EXPERT REVIEWS

Neurofeedback in children with ADHD: validation and challenges

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Neurofeedback (NF), a type of neurobehavioral training, has gained increasing attention in recent years, especially concerning the treatment of children with ADHD. Promising results have emerged from recent randomized controlled studies, and thus, NF is on its way to becoming a valuable addition to the multimodal treatment of ADHD. In this review we summarize the randomized controlled trials in children with ADHD that have been published within the last five years and discuss issues such as the efficacy and specificity of effects, treatment fidelity and problems inherent in placebo-controlled trials of NF. Directions for future NF research are outlined, which should further address specificity and help to determine moderators and mediators to optimize and individualize NF-training. Furthermore, we describe methodological (tomographic NF) and technical ('tele-NF') developments that may also contribute to further improvements in treatment outcome.

Keywords: ADHD • attention-deficit/hyperactivity disorder • evaluation • mediators • moderators • neurofeedback • self-regulation • slow cortical potentials • specificity • θ/β training • SCPs

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Progress in neurofeedback (NF)-research for children with ADHD during recent years encouraged us to provide an update on our 2007 NF review [1].

ADHD, one of the most common childhood psychiatric disorders, is characterized by age-inappropriate levels of inattention, motor hyperactivity and impulsivity [2]. Different neuropsychological models exist in order to explain difficulties in self-regulation underlying these key symptoms, for example, delays in brain development [3], a general cortical hypoarousal [4], deficits in the allocation of neuropsychological resources [5], alterations in the reinforcement/extinction of behaviour [6], or a maladjustment of interacting neuronal networks [7]. Because ADHD has serious developmental implications in the short and long term that encompass difficulties in social adaptation [8], educational attainment [9] and quality of life [10], treatment should begin as early as possible.

Currently, treatment options encompass child-, family- and school-oriented cognitive, behavioral and educational interventions subsumed as cognitive behavioral interventions [11], as well as medication: primarily stimulants (e.g., methylphenidate) and selective norepinephrine reuptake inhibitors (e.g., atomoxetine) [12–15]. In principle, clinical guidelines recommend a multimodal treatment [16]. In the short term, stimulant medication is considered the most effective treatment [17]. However, side effects, a considerable rate of nonresponders, and reservations against medication are serious limitations of drug treatment [12,16]. Adequate treatment of ADHD in children is still subject to controversies. Neuropsychological/physiological models for ADHD offer new starting points for further effective treatment modules. In this respect, NF is a possible option. In 2007, we published a review article on NF focusing *inter alia* on ADHD. In this review, we suggested that randomized controlled trials (RCTs) be conducted because evidence for the effects of NF at the clinical (behavioral) level was lacking. Within the last 5 years, NF research on ADHD has increased (e.g., four RCTs have been published). The aims of the present article are to provide an update on NF treatment for ADHD and to delineate issues to be addressed in future studies. In the first part of the review, we outline methodological concepts of NF and summarize the RCTs, referring to the feasibility and efficacy of NF in children with ADHD. Both behavioral and neuronal levels are considered.

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The second part of the review discusses open questions and controversies as well as methodological options and constraints in the evaluation of NF.

Methodological concept & validation

Differences in mental states and distinct cognitive processes are reflected in specific brain electrical activity (EEG; event-related potentials [ERPs], evoked potentials) patterns [18,19]. Thus, it is reasonable that NF training, in which the voluntary modulation of brain electrical activity patterns is learned, could also induce changes (improvements) at the behavioral level.

Definition

NF can be considered as a theory-driven treatment based on operant learning strategies [20]. The simultaneous and contingent feedback of neurophysiological signals is provided with the aim to learn to control the processes underlying these signals and thereby enhance (cognitive–emotional–behavioral) self-regulation. Changes in neurophysiological activity in the desired direction are reinforced by auditory and/or visual feedback. Feedback is usually presented in the form of simple computer games in which children can earn points (e.g., by moving objects on the screen).

In a series of training sessions, the regulation skills are acquired and as the training proceeds, it addresses how to use these competences in daily life, for example, when and how to apply the learned strategies and link their use to cues ('intended transfer', comparable to the use of verbal self-instructions). With time, this initially controlled cognitive process may develop (e.g., via social reinforcement) to become automatic [1].

Successful application of NF protocols in recent studies accentuated efforts to transfer these neuroregulation skills to daily life, linking NF to the canon of cognitive behavioral interventions [21,22]. This concerns a more psychological level, including cognitive-attributional concepts like self-efficacy, locus of control, achievement motivation and social reinforcement.

NF protocols in ADHD

For children with ADHD, brain electrical activity patterns representing attentional processes and executive functioning, respectively, are targeted with NF.

In θ/β frequency band training, the task is to maintain a state of cortical activation (i.e., an attentive and focused but relaxed state) by reducing activity in the θ band of the EEG (4–8 Hz) and increasing activity in the β band (13–20 Hz). Alternatively, a decrease of the θ/β ratio can be achieved through training.

In several studies, ADHD was associated with increased slow wave activity (θ, 4–8 Hz), most pronounced at posterior regions, and/or reduced α (8–13 Hz) and/or β (13–30 Hz) activity in the resting EEG (for a review, see [4]) as well as during attention task processing [23]. This neurophysiological deviation is typically provided as a rationale to use θ/β training in children with ADHD. However, EEGs are influenced by situational factors and thus, are determined by trait and state variables [24]. It also has to be noted that θ activity does not reflect a unitary phenomenon. For example, frontal–midline θ is associated with working memory processes and not related to the θ findings in ADHD.

As described by Egner and colleagues in healthy adults, a frequency band training such as, θ/β training is not necessarily accompanied by changes in the resting EEG in the frequency band addressed in the training (although this might depend on the baseline EEG) [25].

NF can also be seen as a tool for enhancing specific cognitive or attentional states ('peak performance'). In this respect, children with ADHD may rather learn compensatory strategies than fix an initial deficit in EEG activity. The so-called quantitative EEG NF is based on the assumption of 'repairing' an EEG deficit. A multielectrode (10/20 system) EEG is recorded, analyzed and compared to a 'normative' database. The electrode/frequency constellation with the greatest deviance from the 'norm' is addressed/used in the training.

A training of slow cortical potentials (SCPs) addresses the regulation of phasic cortical excitability to optimize allocation of cortical resources.

SCPs are changes in cortical electrical activity lasting from several hundred milliseconds to several seconds. Negative SCPs reflect increased excitation (e.g., during states of behavioral or cognitive preparation), positive SCPs indicate a reduction of the cortical excitation of the underlying neural networks (e.g., during behavioral inhibition) [26].

