

# Neurofeedback for Attention-Deficit/Hyperactivity Disorder

## A Review of Current Evidence

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### KEYWORDS

- ADHD • Treatment • Neurofeedback • Slow cortical potentials • Frequency bands • Reward

### KEY POINTS

- Among alternative treatment approaches for attention-deficit/hyperactivity disorder (ADHD), neurofeedback has gained empirical support in recent years.
- Via neurofeedback, children with ADHD are trained to regulate their neurophysiologic profile or to bring it closer to that of nonaffected children; learning of self-regulation is thus a key mechanism.
- According to recent meta-analytic evidence, neurofeedback leads to significant decreases of ADHD core symptoms; however, if only probably blinded ratings are applied, these effects were reduced to a statistical trend. The evidence remains inconclusive because subsequent studies could demonstrate neither learning of self-regulation nor significant effects for the best blinded assessments.
- There is a strong need for more evidence from well-blinded, methodologically sound, and sensitive trials demonstrating also learning of self-regulation, before neurofeedback can be assigned the highest level of evidence as a front-line treatment of ADHD.

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- Future research should focus on testing different types of neurofeedback techniques, establishing the quality of the intervention, the long-term stability of effects, and predictors and mediators of response.
- Neurofeedback may be used within a multimodal treatment setting.

**Abbreviations**

ADHD	Attention-deficit/hyperactivity disorder
CNV	Contingent negative variation
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
QEEG	Quantitative electroencephalography
SCP	Slow cortical potential
SMR	Sensorimotor rhythm

**INTRODUCTION/BACKGROUND*****Target of Treatment***

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood with an estimated prevalence of about 5% in school-aged children.<sup>1</sup> Core symptoms include impaired attention and/or hyperactivity/impulsivity. ADHD often has a chronic course with up to 65% of affected children displaying ADHD symptoms in adulthood.<sup>2</sup> ADHD is associated with high levels of externalizing (eg, oppositional-defiant and conduct disorders) and internalizing (eg, depression and anxiety) comorbidity as well as learning disorders and leads to impairment in various domains, including poor academic performance, lower occupational success, poor social relationships, and higher risk-taking behavior.

***Need for the Treatment***

Because of the significant impact of ADHD on children's functioning, considerable effort has been directed at developing effective treatments. Although treatment with psychostimulant and non-psychostimulant medication is efficacious<sup>3</sup> and widely used, it has several limitations: a considerable minority of children treated with stimulants either fail to show an improvement in ADHD symptoms or suffer adverse effects on sleep, appetite, growth, and, less commonly, the cardiovascular system.<sup>4,5</sup> In addition, normalization is rare, and long-term effectiveness remains to be established. Some parents, patients, and/or clinicians have a preference for nonpharmacologic treatments. In summary, these limitations highlight the need for therapeutic innovation in ADHD to develop effective nonpharmacologic interventions that can improve short-term and long-term outcomes.

A range of nonpharmacologic interventions is available to treat ADHD (eg, psychological interventions, dietary elimination strategies, nutritional supplements, and herbal and homeopathic treatments). Evidence for the efficacy of some of these approaches has been partly supported in systematic reviews and meta-analyses, for example, Refs.<sup>6–10</sup> Because of the inclusion of nonrandomized controlled trials designs, non-ADHD samples, and/or non-ADHD outcomes, current meta-analyses allow only limited

conclusions to be drawn regarding the effect of these interventions on core ADHD symptoms.<sup>11</sup> Among nonpharmacologic treatment approaches, neurofeedback has emerged as a promising noninvasive treatment for children with ADHD. Neurofeedback is a form of biofeedback, which itself is based on behavior therapy. It may be best described as a training of self-regulation aiming to achieve control over brain activity patterns or to normalize them and thereby reduce the symptoms of ADHD. Neurofeedback with electroencephalography (EEG) (EEG-biofeedback) has been used as a treatment strategy since the 1970s.<sup>12</sup> Initially, the lack of suitably controlled large-scale studies inhibited the acceptance of neurofeedback within the wider psychological, psychiatric, and educational communities. Neurofeedback over time has gained more empirical support.<sup>6</sup> This article reviews the underlying theory and empirical research on the use of neurofeedback in children and adolescents with ADHD.

