochrane Risk of Bias tool.

Results: We included 13 trials (520 participants with ADHD). Significant effects were found on ADHD symptoms rated by assessors most proximal to the treatment setting, that is, the least blinded outcome measure (standardized mean difference [SMD]: ADHD total symptoms = 0.35, 95% CI = 0.11−0.59; inattention = 0.36, 95% CI = 0.09−0.63; hyperactivity/impulsivity = 0.26, 95% CI = 0.08−0.43). Effects were not significant when probably blinded ratings were the outcome or in trials with active/sham controls. Results were similar when

only frequency band training trials, the most common neurofeedback approach, were analyzed separately. Effects on laboratory measures of inhibition (SMD = 0.30, 95% CI = −0.10 to 0.70) and attention (SMD = 0.13, 95% CI = −0.09 to 0.36) were not significant. Only 4 studies directly assessed whether learning occurred after neurofeedback training. The risk of bias was unclear for many Cochrane Risk of Bias domains in most studies.

Conclusion: Evidence from well-controlled trials with probably blinded outcomes currently fails to support neurofeedback as an effective treatment for ADHD. Future efforts should focus on implementing standard neurofeedback protocols, ensuring learning, and optimizing clinically relevant transfer.

Key words: ADHD, neurofeedback, nonpharmacological treatment, meta-analysis, risk of bias

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age-inappropriate and impairing inattention and/or hyperactivity/impulsivity.[1,2] Among currently available treatment options, psychostimulant and nonstimulant medications are efficacious, at least in the short term, and widely used.[3] Nonpharmacological interventions—both dietary and psychological—have also been extensively investigated.[4-7] Among nonpharmacological approaches, neurofeedback has been considered a promising ADHD treatment strategy since the early 1970s.[8-10] When applied to ADHD, neurofeedback is intended to reduce ADHD symptoms by targeting aberrant patterns of brain activity thought to underpin the condition. Neurofeedback is implemented through the training of self-regulation using operant reinforcement procedures; learning of self-regulation is thus a key mechanism. To achieve this aim,

electroencephalogram (EEG) indices of interest are converted into visual or acoustic signals and fed back automatically in real time to the patient. For instance, cortical activity may be represented by the height or speed of a ball, plane, or cartoon character presented using animation on a computer screen. In this case, learning occurs when the object rises, falls, or advances more quickly in response to patients' regulated changes in brain activity. Two general neurofeedback approaches have been used to treat ADHD: frequency band training (FBT) and slow cortical potential training (SCP). When applied to ADHD, the former is intended to target alterations in cortical electrical oscillations thought to be associated with ADHD, namely elevations of slow, relative to fast, brainwave activity, especially in the frontal lobes (e.g., theta versus beta frequency[11]). The latter aims to regulate cortical excitation thresholds by focusing on activity generated by external cues (similar to event-related potentials), focusing primarily on EEG components registered in the late latency range, that is, several seconds after the cue. For instance, this form of training has been used to target the contingent negative variation (CNV) that occurs during this time window and is involved in effective preparation, decision

making, and time estimation, which have all been found to be deficient in individuals with ADHD, or at least in subgroups of them.[12,13]

The efficacy of nonpharmacological treatments for ADHD, including neurofeedback, has been subject to a number of earlier meta-analytic reviews.[14-16] However, these have sometimes been difficult to interpret because of the inclusion of studies with weak experimental designs (e.g., no control arm, nonrandom allocation, or the use of nonblinded measures), as discussed by Sonuga-Barke et al.[17] On behalf of the European ADHD Guidelines Group (EAGG), Sonuga-Barke et al.[17] attempted to address these limitations through a meta-analysis of nonpharmacological interventions that included only randomized controlled trials (RCTs). It also addressed the issue of blinding by comparing outcomes rated by individuals judged to be most proximal to the therapeutic setting (often parents poorly blinded and invested in the therapeutic outcome) and those provided by reporters judged to be probably blinded. They found that the effects of neurofeedback on ADHD total symptoms based on most proximal ratings were highly significant (standardized mean difference [SMD] = 0.59, 95% CI = 0.31, 0.87). However, when only probably blinded measures were used, the effects became nonsignificant (SMD = 0.29; 95% CI = −0.02 to 0.61). More recently, Micoulaud-Franchi et al.[18] followed a similar approach, focusing their analyses on ADHD core symptoms, but with a smaller set of studies (n = 5) limited to trials with particular control conditions. As in Sonuga-Barke et al.,[17] they found a significant, positive effect of neurofeedback on ADHD core symptoms when considering most proximal raters. Probably blinded scores were attenuated and were significant only for symptoms of inattention.