Frontostriatal networks contribute to the generation of negative and positive SCPs in SCP training with positivities accompanied by deactivation of, for example, the motor cortex [27,28]. SCP changes learned during NF training do not only reflect nonspecific phasic alertness but are associated with effects at the behavioral (performance) level (for review, see [29]).

One of the established ADHD models suggests a dysfunctional regulation of energetic resources in ADHD [5]. At the neuronal level the regulation of energetic resources is reflected by slow cortical potentials. This model is supported by the finding of ERP studies that, the contingent negative variation (CNV), a SCP elicited such as in cue trials of a continuous performance test reflecting anticipation and/or preparation, is reduced in children with ADHD (for a review, see [30]). Hence, SCP training (in which surface-negative and surface-positive SCPs have to be voluntarily generated over the sensorimotor cortex) could address this regulation deficit and thus, help children with ADHD to improve their behavior. Children with ADHD and attentional problems can learn to modulate their SCPs voluntarily [21,31,32]. Clinical outcome was predicted by the ability to produce a negative potential shift in transfer trials (i.e., trials without contingent feedback).

Even more importantly, SCP training was associated with CNV effects (e.g., a CNV increase in a cued continuous performance test; [33]). Doehnert and colleagues also reported effects in the resting EEG, namely a reduction of the θ/β ratio at Cz for children with combined-type ADHD and a slight increase of activity in the upper α band (10–12 Hz) for the complete group [34].

Clear knowledge about the neuronal basis for the effects of both NF protocols is lacking (for a comparison of θ/β and SCP training, see Table 1). A better understanding of the underlying

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neurophysiological processes would probably help to specify indication criteria or prevent nonresponse, especially in light of the potentially different EEG subtypes of ADHD [35], suggesting different needs for specific EEG tuning.

Randomized controlled NF trials in ADHD

A series of earlier studies, which were reviewed in more detail elsewhere [1,36], provided evidence for the positive effects of NF treatment in children with ADHD. For θ/β training (e.g., [37,38]) and SCP training (e.g., [21,32,33]), a decrease of behavioral problems and improved cognitive performance has been reported. Comparable effects for NF (θ/β) and methylphenidate were obtained in two studies [37,38]. However, both were nonrandomized trials and in these reports, detailed information about the titration/medication procedure is missing, or the procedure was not consistent with clinical guidelines.

The studies conducted thus far have obvious shortcomings (e.g., insufficient statistical power, lack of an adequate control group, no randomization, no follow-up) [1,39]. Therefore, the results of the first meta-analysis [36], which mainly based on these studies, do not allow general conclusions about the efficacy of NF training in children with ADHD to be drawn. The results indicate that, at least for some of the patients (who specifically ask for NF or decide against medication), positive effects can be expected. Clinically relevant reductions were obtained for symptoms such as inattention (effect size [ES] = 0.8), impulsivity (ES = 0.69) and, to a lesser extent, hyperactivity (ES = 0.4).

In some studies, the neuronal mechanisms underlying successful NF training were investigated, providing evidence that children with ADHD are able to better activate and regulate their neuronal resources after the training [33,34,40].

Our group was the first to conduct a randomized-controlled NF trial in children with ADHD with a sufficiently large sample size to reliably detect at least medium effects. For ethical and methodological reasons, we preferred computerized attention skills training over placebo (sham) NF training. The attention skills training contained tasks/games addressing, for example, visual and auditory perception and vigilance (Table 2).

NF and attention skills training were designed as similarly as possible concerning the setting and the demands upon the participants (e.g., performing attention-demanding tasks on a computer, using the same amount of training units and exercises, as well as the same trainer, development of strategies for focusing attention, transfer in daily life and 'homework').

We also intended to compare θ/β training and SCP training at the intra-individual level in a crossover design. Therefore, the NF training consisted of two blocks of 18 training units each. Thus, our study had an artificial scientific setting (relatively short, noncoordinated training blocks) and was not intended to maximise treatment outcome.

At the behavioral level (parent and teacher ratings), NF was superior to the control training concerning ADHD core symptomatology and associated domains (e.g., oppositional behavior). For the primary outcome (improvement in the total score of the German ADHD rating scale, FBB-HKS [41]), a medium effect size of 0.6 in relation to the control training was obtained. However, the responder rate (>25% reduction of the primary outcome measure) was only slightly above 50%. Behavioral improvements were comparable for both NF protocols [42].

Because parents of the NF group and the control group did not differ in expectations or satisfaction with the treatment, these nonspecific ('placebo') factors should not have influenced the results.

Owing to comparable settings and demands for NF and the control training, the superiority of NF training effects, was primarily ascribed to specific factors of the NF treatment. Superiority of the NF-group was still evident at a 6-month follow-up [43].

Training effects at the neurophysiological level were studied by means of the resting EEG (2-min eyes-open) and event-related potentials (recorded during the attention network test [44]).

In the resting EEG, a reduction of θ activity after the combined NF training was found that was not specific for the θ/β training block. No pre-post effects were obtained for the β band.

For θ/β training and SCP training, specific associations between EEG patterns and improvements at the behavioral level (mainly related to hyperactivity/impulsivity) were obtained. Behavioral

Table 1. Comparison of the two neurofeedback protocols typically applied in children with ADHD: θ/β training and slow cortical potential training.

θ/β training	SCP training
Tonic aspects of cortical activation	Phasic aspects of cortical activation/ excitability
Training in one direction (θ ↓, β ↑): attentive and focused but relaxed state	Negativity trials: increase of excitability, raising attention Positivity trials: decrease of excitability, relaxed state
ADHD → central nervous underactivation	ADHD → dysfunctional regulation of energetical resources
Longer training trials (e.g., 5 min length)	Approximately 100–150 relatively short (e.g., 8 s) trials in a training unit
Calculation of baseline values at the beginning of a training unit (e.g., 3-min trial)	Calculation of a reference value at the beginning of each trial (e.g., 2-s period)
	Prone to artefacts due to different amplifier settings (near-DC recordings)

DC: Direct current.

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Table 2. Summary of recent randomized controlled neurofeedback trials in children with ADHD.