## INTERVENTIONS

### *Theoretic Overview: Why Does Theory Suggest the Treatment Should Work?*

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The growing acceptance of neurofeedback can be understood against the backdrop of an increased understanding of the neurodevelopmental basis of ADHD. The rationale for using neurofeedback as an intervention in ADHD derives from the consistent observation of altered brain activation in many children with ADHD detected in EEG and imaging studies. By repeated training of improved cortical (or subcortical) self-regulation, neurofeedback aims to address these deficits by making use of the brain's plasticity. Available treatment protocols mainly address 2 different kinds of deviant cortical activity in ADHD children: although EEG frequency band training is directed at the modification of oscillatory brain activity (eg, the reduction of slow wave activity and increase of faster activity), the training of slow cortical potentials (SCPs) addresses the regulation of phasic cortical activity to optimize allocation of cortical resources. Key findings of EEG studies in ADHD are summarized in the following paragraphs to clarify the theoretic background for the choice of electrophysiologic treatment targets.

#### ***EEG frequency band studies***

EEG research dating back 80 years has established the presence of various abnormalities of oscillatory brain activity in children with ADHD (then named "behavior problem children"). These early cross-sectional studies used visual evaluation of paper recordings of EEG; the most common finding was an increase in slow-wave activity, often in frontal regions.<sup>13,14</sup> Findings of "cortical slowing" have been replicated by a variety of studies applying quantitative electroencephalography (QEEG). QEEG applies computerized mathematical algorithms (typically spectral analysis using fast Fourier transformation) to convert raw EEG data into frequency bands of interest for statistical comparisons between conditions and groups or against norms. Traditionally, 5 wide frequency bands have been studied, typically defined as delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–30 Hz), and finally, also gamma (30–70 Hz). The absolute and relative power (ie, percentage of total power) in each frequency band is then calculated. Pediatric EEG differs from adult EEG because of developmental maturation. Decreases in the lower frequency bands are most prominent during the first years of life but continue until adulthood and parallel decreases in hemodynamic fluctuations,<sup>15</sup> whereas increases in relative alpha and beta typically continue until adolescence or adulthood.<sup>16</sup> Most EEG and QEEG studies have initially reported that a substantial group of ADHD children show elevated levels of slow wave (delta and theta) activity in comparison with healthy children and psychiatric controls.<sup>17,18</sup> The most reliable measures of this have been

increased relative theta power, whereas reduced amounts of relative alpha and beta 18 are less consistent. In addition, the theta/alpha and theta/beta ratios have been claimed to be reliable measures differentiating ADHD and control children.<sup>19</sup> Meanwhile, several studies using cluster analysis have reported distinct EEG-defined subgroups within their ADHD samples,<sup>20,21</sup> comprising among others a cortical hypoarousal subtype (increased relative theta and theta/beta ratio), a subtype indicative of a maturational lag, and a hyperarousal subtype (excess of beta activity). Because of more recent results, however, doubt has been cast on claims that the theta and beta ratio may serve as simple and reliable QEEG markers for ADHD, which has led to a major paradigm shift toward neurophysiologic subtyping. Indeed, increasing evidence across clinical groups and studies now indicates that the theta or theta/beta increase is not a specific marker of ADHD<sup>22,23</sup> and may also be more closely related to impaired activation following task demands rather than to hypoarousal,<sup>24</sup> thus implicating somewhat different regulation mechanisms.<sup>25</sup> As a consequence, subgrouping or clustering approaches to QEEG deviance characterization may better characterize ADHD as a heterogeneous disorder.<sup>26</sup> The longitudinal stability of alterations in EEG frequency bands due to ADHD from childhood into adulthood has also been questioned in recent years.<sup>22,27</sup>

### ***Studies of event-related SCP***

Event-related potentials (ERPs) are small voltage fluctuations in the EEG resulting from evoked brain activity. ERP components reflect, with high temporal resolution, the patterns of neuronal activity in response to stimuli. ERPs in ADHD allow the examination of electrical representations of preparatory and preattentive processes, auditory and visual attention systems, the frontal inhibition system, and time processing. With regard to ADHD, the most replicated and robust findings in early components are a lower amplitude, longer latency, and different topography of the P300 in affected children compared with healthy controls.<sup>28</sup> However, neurofeedback of ERPs almost exclusively addresses changes in later, slower, or sustained components, which are registered in a latency range of 500 to 1000 ms after cue presentation (SCPs). SCPs represent changes of cortical direct current electrical activity and have been related to the level of excitation of underlying cortical regions. Negative SCP shifts may reflect the depolarization of large cortical cell assemblies leading to higher excitability and the allocation of more neuronal resources; positive shifts reflect reduced excitability or even inhibition.<sup>29</sup> Experimental evidence from animals and humans supports the idea that the contingent negative variation (CNV) of the typical SCP is closely related to cognitive preparation, decision-making, and time estimation. Larger CNV amplitudes reveal greater activation in sets of neurons involved in time processing.<sup>30</sup> Although alterations of some faster cognitive and inhibitory ERP components such as P300 in ADHD patients diminish in early adulthood (partly compatible with the developmental lag model), decreased CNV amplitudes remain detectable even in young adult ADHD subjects, regardless of their remission status.<sup>31</sup> These results seem to indicate residual attentional dysfunctions and timing deficits even in young adults with clinically remitted ADHD.