Applying the same meta-analyses protocol used in recent EAGG reviews of behavioral interventions[5] and cognitive training,[4] we here extend the focus of meta-analytic evidence relating to neurofeedback for ADHD in a number of ways. First, we included, among the outcomes, not only specific ADHD behavioral dimensions (i.e., inattention and impulsivity/hyperactivity) but also ADHD-related neuropsychological deficits such as inhibitory dysfunction. The latter may be important, as they may take us closer to neural mediators of the behavioral effects of neurofeedback.[9] Second, we addressed the relative efficacy of different types of neurofeedback by restricting subanalyses to specific types of treatment protocols, namely, FBT. Third, we examined the impact of different aspects of trial design (e.g., use of a sham/placebo design) or pragmatic "dosage" characteristics of neurofeedback implementation (i.e., number of sessions). Fourth, we addressed the crucial question of whether neurofeedback-related learning at the neural level was investigated and/or demonstrated in available trials.[9] Fifth, we examined whether the neurofeedback protocols used in these studies could be considered "standard" in terms of the criteria discussed by Arns et al.,[19] which include elements related to EEG bands/measures, electrode placement and type, and feedback following learning. Finally, we applied, for the first time in a meta-analysis of neurofeedback for ADHD, a rigorous assessment of study bias, namely, the Cochrane Risk of Bias tool (RoB).[20]

METHOD

The EAGG protocol was originally registered on the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO, protocol number: CRD42011001393). As in previous work,[4,5] the original protocol was adapted to take account of the broader scope of this systematic review/meta-analysis. Most crucially, given that the scope of this analysis included neuropsychological measures, the mandatory requirement for studies to have ADHD symptoms-related outcomes no longer applied (i.e., we included also studies presenting only neuropsychological outcomes).

Inclusion and Exclusion Criteria
To ensure high levels of methodological adequacy as recommended by the Cochrane group and to avoid the inevitable bias caused by dependence on investigators agreeing to provide data from unpublished studies,[20] only published studies were included. Only RCTs using neurofeedback training were retained. Participants in the trials were required to be between 3 and 18 years of age and to have a diagnosis of ADHD (any subtype) or hyperkinetic disorder (HKD) or to meet accepted cut-offs on validated ADHD symptom rating scales. Trials that selected children with ADHD who had rare comorbid disorders (e.g., Fragile X syndrome) were excluded. Control conditions allowed were "treatment as usual," "wait list," "active," or "placebo/sham" (i.e., involving other forms of alternative training regimen). As per the EAGG protocol, trials in which neurofeedback was compared only with optimized medication or in which neurofeedback was added to optimized medication were excluded. Trials in which medication was part of background normal clinical provision in either the control or the active arm were included.

Search Strategy
Details about the search strategy/syntax for each database are reported in Supplement 1, available online. The final search was updated on August 30, 2015. Independent searches were conducted by 2 authors (S.C. and M.F.), leading to the same number of references.

Outcome Measures
To provide analytical robustness and in line with previous EAGG meta-analyses,[4,5,17,20] analyses of outcome domains were considered reliable only if at least 5 RCTs were available. The planned outcomes included the following: ADHD symptoms (total ADHD and inattention and hyperactivity/impulsivity symptoms separately), neuropsychological laboratory-based measures, measures of academic functioning, and rating of severity of symptoms of comorbid conditions (e.g., oppositional defiant disorder or anxiety disorders).

Study Selection
Retrieved references were independently screened and blindly double coded for eligibility by 2 authors (S.C. and M.F.). Any disagreement was resolved by a senior author (E.S.-B.).

Study Bias Assessment
Study quality was assessed independently by pairs of raters from the authorship group using the Cochrane RoB tool.[20] The RoB domains included selection bias, performance bias, detection bias, attrition bias, and other bias. Any disagreement was resolved through consensus.