Study (year)	Objectives	Subjects	NF training
Gevensleben *et al.* (2009a, 2009b, 2010); Wangler *et al.* (2011)	Behavioural, cognitive and neurophysiological (EEG, ERPs) effects of θ/β training and SCP training Maintenance of behavioral effects (6-month follow-up) Prediction of training success	NF training: 59 children (51 boys, eight girls) Control training: 35 children (26 boys, nine girls); DSM-IV combined and inattentive subtypes Age: 8–12 years Without accompanying therapies during study participation	36 training units of approximately 50 min, separated in two blocks of 18 units (nine double-unit sessions). 2–3 sessions per week One block of θ/β training and one block of SCP training (crossover design) θ/ β training: increase of β (16–20 Hz) activity and decrease of θ activity; feedback electrode: Cz; 5-min and 10-min trials SCP training: 100–120 negativity and positivity trials (8 s) per training unit Feedback and transfer trials Transfer into daily life included in the training
Holtmann *et al.* (2009)	Behavioral, cognitive (response inhibition) and ERP effects of θ/β training	NF training: 20 children (18 boys, two girls) Control training: 14 children (13 boys, one girl) ICD-10 diagnoses: F90.0, F90.1, F98.8 Age: 7–12 years 27 children on psychostimulants	NF embedded in a 2-week multimodal day-clinic program in school holidays (e.g., social competence, psychoeducation, relaxation, short individual therapy interviews) plus 10 weekly sessions of parent training 20 sessions of θ/β training (2 sessions per day); three blocks of 10 min (48 trials) in one session Feedback electrode: Cz Feedback and transfer trials
Lansbergen *et al.* (2011)	Behavioral and EEG effects of an individualized NF training Feasibility of a double-blind, placebo-controlled trial	NF training: eight children Control group: six children DSM-IV criteria Age: 8–15 years Deviations from a EEG database Nine children receiving medication but with 'room for improvement'	30 sessions of 45 min in ~4 months (2 sessions per week) 20 min of uninterrupted neuro-regulation Individualized NF training (focus on reduction of θ and increase of SMR activity) Thresholds were adapted automatically every 30 s. Positive feedback was received in 80% of the time
Bakhshayesh *et al.* (2011)	Behavioral and cognitive effects of θ/β training	NF training: 18 children (13 boys, five girls) Control group: 17 children (13 boys, four girls) ICD-10 diagnoses F90.0 and F98.8 Age: 6–14 years Seven children (NF: four, control: three) receiving stimulant medication	30 sessions of approximately 30 min in 10–15 weeks Several 3-min trials per session θ/β training: increase of β (16–20 Hz) activity and decrease of θ activity (4–8 Hz) Feedback electrode: FCz + CPz Children were instructed to use concentration to do the training.

CNV: Contingent negative variation; d: Effect sizes; d_{corr}: Effect sizes; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EMG: Electromyography; ERP: Event-related potential; ICD-10: International Classification of Diseases 10 revision; NF: Neurofeedback; SCP: Slow cortical potentials.

improvements after the θ/β training block were associated with higher pre-training θ activity, as well as to a larger reduction of θ activity, mainly at parietal-midline sites. For the SCP training block, smaller parietal α activity and a larger increase of central α activity were related to larger behavioral improvements [45]. The CNV in the attention network test was specifically increased after SCP training. This lasting effect indicates that NF allows neuroplastic changes to be induced in the developing brain and, thus, improved neuronal networks (see also the report of Ros and colleagues, who demonstrated neuroplastic changes after one session of NF [46]). Furthermore, children with a higher baseline CNV (i.e., initially being able to recruit more resources) showed greater improvement in their parental behavior ratings. They appear to accomplish the transfer into daily life better than

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Table 2. Summary of recent randomized controlled neurofeedback trials in children with ADHD (cont.).

Control training	Results	Ref.
Computerized attention skills training paralleled concerning the setting and the demands placed upon the children	ADHD symptomatology (German ADHD rating scale, FBB-HKS): – Neurofeedback training > attention skills training – Medium effect size for the primary outcome measure (Cohen's d = 0.6) – Improvements after NF training in the symptom domains inattention and hyperactivity/impulsivity: 25–30% – Responder rate in NF group (>25% improvement in the FBB-HKS): 52% – Comparable effects for θ/β and SCP training Positive effects in other questionnaires (e.g., oppositional behavior) Comparable effects for parents and teacher ratings; 'placebo' scales: no differences between NF and control group with respect to parental attitude towards the treatment Follow-up: approximately two thirds of the children completing the training could be included (per protocol analysis). Effects were maintained EEG: – Reduction of θ activity after the complete NF training, not specific for θ/β training – Specific associations between clinical improvements and EEG measures (pretraining, changes from pre- to post-training) for the θ/β block and the SCP block, respectively ERPs: – CNV increase (in attention network test) after SCP training – No specific P3 effects Prediction: for example, SCP training: pre-training alpha activity (parietal midline) and pretraining CNV explained ~30% of the variance of the FBB-HKS total score improvement	[42,43,45,47]
Attention skills training embedded in the same multimodal program as described above Tasks for improving *inter alia* discriminating abilities, reactivity and inhibition, Increasing difficulty level	Comparable reduction of inattenion, hyperactivity and impulsivity (German ADHD rating scale, FBB-HKS) for both treatments Reduction of the FBB-HKS total score: 20% A small advantage for the attention skills training concerning inattention (d_{corr} = 0.4) and marginally larger effects of NF concerning hyperactivity (d_{corr} = 0.13) and impulsivity (d_{corr} = 0.14) Stop signal task: stronger reduction of impulsivity errors (compared with the control training; d_{corr} = 0.91) and increase of the frontal no-go-N2 after NF training	[48]
Placebo training (feedback calculated from a simulated EEG)	Reduction of ADHD symptomatology NF was not superior to the placebo condition 75% of the NF and 50% of the placebo group rated that they received placebo training Tendency for increase of θ and SMR activity in the resting EEG (eyes closed) after the NF training	[49]
Biofeedback training (EMG at frontalis muscle) Children were instructed to use relaxation to do the training.	Superiority of NF compared to the control training (Klauer's d_{corr}): – Behavioral level (German ADHD rating scale): large effect for inattention (0.94); small to medium effects for hyperacivity (0.51) and impulsivity (0.39) – Cognitive level: mainly medium to large effects for performance measures in attention tests (paper–pencil tests; continuous perfomance task) Effects mainly not significant due to small sample size; decrease of θ/β ratio and EMG level in training trials in the NF and the control group, respectively.	[52]

CNV: Contingent negative variation; d: Effect sizes; d_{corr}: Effect sizes; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EMG: Electromyography; ERP: Event-related potential; ICD-10: International Classification of Diseases 10 revision; NF: Neurofeedback; SCP: Slow cortical potentials.

children who have to build up these resources first. We compared this finding "to an athlete in sports, who, in parallel, has to build up muscles for a powerful performance and to work on his technique to utilize his muscle power. The more muscle power he already has, the more time he can spend on improving his technique" [47]. In this respect, the baseline CNV moderates the outcome of the SCP training.