### ***Description: How Is the Treatment Delivered?***

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The aim of neurofeedback training can be thought of in 1 of 2 related ways: first, to teach ADHD children to adapt their neurophysiologic profile to more closely approximate that of typically developing children. Second, to help them learn to regulate attentional states and brain functions better on demand, resulting in subsequent improvements of symptoms. The self-regulation of cortical activity is realized through a process of

operant learning using real-time representation of EEG parameters. Many different animated feedback presentations that are suited for children and adolescents are now available. EEG measures of interest are converted into visual or acoustic signals and fed back in real time. In some feedback animations, the cortical activity is, for example, represented by the height or speed of a feedback object (eg, a ball, plane, or cartoon character moving across the screen). If the EEG activity is regulated in the desired way, the object rises, falls, or advances more quickly. In other animations, the patient must try to view a movie, or change the color of an object on the screen by generating the neural activity of interest. To date, no studies directly assessed the effects of feedback modality (visual or auditory or combined) on outcome measures.<sup>32</sup> Successful trials are immediately rewarded by a tone, a “smiley,” or points. Therefore, neurofeedback may be regarded as “a fine-grained form of cognitive behavior modification.”<sup>33</sup> Individual parameter thresholds are typically adjusted throughout the course of the training so that an encouraging amount of positive feedback is guaranteed. Like other operant training approaches, neurofeedback requires a transfer from the training context to the everyday life of the patient. Therefore, some training trials without feedback can be incorporated to catalyze generalization.

### ***Training protocols***

Based on the above-mentioned alterations of electrophysiologic parameters (QEEG and ERPs) in ADHD, clinicians utilize 2 basic types of training protocols. In neurofeedback, the term “protocol” also refers to a wide range of details that form a part of the overall training paradigm (eg, a specific selection of reinforcement and inhibitory parameters), and the EEG-montage to deliver the training.<sup>32</sup> In ADHD, a conventional QEEG neurofeedback protocol for reducing inattention and impulsivity consists of operant suppressing of theta activity and enhancement of beta activity.<sup>34</sup> To reduce hypermotoric symptoms, enhancement of sensorimotor rhythm (SMR; low beta 12–15 Hz activity) is sometimes used in addition to this theta-beta protocol. Based on the electrophysiologic evidence of altered SCPs in ADHD, a different protocol has emerged aiming at the modifications of SCPs to regulate cortical excitation thresholds.<sup>35,36</sup>

### ***Empirical Support***

The quality of study design and reporting regarding the effectiveness of neurofeedback on ADHD have both clearly improved in recent years.<sup>37,38</sup> Several controlled studies produced evidence of short-term improvements in core symptoms, neuropsychological functions, and electrophysiologic correlates of ADHD; for overviews, see Refs.<sup>39–42</sup> Meanwhile, meta-analyses have been published on the effects of neurofeedback on ADHD symptoms. The first meta-analysis on the effects of neurofeedback on ADHD core symptoms<sup>6</sup> included data on 467 subjects from 10 prospective, controlled trials. Control conditions comprised waiting list groups, interventions like EMG-feedback, and computerized cognitive training and stimulant pharmacotherapy. Mean effect sizes (Cohen’s  $\delta$ ) for neurofeedback were 0.81 for inattention, 0.39 for hyperactivity (both assessed via rating scales), and 0.68 for impulsivity as measured by continuous performance tests. No differential improvement was observed between the 2 basic protocols (QEEG and SCP), in line with direct comparisons.<sup>43,44</sup> Some of the studies included in this meta-analysis have, however, been criticized for lacking appropriate controls and follow-up, failing to randomly allocate participants to treatment conditions, using poor diagnostic criteria, and using subjective and unblinded outcome measures.<sup>37,40</sup> In addition, they failed to take into account the influence of the training setting provided during extensive biofeedback.