The prediction of the behavioral outcomes could be improved for SCP training by calculating regression models for the EEG and ERP measurements. Concerning the German ADHD rating scale, the FBB-HKS total score, nearly 30% of the variance could be explained by the CNV and α activity pretraining variables. However, the findings currently do not have direct practical relevance, but rather, indicate that NF training could be optimized

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and individualized based on a subject's neurophysiological profile. Interestingly, in the linear regression models applied in our study, age and IQ were not significant predictor variables. However, these findings could be different if, e.g., a broader age range than 8–12 years was considered and the effects need not be linear.

Overall, our study suggests that NF training (θ/β, SCP) may be considered as an empirically supported treatment module for ADHD. Moreover, new findings about the mechanisms underlying a successful training were obtained.

Aside from papers related to our trial, further randomized controlled NF trials on ADHD have recently been published. Holtmann and colleagues studied the effects of 20-session θ/β training and also used attention skills training as a control condition [48]. Both trainings were embedded in a two-week day-clinic programme in school holidays containing different behavior therapy elements. In addition, parents received parent training. At the behavioral level (parent ratings), improvements in the core symptom domains were comparable for NF and attention skills training, with a small advantage displayed by attention skills training concerning inattention. However, in the stop-signal task, conducted pre- and post-training, a larger reduction of impulsivity errors was found in the NF group. At the neurophysiological level, this effect was accompanied by an increase of the no-go-N2 amplitude only in the NF group. The authors concluded that θ/β training may be associated with improved inhibitory control and, thus, specifically affect impulsivity.

It should be noted that the 20-session NF training itself was rather short and may have prevented larger training effects. In addition, the multimodal approach does not allow an isolated evaluation of the NF effects. Also, subtle neuropsychological and neurophysiological effects of NF might not be recognized by parents within the noise of day-to-day behavior.

Lansbergen and colleagues reported a pilot study that was designed to test the feasibility and safety of using a double-blind placebo feedback-controlled design and to explore the initial efficacy of individualized EEG-NF training in children with ADHD [49]. Individualized NF training with a focus on θ and sensorimotor rhythm (SMR) activity was applied. SMR, which may be associated with thalamocortical inhibition, is also considered in NF training instead of activity in the typical β band of the EEG, particularly to target hyperactive symptoms [36]. Only ADHD children with clear EEG deviances (1.5 standard deviations) compared to the NeuroGuide database [50] were included in the study.

Significant reductions of ADHD symptomatology (parent ratings) over time were observed, but changes were similar for both groups. However, according to the clinical global impression-improvement scale, only minor effects occurred. No adverse events were reported.

It should be noted that the sample size (eight children in the NF group vs six children in the placebo group) does not allow any conclusions to be drawn based on statistics concerning the training outcome, nor with respect to the design of the study. Moreover, when evaluating the feasibility of a placebo-controlled trial, both the placebo training and the quality (fidelity) of the NF training should be considered.

NF protocols were used which as such have not been investigated before with, for example, often rewarding SMR at locations where that rhythm does not exist (e.g., frontal electrodes). Therefore, it has to be questioned if these unconventional protocols allow a 'real' NF training.

In 'real' NF training, thresholds were continuously adapted every 30 s, and children received positive feedback approximately 80% of the time; they were rewarded irrespective of their regulation behavior. Thus, they were rewarded even if the target EEG pattern moved to the wrong direction. Given this, it is unclear if the participants learned to modulate their EEG in the desired direction. A movie was chosen as a feedback animation with the quality of the picture being regulated via brain electrical activity. Therefore, it may be difficult to disentangle if participants spent effort in regulation (i.e., the primary purpose of NF training) or just followed the movie. More specifically, adjustments of EEG activity and, hence, the improvement of the picture quality, might have been triggered by (exciting/thrilling) movie sequences (i.e., were regulated by the situation [stimulus-reinforcer association] and not by the subject [response-reinforcer association [20]]).

No effort was spent to implement the transfer into daily life. At the end of the training, 75% of the children and their parents in the NF group thought that they received placebo training. Thus, it seems unlikely that basic factors of cognitive behavioural interventions (e.g., effort and self-efficacy [51]) were covered by the training.

The authors conclude that it is feasible to run a placebo-controlled trial to evaluate the efficacy of NF in ADHD, although a double-blind design may not be feasible because using automatically adjusted reward thresholds may not work as effectively as manually adjusted reward thresholds.

However, in our opinion, the feasibility of such a research design cannot be evaluated if the treatment fidelity is not assured.

In a further RCT, θ/β training was compared to electromyography biofeedback training (reinforcer-controlled design) [52]. In the course of the training, θ/β ratios were reduced in the NF group and EMG levels decreased in the control group in the baseline condition, as well as during the regulation trials. Parents of the NF group children reported significant (~35%) reductions in primary ADHD symptoms. In addition, a significant superiority and a large effect size for NF was obtained compared to the control training (d_{corr} = -0.94) for reductions in inattention. For hyperactivity and impulsivity, only medium and small effect sizes, respectively, were observed, which did not reach the level of statistical significance. In paper–pencil and computer-based attention tests, several medium and large effects were observed.

It must be noted that the sample size (18 θ/β, 17 control) did not allow reliable detection of a medium effect size of d = 0.5. Hence, medium effects at the clinical and neuropsychological levels were not significant.

The authors discuss that the EMG biofeedback training could induce specific effects, mainly on hyperactivity and impulsivity, but seem to favour the interpretation that nonspecific factors (e.g., behavioral contingencies, self-efficacy and a structured learning environment) contribute to the positive effects observed after

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training. In our opinion, the opposite seems to be more likely *inter alia* because earlier relaxation studies reported effects particularly concerning the reduction of restlessness [53].