A subsequent meta-analysis from the European ADHD Guidelines Group,<sup>11</sup> using a more rigorous and selective approach, included 8 studies meeting high methodological standards (Table 1). Neurofeedback yielded a significant ( $P < .0001$ ) treatment effect (effect size [ES] = 0.59; 95% CI: 0.31–0.87) using ADHD scores from raters (often unblinded) closest to the therapeutic setting. These effects were substantially reduced to a statistical trend ( $P = .07$ ) when probably blinded ratings were applied (ES = 0.30; 95% CI: –0.02–0.61). Because blinded assessments were only available from 4 of the 8 included studies, the authors concluded that better “evidence of efficacy from blinded assessments is required before Neurofeedback is likely to be supported as ADHD treatment.”<sup>11</sup> Since then, and by March 2014 (when this article was finalized), several neurofeedback studies targeting children with ADHD meeting similar rigorous inclusion criteria and using at least partly blinded measures have been published (Table 2). Although these recent studies were well controlled, most used partly innovative but nonstandard protocols or equipment and none demonstrated systematic learning of cortical control (considered a prerequisite for specificity, see later discussion). Although only the largest study found a significant advantage for neurofeedback over control treatment on any primary outcome, the nonsignificant advantage reached small to medium effect size for some blinded primary outcomes in all studies. The smallest study<sup>25</sup> compared neurofeedback (tomographic SCP plus frequency neurofeedback) to EMG biofeedback with effective parent blinding. The advantage for tomographic neurofeedback was not significant but reached a medium effect size for all (blinded) parent ratings (ES = 0.57 for the total ADHD score). The larger study comparing individualized frequency training to sham control<sup>45</sup> included the data from Ref.<sup>46</sup> No significant advantage for the (blinded) primary outcomes was observed, but the effect for the decrease of hyperactivity/impulsivity symptoms reached a small to medium effect size (ES = 0.31, computed from their data). The largest recent study<sup>47</sup> used school-based neurofeedback. Although blinding of participants, parents, and teachers was not attempted in this study, blinded behavioral classroom observations indicated a significant reduction (ES = 0.43) of verbal-motor ADHD (off-task) behaviors corresponding to hyperactivity/impulsivity after the intervention,<sup>47</sup> as well as at follow-up when using a nonlinear model of change.<sup>48</sup> The advantage of neurofeedback was also maintained for blinded classroom observation when compared with an active computer training, including attention and working memory games of similar duration and intensity. However, when teacher ratings were used as the best blinded outcome for,<sup>25,45</sup> and when the classroom observations of inattention were included for,<sup>49</sup> following the protocol of,<sup>11</sup> these moderate effects were reduced substantially and no longer significant. This considerably less positive picture, and the lack of stability across properly blinded outcomes, may reflect reduced bias (due to an unknown mechanism given proper blinding), but could also suggest that teacher and classroom observations are less sensitive to neurofeedback effects on core ADHD symptoms than parent ratings. The results highlight the need for future studies to examine in more detail the reasons for the differences between outcomes.

### **Methodological issues**

The most recent neurofeedback meta-analysis<sup>11</sup> has been criticized for underestimating neurofeedback efficacy because it included trials with training approaches with nonstandard protocols impeding learning and uncontrolled changes in medication dosage.<sup>50</sup> However, these criticisms reflect mainly problems inherent in the field rather than the meta-analysis per se. Controlling for medication changes (through sensitivity analysis) was indeed considered important and part of the authors' protocol,<sup>11</sup> but

**Table 1**  
**Characteristics of studies included in the meta-analysis of the European ADHD Guidelines Group**

Study	Design	Duration of Treatment; Number of Sessions	Treatment	Control Condition	N		Age Range in Years
					Treatment	Control	
Bakshayesh et al, <sup>76</sup> 2011	RCT; parallel groups	30 sessions; 10–15 wk	Theta-Beta	EMG	18	17	6–14
Beauregard & Levesque, <sup>60</sup> 2006	RCT; parallel groups	40 sessions; 13 wk	Theta-Beta	No treatment	15	5	8–12
Gevensleben et al, <sup>44</sup> 2009	RCT	36 sessions, 2 mo	18 sessions Theta-Beta + 18 sessions SCP in balanced order	Attention skills training	59	35	8–12
Heinrich et al, <sup>35</sup> 2004	RCT	25 sessions; 3 wk	SCP	Waiting list	13	9	7–13
Holtmann et al, <sup>77</sup> 2009	RCT, parallel groups	20 sessions in 2 wk	Theta-Beta	Attention skills training	20	14	7–12
Lansbergen et al, <sup>46</sup> 2011	Stratified, RCT	30 sessions, 3 mo	Individualized frequency band training	Placebo, neurofeedback	8	6	8–15
Linden et al, <sup>34</sup> 1996	RCT	40 sessions, 6 mo	Theta-Beta	Waiting list	9	9	5–15
Steiner et al, <sup>49</sup> 2011	RCT	Average 23.4 sessions, 4 mo	Theta-Beta	Waiting list	13	13	Not reported Mean 12.4 ± 0.9

Abbreviation: RCT, randomized controlled trial.

Adapted from Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170(3):280.

Table 2 Characteristics of studies published following the meta-analysis of the European ADHD Guidelines Group meeting inclusion criteria or testing neurofeedback against medication							
Study	Design	Duration of Treatment; Number of Sessions	Treatment	Control Condition	N		
					Control	Treatment	
					Age Range in Years		
Van Dongen-Boomsma et al, <sup>45</sup> 2013	Stratified, RCT	30 sessions, 3 mo	Individualized frequency band training	Placebo, neurofeedback	22 19	22 19	8–15 Mean 10.62 ± 2.25
Maurizio et al, <sup>25</sup> 2014	RCT	36 units in 18 sessions, 6 mo	SCP and Theta-Beta (tomographic)	EMG biofeedback (matched)	13 12	13 12	8.5–12.9 Means 10.6 ± 1.3, 10.0 ± 1.2
Steiner et al, <sup>47</sup> 2014	RCT	40 sessions, 5 mo, at school	Theta-Beta	Community treatment/standard care	34 36	34 36	Not reported Mean 12.4 ± 0.9
Duric et al, <sup>55</sup> 2012	RCT, head-to-head, combination	30 sessions, 2.5 mo	Theta-Beta	Medication Medication + Theta-Beta			6–18
Meisel et al, <sup>56</sup> 2013	RCT, head-to-head	40 sessions, 5 mo	Theta-Beta	Medication management	12 11	12 11	7–14 Means 9.53 ± 1.8, 8.9 ± 1.53
Ogrim & Hestad, <sup>54</sup> 2013	RCT, head-to-head	30 sessions, 7–11 mo	Theta-Beta	Medication management			7–16

Abbreviation: RCT, randomized controlled trial.

Adapted from Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170(3):280.



required a larger number of probably blinded studies.<sup>51</sup> The lack of standards regarding neurofeedback protocols is even more problematic for the field. Controlled studies on the optimal frequency bands, scalp sites, feedback timings, and thresholds are largely lacking, and clinical practice is still based on early animal studies and divergent clinical experience without control. This seems particularly problematic for QEEG (frequency band) training, whereby recent evidence no longer supports the presumption that increased theta and beta or SMR reduction are reliable ADHD markers (discussed above). These findings question the standard unidirectional “normalization” rationale of QEEG neurofeedback and suggest instead the adoption of bidirectional,<sup>52</sup> individualized,<sup>46,53</sup> or SCP-based regulation approaches. In addition, allowing “probably blinded” rather than strictly blinded measures in the largest studies may well have counterbalanced this bias in this meta-analysis.

A particularly relevant question from a clinical point of view is how neurofeedback compares to standard medication in the short term. Arns and coworkers<sup>6</sup> included a meta-analysis of 5 such head-to-head comparison studies of neurofeedback with stimulant medication and found no difference for impulsivity ratings. Although these studies were not randomized or blinded, the findings are difficult to explain through expectancy bias, which would be likely in favor of the “gold-standard” stimulant treatment in such a comparison. Several randomized controlled trial studies have since compared neurofeedback to medication alone or in combination (see **Table 2**). Although one of them<sup>54</sup> found neurofeedback effects inferior to medication effects, the other 2 studies<sup>55,56</sup> found no differences between medication and neurofeedback effects, and one study<sup>55</sup> reported that neurofeedback or medication alone was as effective as the combination.