Thus far, no valid direct comparisons between NF and cognitive-behavioral or medication-treatment are available. Cognitive-behavioral treatment and NF reach medium effect sizes of approximately 0.60 (between-group-design, change-scores [11,42], which is comparable to the effect sizes of approximately 0.70 (standardized mean difference [SMD], the difference in the outcome scores between a medication and a placebo group divided by the pooled standard deviation) achieved by selective norepinephrine reuptake inhibitors (e.g., atomoxetine, [12]). Effect sizes of stimulant medication averages at around 0.70–1.0 (SMD) [13]. Influences of different research designs (placebo-control, double-blind vs active/passive control; randomization vs nonrandomization) or the calculation of effect-sizes hinders the comparison of effect-sizes.

Challenges

Several controlled studies show positive effects of NF on different outcome levels (e.g., behavioral, neuropsychological and neurophysiological variables) for children with ADHD. Although most of the studies suffer from methodological shortcomings, the increasing quality of recent results leads one to conclude that NF seems to be on its way to become an accepted treatment in ADHD. However, questions concerning empirical support (efficacy, specificity, clinical significance) and feasibility (including optimal application) of NF might only be validly answered with a fundamental knowledge about the mechanisms of action of a treatment, including moderators and mediators of the intervention.

Considering the different possibilities of applying NF, efficacy and specificity will have to be further examined using 'established' NF-applications, which proofed to be effective in previous trials (treatment fidelity). Specificity in this regard means that "the intervention offers any benefit to the patient beyond simply being in treatment" [35].

Addressing these points will require several well-conducted trials focusing on individual variables, as well as a reliance on minimum standards of application of NF settings and protocols that have demonstrated efficacy in previously successful trials.

Empirical support

Chambless and Hollon established guidelines for evaluating evidence-based psychosocial interventions [54]. These guidelines were adapted for psychophysiological interventions by La Vaque and Hammond [55]. Substantial requirements concerning the evaluation of a treatment encompass (among other things) an appropriate control group, a sufficient sample size (test strength/power), valid diagnostic instruments and dependent variables, as well as valid and replicable therapeutic interventions and the collection of long-term effects [56].

There are contradictory opinions concerning the empirical validation of NF for ADHD. In light of the existing data, Sherlin and colleagues argue that NF is already an acclaimed and well-established treatment for ADHD [57], fulfilling criteria for rating as an efficacious and specific treatment [58] (level 5 of the guidelines for evaluation of clinical efficacy of psychophysiological interventions [55]). By contrast, Lofthouse and colleagues argue that randomised, double-blind, placebo-controlled trials are needed [59]. Lofthouse and colleagues also argue that non-blind control designs with alternative (*bona fide* or experimental) control conditions do not adequately control for unspecific effects such as potential child, rater or experimenter expectancy, as well as nonspecific treatment effects. If the main interest is to detect mechanisms of action, this claim is appropriate. However, concerning the question of efficacy, it goes beyond the guidelines for empirically supported interventions by the American Psychological Association [54,60] or the guidelines for neurophysiological interventions [55]. Both guidelines consider *bona fide* or alternative treatments as valid controls to detect efficacy, acknowledging the pitfalls of blinded, sham-controlled studies in nonpharmacological psychotherapy research. The feasibility of sham control has not yet been documented in NF-ADHD research.

Beyond the efficacy of NF in ADHD, empirical support encompasses the notion of the safety of a treatment, which so far has not sufficiently been documented in NF research in ADHD [59], but was considered systematically only in the study of Lansbergen and colleagues [49].

Specificity of NF treatment: the placebo & double-blinding claim

In drug research, double-blind, placebo-controlled trials are viewed as the optimal research design (the gold standard). However, evaluation research in psychotherapy differs in key issues from medication research [61,62]. Placebo-control and blinding encompass serious difficulties and are (for good reasons) not well established in the evaluation of cognitive behavioral treatments. There is no doubt that double-blind, placebo-controlled trials could provide strong evidence for the efficacy and specificity of a given treatment, and they are the first choice wherever applicable (even if blinding in medication-trials often is not assured [63]). However, there are ways to demonstrate the efficacy and specificity of a treatment if the double-blind, placebo-controlled trials involve serious shortcomings. The discussion of placebo control in psychotherapy research is by no means new and ethical as well as methodological issues has been discussed in more detail elsewhere [61,64]. In this review, we focus on the major methodological concerns in the evaluation of NF.

Double-blind, placebo controlled trials in cognitive behavioural interventions inform us about the efficacy of a treatment if neither the patient nor the therapist knows what they are doing. This might work well for medication but seems an inappropriate requirement for psychotherapeutic treatments. In medical research, the distinction between specific and nonspecific effects is rather clear. Specific variables are limited to the mechanism of the drug/medication, further (psychological) variables such as the expectancies and convictions of the therapist or the patient constitute nonspecific and likely confounding variables. Thus, attempts are made to rule them out. In psychotherapeutic interventions

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generally and especially in NF, it is not possible to clearly differentiate nonspecific from specific effects because assumed specific effects (enhanced self-regulation via enhancement of neuroregulation) depend on nonspecific variables (e.g., expectation of success). These factors may be ruled out in medication studies, but diminishing them in psychotherapy studies might impair the outcome [51,64]. However, following the declaration of Helsinki, patients in clinical trials must be informed about the realization of a placebo condition [65]. Expecting to be part of the placebo-group may seriously distract mediators of NF (especially self-efficacy and effort). Unfortunately, NF in particular seems to induce the assumption that one is part of the placebo control. In previous placebo-controlled trials of NF, up to 80% of the participants of the NF group estimated (after treatment) that they received placebo feedback [49,66]. This might be explained by the impression of uncontrollability, especially at the beginning of the training, but also throughout the treatment.

In time-consuming psychotherapeutic evaluations, conducting a trial that includes a placebo control group may lead to nonrepresentative groups. The more unattractive the control group, the more selective the sample (e.g., who participates in an NF study, putting up the enormous effort it takes to engage in training for ~9 months and accepts the risk of a sham-treatment).

NF experts argue that it is necessary that a trainer track the EEG signals simultaneously to control for artefacts, relate artefacts to simultaneous behavior movement/body tension and provide continuous feedback to the participant. Particularly in children, a main focus lies on assisting them in acquiring adequate regulation strategies and giving them additional feedback of their adequacy in reference to the EEG signals. Blinding would eliminate these interventions.

However, no evidence concerning these claims is available. Regardless, considering the aforementioned apprehensions, the feasibility of double-blind and placebo-controlled trials in children with ADHD has to be verified first before drawing conclusions about efficacy of NF after such studies.