### ***Relation between training performance and clinical improvement***

A key question regarding the specificity of the effects is whether treatment success is related to the degree of effective learning during neurofeedback (ie, the learning curve at the neural level). Some studies reported correlations between measures of improved cortical self-regulation and clinical gains. In one SCP study,<sup>36</sup> participants were divided into groups of successful or unsuccessful regulators, based on the ability to produce the required EEG activity in negativity trials without feedback. Children who showed good performance in cortical self-regulation demonstrated a better clinical outcome at the end of training than the unsuccessful regulators. Evidence from Ref.<sup>57</sup> points in a similar direction. Although only half the children in their neurofeedback condition learned to regulate cortical activation during a transfer condition (without direct feedback), the neurofeedback training performance of these good performers was closely related to clinical improvement in hyperactivity ( $r = 0.81$ ) and impulsivity ( $r = 0.75$ ). However, the poor regulators also showed comparable clinical improvement, indicating considerable nonspecific effects. Neurofeedback may also involve learning to reduce motor activity through artifact feedback and instructions to sit still, but this type of learning does not seem to directly account for clinical improvement.<sup>52</sup> Similarly, although learning was superior for EMG biofeedback (targeting motor control, the control condition) compared with neurofeedback (targeting cortical control) in one study,<sup>25</sup> the clinical effects did not reflect that advantage and even nonsignificantly favored neurofeedback. These results also illustrate that learning in the control condition may be required to match motivation and the experience of self-efficacy and suggest that sham control conditions that do not allow learning may not be suitable.

Together, these findings indicate that although learning can correlate with clinical improvement and thereby provide important evidence for the specificity of effects,

the relation may not be trivial, may involve learning of other behavioral and physiologic states than the targeted ones, and may involve delays until evident in clinical improvement. Demographic, symptomatic, or other patient characteristics, which might predict successful neurofeedback learning and transfer performance, have not yet been identified.<sup>6,57</sup> In summary, the increased use of blinded ADHD measures and multiple control conditions in recent neurofeedback research is encouraging, but most recent results remain ambiguous without evidence for the learning of self-regulation<sup>25,58</sup> and leave open whether the neurofeedback protocols were compromised. Effect size considerations still tend to support some efficacy for neurofeedback, at least when considering some blinded outcomes, and may yield a slightly more positive picture than offered in the recent meta-analysis,<sup>11</sup> but evidence from larger studies using standard neurofeedback and examining learning under way<sup>59</sup> will be crucial to allow firmer conclusions. Also, most of these findings were obtained for groups including a considerable proportion of medicated ADHD patients, and most support the use of neurofeedback only in multimodal treatment schemes (but see Ref.<sup>55</sup>). However, the best blinded controlled effects were nonsignificant in the small group studies and remained considerably reduced when compared with more proximal ratings. These recent studies also raise the possibility that “good,” partly active control conditions, may themselves bring about considerable improvement in ADHD symptoms, with 19% symptom reduction for EMG biofeedback<sup>25</sup> and 17.8% for sham neurofeedback,<sup>45</sup> compared with 9.4% reduction for the computer training control in the largest study.<sup>44</sup> Further research should clarify whether these sizable and clinically relevant effects are just nonspecific placebo effects mediated by expectancy, or whether active attempts to learn physiologic self-regulation through feedback and transfer, even though unsuccessful by design or targeting peripheral control, induce similar brain plasticity as implicated for neurofeedback.

### ***Imaging studies***

Neurofeedback appears to involve regulation of an extended cortical and subcortical network, with partly distinct regions for central negativity (activation) and positivity (deactivation) trials following successful SCP training. In a first controlled functional magnetic resonance imaging (fMRI) study on neurofeedback in ADHD,<sup>60</sup> it was reported that the enhancement of SMR, beta activity, and the suppression of theta activity led to a normalization of neural activity within brain regions key to selective attention and response inhibition (ie, the anterior cingulate cortex, caudate nucleus, and substantia nigra). As these studies lack an active control condition, the possibility that the effects may be explained by unspecific variables of the treatment setting cannot be excluded. An essential part of neurofeedback training is the reinforcement of desired “behavior,” which will in itself induce the production of cortical (and, at least indirectly, subcortical) brain alterations in regions known to be involved in reinforcement processing. Via visual feedback, the trainee receives a high amount of rewarding stimuli throughout the training. It could, therefore, be hypothesized that part of the clinical outcome could be mediated by effects on the reward system. Simultaneous EEG-fMRI imaging findings during reward anticipation in fact demonstrated that negative SCPs (CNV activity) correlated with cortical and subcortical reward system activation.<sup>61</sup> Evidence to support this prediction in ADHD is still limited, but preliminary results of an ongoing study seem to point in this direction.<sup>62</sup> Although participants with ADHD showed a significant hypoactivation in the neural reward pathway before training compared with healthy controls,<sup>20</sup> sessions of SCP-neurofeedback led to a modification and partial functional normalization in pivotal reward-related structures.