Clinical significance

Clinical significance refers to the consideration that a treatment effect may be of clinical relevance if the treatment leads to notable changes in daily life [67]. It may be defined and measured by symptom reduction (return to normative levels or provide detachment to pathological levels) and subjective judgments that encompass the assessment of quality of life and global functioning, among others. As noted by Kazdin, clinical significance depends on initial problems (brought to therapy) and individual goals of a treatment [68].

Effect sizes and response rates obtained such as those in our study [42] do not allow to deduce clinical significance for NF in ADHD and the appropriateness of technical and personal efforts of this method. However, based on the potential optimisations of the training (including moderators/mediators and integration of NF in cognitive behavioral treatment settings) outlined below, it seems likely that NF will turn out as a clinically significant treatment for children with ADHD. Of course, this point will have to be assessed systematically.

Fidelity of NF training

Questions concerning empirical support of NF in ADHD cannot be answered in general in view of the many different ways of applying NF encompassing for example, differences in feedback-protocols.

Thus, future single RCTs can provide evidence only about the efficacy of certain protocols under certain conditions (which protocol[s] work for which children under which circumstances) (see also Box 1). To date, there is no defined 'optimal' NF training in children with ADHD. Hence, different approaches must be tested. In any case, the fidelity of the NF training has to be ensured. This point was, for example, not well addressed in the study of Lansbergen and colleagues [49]; see the 'Methodological concept and validation' section.

The realization of the protocol (fixed vs adaptive thresholds and the modality of feedback) must be considered. The repertory of feedback animations might also be crucial for the outcome of the NF treatment. Feedback animations should provide a valid response–reinforcer association and not be 'overshadowed' by salient stimulus–reinforcer associations [20]; thus, these authors recommend discrete rather than complex, attention-catching feedback. Conversely, boring, monotonous feedback may diminish motivation and thus impair outcome.

The way the NF training is introduced to the participants should also be considered. In the (nonclinical) trial by Logemann and colleagues [66], participants were explicitly instructed that no effort was needed and that the learning process of interest runs subconsciously. This approach is quite different to the one applied in successful studies in children with ADHD [21,32,42]. In these studies, participants were encouraged to strive towards achievement of regulation capability; transfer trials were conducted and participants practised regulation abilities at home and/or in school.

Mechanisms of action

Much is hypothesized, but not much is known about the mechanisms of action in NF in ADHD. While from a practitioner's perspective, determining if a treatment is effective is of primary interest, it also seems desirable to understand how an intervention works (it should be kept in mind that insufficient knowledge about mechanisms of action is shared by most of the nonpharmacological and pharmacological psychotherapeutic interventions [69,70]. This seems particularly important referring to NF, which is characterized by different treatment approaches (e.g., different EEG-protocols and settings).

Based on a preliminary conceptual framework (Figure 1), we will discuss possible 'active ingredients' of NF in the following section. Detailed knowledge of the mechanisms and variables permitting and relating the operant learning of a single EEG-pattern (e.g., enhanced SCP-regulation capability) to better adjusted behavior in distinct situations in daily life is largely lacking. Presumably, there are effects on the neurophysiological level (neuroregulation) and on the psychological level (self-regulation of attention and self-efficacy) as well as on the psychosocial level (social reinforcement, parental appreciation), that will not be independent from

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each other. The acquisition of neuroregulation is assumed to follow basic (operant) learning principles [20], although it should be noted that some children have difficulties learning neuroregulation at all [21,32] and that it is not really known how to facilitate the learning process. The selective reinforcement of EEG-changes in the desired direction is supposed to lead to stable changes in EEG activity, ultimately leading to behavioral change. However, analysis of the interrelation of regulation capability and its proposed causal influence on behavioral outcome would require assessment of the development of regulation capability, changes in EEG-activity and behavioral changes at multiple time points, with a special focus on the timeline of the changes, to reliably demonstrate changes in neuroregulation preceding changes in behavior [69]. Although there could be a correlation between regulation capability and behavioral outcome [22,32], the causality of the relation is unclear. Additional factors, such as enhanced self-efficacy or positive reinforcement of achievement behavior, might account for improvement in both or mediate behavioral improvement.

An even more fundamental question is how regulation capability accounts for behavioral changes. The differentiation between negativities and positivities in transfer trials in SCP training may be considered. On the other hand, self-control over negative SCPs may be more important for one child and self-control over positive SCPs more relevant for others. Some children may learn regulation during the training sessions quite well but do not manage to use their strategies in daily life. Does the intended transfer of regulation strategies actually improve outcome? These points hamper the analysis of associations between regulation capability during the training and effects at the behavioral or neurophysiological level.

Not enough evidence is available concerning cognitive (attributional) mechanisms influencing NF outcomes in ADHD and their relationship to neurophysiological changes. Indeed, how much are variables such as self-efficacy, locus of control, achievement motivation or social reinforcement relevant for the acquisition of regulation capability and how do they influence (or how are they influenced by) the outcomes of NF treatment, especially in view of generalization of effects (transfer to everyday life)? On the neurophysiological level, (protocol-) specific changes in distinct neurophysiological parameters after NF suggest that neuroregulation during treatment accounts for these treatment effects. As described in the 'methodological concept & validation' section of this review, the enhancement of the CNV after SCP training is the best replicated finding [33,47]. In addition, effects in distinct frequency bands after θ/β training are documented [45]. However, it is not clear if these accompanying EEG changes are sufficient or necessary determinants for a positive outcome of NF.

The same holds true for the intended transfer of NF-strategies into daily life, although the results of the study of Schafer and Moore [11,69,71] clearly indicate the necessity of intended transfer to take place.

Moderators

General significant moderators in psychotherapy research come into question when discussing the influences of NF output. Major variables concerning the participant are age, sex, the severity of the disorder, comorbidities and parental/familial/social factors, as well as personality traits such as locus of control or achievement motivation [11,69]. Some evidence has already been gained that support by the parents could affect NF outcome [21,38]. In the case of NF, specific variables have to be considered beyond these general moderator variables.

Neurophysiological characteristics of the subject, such as distinct EEG or ERP measures, likely influence the result of a treatment. There is evidence that children with ADHD differ in their EEG profile; thus, there may be different EEG-types of ADHD that are not correlated to diagnostic subtypes [35]. Furthermore, diagnostic subtypes might differ in their EEG profile [72]. If one concludes that these EEG deviations are causes of the ADHD symptoms, individualized protocols may enhance treatment outcome by targeting an individual's dysfunctional EEG pattern. By performing pre-selection based on the θ/β ratio and applying neurofeedback accordingly, Monastra *et al.* achieved effect sizes significantly larger as compared to all other neurofeedback studies [38]. In our study patients with higher θ activity improved more than patients with lower θ activity after the θ/β training

Box 1. Variables related to participant and neurofeedback training that could affect the outcome of a neurofeedback training in children with ADHD. These have to be considered when interpreting the results of a neurofeedback study.