### ***Stability over time***

A major advantage of neurofeedback and other neurotherapeutic approaches<sup>63</sup> over typical pharmacologic interventions (as for other behavioral, learning-based interventions) is the potential for sustained, long-term benefits after successful completion of treatment. Investigations<sup>36</sup> indeed found positive effects on ADHD symptoms being stable 6 months after training. Similarly, 2 studies<sup>48,63</sup> reported sustained advantages following neurofeedback at 6-month follow-ups, and one study<sup>64</sup> even reported stability after 2 years, following neurofeedback and a few booster sessions. However, interpretation of these findings is complicated by the fact that most ratings of long-term effects (except for the behavioral observation measure in Ref.<sup>48</sup>) were not blinded and thus subject to bias.

Despite evidence for beneficial effects of neurofeedback on ADHD symptoms, the National Institute for Health and Clinical Excellence (NICE) guidelines on ADHD do not recommend it as a treatment option,<sup>65</sup> but the most recently published studies were not yet part of the NICE review process.

## **CLINICAL DECISION-MAKING**

### ***Who Is Most Likely to Respond?***

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To guide the decision whether a training approach which is as intensive and time-consuming as neurofeedback is justified for a given patient, a better understanding is needed of how treatment effects are related to individual clinical and neurocognitive characteristics and electrophysiologic markers. Predictors and mediators of response in subgroups of ADHD patients and/or individual patients have only been studied in some of the most recent trials. Initial evidence for predictive and protocol-specific EEG or ERP markers is encouraging, as detailed in the following subsections.

### ***Relation between pretreatment EEG characteristics and clinical improvement***

Pretraining EEG measures seem to indicate later treatment response at least for SCP training (while similar findings have not yet been reported for EEG frequency band training). A larger pretraining CNV is associated with a larger reduction of ADHD symptoms for SCP training, accounting for about 20% of the variance in outcome.<sup>66</sup> Similarly, pretraining alpha resting activity is associated with behavioral improvements. Concerning the improvement of ADHD core symptoms induced by the SCP training, nearly 30% of the variance was explained by the combined predictor variables CNV and alpha activity.

### ***Training intensity***

Positive changes on the behavioral, neurophysiologic, and neuropsychological levels have been reported after as few as 20 and as many as 40 sessions of neurofeedback. Although no trial has systematically examined the number, frequency, and duration of sessions required to elicit a positive and enduring effect, a meta-analysis of 6 indicated a moderate positive correlation ( $r = 0.55$ ) between the treatment effect on inattention and the number of training sessions across studies. Achievement of cortical self-regulation via neurofeedback was also related to the individual's ability for visual imagery.<sup>67</sup> This line of thought has not been further pursued in recent years, but the limited strength of the reported correlations ( $r = 0.37$ ) and clinical experience suggests that imagery may only explain a small proportion of the interindividual variance in learning and treatment outcome and that other factors may play a substantial role in the mechanisms responsible for treatment response to neurofeedback.

***Role of parents and parenting style on treatment success***

Parenting style may moderate the effectiveness of neurofeedback. Patients whose parents were systematically using reinforcement principles in their normal practice were more likely to demonstrate a reduction in the frequency of core ADHD symptoms following neurofeedback training than children of parents with a nonsystematic parenting style.<sup>68</sup> When “systematic” parenting approaches were used, improvements were even maintained when the concomitant medication was discontinued. Similar results<sup>57</sup> indicated that parental support significantly mediates clinical improvement for both learners and nonlearners of self-regulation. Other less specific factors, such as effort, time (and attention!) invested, improved feedback and reward processing, and learning to reduce motor hyperactivity and to sit still to avoid artifacts,<sup>52</sup> may also contribute to the considerable effects common to neurofeedback and partly active control trainings.

***What Outcomes Are Most Likely to Be Affected by Treatment?***

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Neurofeedback aims at the improvement of ADHD core symptoms and their underlying neuropsychological pathways. Regarding the 3 symptom domains of ADHD, current evidence suggests stronger effects of neurofeedback on attention and impulsivity than hyperactivity.<sup>6</sup>

***What Are the Contraindications for Treatment?***

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There are no known contraindications for standard neurofeedback protocols. However, because epilepsy has been treated with SCP downregulation targeting positivity/deactivation,<sup>69</sup> epilepsy may represent a contraindication for the typical SCP upregulation protocol (ie, targeting negativity/activation in ADHD). Further research is required for this.