Subject

Diagnosis
- Diagnostic subtype, severity, comorbidity

Subject variables
- Age, sex, IQ, personality

Neuropsychological functioning
- Executive functions, attentional functions, delay aversion

Neurophysiological profile
- EEG patterns (e.g., theta, alpha, beta / SMR activity)
- EP components (e.g., CNV, P300)
- Activation patterns in neuronal networks / brain structures

Neurofeedback training

Protocols
- θ/β (SMR), SCP training, individualised training etc.
- Feedback electrode(s)
  - Midline vs lateral
  - Frontal vs central vs parietal
  - Single- vs multichannel (tomographic)

Application
- Number, frequency and duration of training sessions
- Thresholds: fixed vs adaptive
- Instructions and therapeutic support, therapeutic rationale
- Modality (auditory and/or visual)
- Feedback animations (e.g., bars, moving elements, movie)

CNV: Contingent negative variation; EP: Evoked potentials; SCP: slow cortical potentials; SMR: Sensorimotor rhythm.

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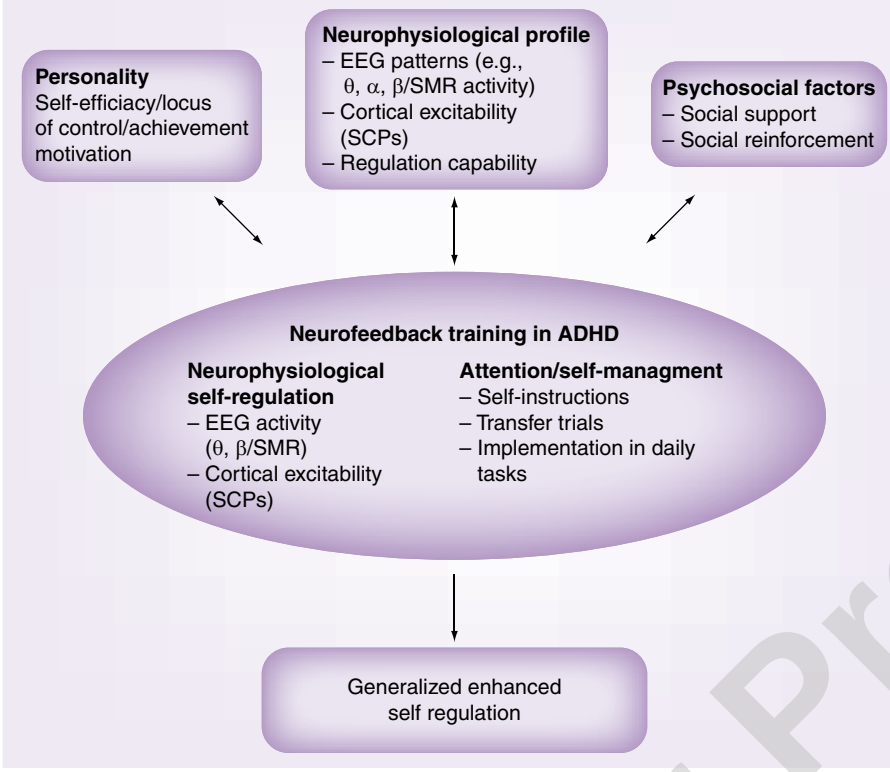

Figure 1. Hypothetical model of the 'active ingredients' of neurofeedback training in ADHD. Improvements in the neurophysiological regulation skills – and, thus, improved/ strengthened neuronal networks – are regarded as a central mechanism. Regulation skills and the transfer of the acquired self-regulation strategies into the everyday life interact with personality variables such as self-efficacy and achievement motivation, with the neurophysiological profile of a subject as well as social reinforcement processes. Thus, these variables also contribute to the success of neurofeedback training.
SCP: Slow cortical potential; SMR: Sensorimotor rhythm.

block [45]. These findings suggest that the effects of NF could be increased by taking a patient's neurophysiological profile into account.

Thus far, no direct comparison between a standard against individualized protocols has been conducted. Furthermore, no data are available about differences in outcomes between different ADHD-EEG subtypes (e.g., high θ/β ratio vs high β) after treatment with the same standard protocol.

Cortical excitability seems to moderate NF outcome [73]. In line with these results, for SCP-treatment in children with ADHD, we found better outcomes for children with higher baseline-CNV [47]. Again, better initial SCP-regulation at the beginning of NF training was associated with superior regulation ability at the end of the training in five paralyzed adult patients [74]. Not all participants learned how to regulate SCPs, but those who learned it well, learned it quickly. Thus, the ability to acquire regulation capability seems to matter.

Of course, interactions between multiple potential moderator variables must be tested. Moreover, a model that can be applied in clinical practice will surely not depend on a single variable but on several factors. Therefore, multivariate regression models have to be considered.

Mediators

Little is known about mediators, i.e., variables that are influenced by treatment and have an impact on the outcome (e.g., improving self-confidence and enhancing parental appreciation/social reinforcement). Some general mediators in psychotherapy are adherence and engagement [75]. In view of NF-evaluation studies, changes in self-efficacy during treatment might be a particularly crucial factor. Self-efficacy is strongly associated with motivation and task performance [76] and, therefore, is seen as a central factor for effort and perseverance of task performance, especially in view of failure and difficulty [77]. Therefore self-efficacy is assumed to be an important factor for NF regulation [74]. Because crucial mediators specific to NF might be variables interacting with the development of regulation capability, which is assumed to be a good predictor of outcome, especially in transfer-trials [31,32], there is good reason to assume, that the acquisition of the regulation capability and intended transfer of NF-strategies to daily life might interact with self-efficacy. Furthermore, self-efficacy itself might increase due to continuous positive reinforcement of successful neuroregulation runs during the treatment. Also increasing social reinforcement and parental appreciation toward the patient's intended or achieved behavioral improvement might mediate outcome. Experimental manipulation or assessment of such mediators is one important but so far often neglected way of elucidating mechanisms of change in therapy research.