***What Are Potential Adverse Effects of the Treatment?***

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To date, no severe or permanent side effects of neurofeedback have been reported, and adverse effects systematically decrease over training as for placebo control with blinded assessment.<sup>45</sup> Headaches and fatigue have been occasionally documented, which seem to be attributable to the intentional demands and associated muscular tension during training sessions.<sup>33</sup> Some patients with a simultaneous and well-tolerated regime of psychostimulants may experience typical medication side effects in the course of neurofeedback training that may require dose adjustment. This phenomenon might be related to the additional stimulating effect of the training.

***How Should the Treatment Be Sequenced and/or Integrated with Drug Therapy and with Other Nondrug Treatments?***

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Although current evidence has not sufficiently addressed the differential efficacy of the existing neurofeedback protocols, evidence from one study suggests that the order of SCP and QEEG can affect results (favoring a start with the simpler QEEG training). Clinical practice may be based on established principles of learning; make use of clear instructions, the importance of regular, short, and repetitive sessions; and transfer into everyday life. Some of the high-quality studies with longer follow-up included “booster sessions” time-tabled after several weeks after treatment to refresh the ability of self-regulation and to maintain treatment effects.

## FUTURE DIRECTIONS

The question whether one of the established training protocols (SCP training and training of EEG frequency bands) is more effective than the other is not yet fully resolved, but the initial evidence for distinct EEG and ERP outcome predictors suggests that the response may depend on the neurophysiologic subtype. Future research on neurofeedback should focus on such differential effects (which intervention works for whom?). Although EEG-based neurofeedback can build on a large evidence base of controlled studies and will continue to dominate for reasons of low cost and ease of use, new neurofeedback techniques based on hemodynamic measures are emerging. Both near infrared spectroscopy neurofeedback<sup>70</sup> and real-time fMRI neurofeedback may offer advantages in terms of targeting well-defined brain regions, and such studies are ongoing.<sup>71</sup> Notably, real-time fMRI additionally opens the possibility for more rapid learning to regulate deep structures, such as the dopaminergic midbrain regions<sup>72</sup> implicated in ADHD along with cortical regions.<sup>73</sup>

### *Additional Outcome Parameters*

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With regard to the multiple identified pathways to ADHD, initial steps have been undertaken to target deficits in executive dysfunction (eg, making use of inhibition or working memory trainings; see the article by Sonuga-Barke and colleagues elsewhere in this issue) and reward-related impairments. All neurofeedback protocols are characterized by reinforcement for the improvement of targeted “neural behavior,” but the impact of training-induced neurobiological and neuropsychological changes on reward-related functions and structures has been rarely studied yet. In addition, temporal processing deficits as the third dissociable neuropsychological component of ADHD have not been explicitly addressed in many intervention studies. Neurofeedback studies aiming at the modulation of the CNV as an on-line marker of temporal coding and time-based decision-making may explicitly address impaired timing as an important treatment outcome.<sup>74</sup>

## SUMMARY

Based on current knowledge, neurofeedback is likely to be used as an element in the broader set of nonpharmacologic treatments for ADHD in multimodal therapy. It has recently been claimed that neurofeedback is “efficacious and specific.”<sup>6,42</sup> However, the authors think that in light of the most recent findings from sham-controlled studies<sup>75</sup> and the analysis of probably blinded measures,<sup>11</sup> there is a strong need for more evidence from well-blinded, methodologically sound and sensitive trials before neurofeedback can be assigned this highest level of evidence as a front-line treatment of ADHD. Firmer conclusions must await upcoming evidence from larger, well-controlled neurofeedback studies, which demonstrate learning of self-regulation in addition to using well-blinded and sensitive outcome measures.

## DISCLOSURES

M. Holtmann served in an advisory or consultancy role for Lilly, Novartis, Shire, and Bristol-Myers Squibb and received conference attendance support or was paid for public speaking by AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lilly, Medice, Neuroconn, Novartis, and Shire. E. Sonuga-Barke has financial disclosures in relation to Shire Pharmaceuticals—speaker fees, consultancy, advisory board membership,

research support, and conference attendance funds. Janssen Cilag has received speaker fees. Visiting chairs at Ghent University and Aarhus University. Grants awarded from MRC, Economic and Social Research Council, Wellcome Trust, Solent NHS Trust, European Union, Child Health Research Foundation New Zealand, National Institute on Handicapped Research, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek–Vlaanderen (FWO). S. Cortese has no current relationships with drug companies. He receives royalties from Argon Healthcare Italy for educational activities on ADHD. Before 2010, he served as scientific consultant for Shire Pharmaceuticals and received support to attend meetings from Eli Lilly and from Shire. D. Brandeis has no disclosures to report.

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