Application challenges: indication, setting & design: preliminary recommendations

Before the application of NF, several variables concerning the participant (diagnosis, comorbidities, general impairment, age, personality and family/social support) and the setting (how many sessions, how often, which system, which protocol[s] and single or group treatment) have to be considered. Not much is known about optimal setting, design and protocol of NF treatment or moderating and mediating factors. Thus, clinical application is guided by hypotheses and experience. However, previous controlled studies with positive NF outcomes on the behavioral level have several factors in common [21,22,42,52]. Some of these factors might be necessary, some may be helpful and some may be dispensable. However, as long as we do not know which factors are necessary and sufficient, research trials and practitioners should not abstain from these common variables without good reason.

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The ages of the participating children usually ranged from 7–14 years. Although it seems reasonable that adolescents and adults would benefit from NF treatment, there are not many valid data available concerning these groups thus far. Standard protocols (e.g., θ/β, θ/SMR and SCP) were applied rather than individualized protocols. Treatment was conducted block-wise with two to three sessions a week, especially at the beginning of the treatment. The NF setting encompassed transfer-effort (transfer trials and homework). Feedback animations provided simple, clearly represented feedback (rather than complex, exciting animations such as movies) to facilitate a reliable response-reinforcer association [20]. Using previous research studies as a basis, approximately 25–40 training units may be conducted.

θ/β training and SCP training seem to be effective protocols. However, no empirical data exist that can be used for clinical practice to determine which of the two protocols (or a combination of both) should be applied for a particular child. Based on clinical experience, some [particularly younger] children have problems dealing with artefacts in SCP training. For these children θ/β training may be more adequate.

To enhance regulation ability, there is the possibility of combining NF runs with follow-up tasks, requiring the resources just targeted during the NF runs. This may help to enhance/stabilize regulation capability as well as the comprehension of the need to transfer strategies into daily life. Transfer of NF strategies (regulation capability) might be crucial.

Expert commentary & five-year view

Within the next 5 years, further RCTs with sufficient power must be conducted in children with ADHD to address the open questions described in 'Challenges'. These trials will provide further accumulation of evidence for effective versus non-effective protocols, as well as applications of NF and knowledge of moderators and mediators of outcome. This will lead to the refinement of indication criteria and optimized patient-specific NF protocols (personalized NF treatment) to enhance efficacy.

Assumed mechanisms of action will be elucidated and reliably linked to comprehensive models of ADHD. Different neurophysio-/psychological models account for ADHD symptoms [3–7], and the conjunction of NF to specific models will be forced. For example, SCP training has already been linked to the ADHD model of dysfunctional energetic resources [5] (see 'methodological concept & validation for details). Consequently, CNV enhancement and increased test performance after SCP training should be related to performance during the training (ability to regulate and learning curve). Thus, NF will be integrated in neuropsychological research, even as a research tool to manipulate neurophysiological variables, examine effects on the neuropsychological level and draw conclusions about the underlying models.

Some efforts have been undertaken to use tomographic NF, aiming at voluntary control over the activation of a specific brain region. Tomographic NF may allow more specific training with a lower number of training sessions [78]. Of course, functional

Key issues

- The quality of recent neurofeedback (NF) research has markedly improved. The results of the latest randomized controlled trials indicate that NF (θ/β training and slow cortical potentials training) is on its way to becoming an efficacious and specific intervention for children with ADHD.
- Beyond the evaluation of efficacy, aspects of underlying mechanisms, moderators, and mediators remain mainly unsolved for NF, as well as for psychotherapy research in general. The following aspects should be targeted in future studies to elaborate a comprehensive model of the mechanisms of action of NF.
  - Which patient variables make a positive outcome more probable?
  - Which treatment variables make a positive outcome more probable?
  - Which NF application (protocol and setting) should be chosen to make the application of the treatment for a certain patient more successful?
  - How can the regulation ability and the intended transfer of NF-strategies to daily life be enhanced?
  - If there are variables that enhance the outcome of NF (e.g., self-efficacy and familial support), will outcome be improved if such variables are also targeted?
  - How can one additionally implement NF in a multimodal treatment of ADHD? For which child under which circumstances the implementation of NF into a multimodal treatment (e.g., encompassing parent counselling, behavioral interventions and stimulant medication) lead to further improvement?
  - Is NF training associated with adverse events (safety aspect)?
- Investigating these questions will be accompanied by answers concerning the efficacy and specificity of NF that will help to improve outcomes.
- There is a disagreement concerning adequate evaluation strategies for NF. Although in pharmacological evaluation research, double-blind, placebo-controlled trials (DBPCTs) provide good evidence for the efficacy and specificity of treatments, conducting DBPCTs in the evaluation of psychotherapeutic interventions is accompanied by several possible shortcomings, and therefore not established. The feasibility of DBPCTs in NF is not verified and therefore, results of DBPCTs in NF evaluation should be interpreted with caution.
- Clearer knowledge of the application and mechanisms of NF (and of cognitive behavioral interventions in general), as well as the availability of more sophisticated NF systems will help to further enhance efficacy of NF and lead to the possibility of using NF in a more flexible and effective way in combination with additional cognitive, behavioral and educational interventions, making it a promising tool in the toolkit of multimodal treatment of children with ADHD.

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MRI NF is too expensive and to hard to apply for clinical practice in the near future for children with ADHD. A cheaper and more practical alternative could be the so-called near-infrared spectroscopy NF, which allows regional cortical but not subcortical activation to be fed back [79]. EEG-based tomographic NF can be realised using, for example, the LORETA algorithm (low-resolution electromagnetic tomography) [80]. However, in a pilot study in children with ADHD, participants only partially learned self-control over brain activity in the anterior cingulate cortex [Liechti M, Maurizio S, Heinrich H et al. First clinical trial of tomographic neurofeedback in attention-deficit/hyperactivity disorder: evaluation of voluntary cortical control (2012), Submitted]. Further studies are necessary to develop this approach and to evaluate its potential in the treatment of ADHD.

As an attempt to enhance the accessibility of NF, as well as the possibility to establish NF strategies in daily life, so-called tele-NF applications are available. After an initial training phase, treatment can also be performed at home, supervised via the internet. Patients practice at home, communication is provided via the internet (webcam) and the trainer can inspect the training (including the recorded signals) online in his office. However, prerequisites are serious, easy-to-use and more robust EEG systems with, those such as, dry electrodes that allow one to record even slow cortical potentials with good quality.

Altogether, clearer knowledge of the application and mechanisms of NF (and of cognitive behavioral interventions in general), as well as the availability of more sophisticated NF systems, will lead to the possibility of using NF in a more flexible and effective way in combination with additional cognitive, behavioral, and educational interventions, making it a promising tool in the treatment of children with ADHD.

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