NEUROFEEDBACK IN ADHD

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NEUROFEEDBACK IN ADHD

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Image by Martijn Arns

EEG-based neurofeedback is used as a treatment approach in attention-deficit / hyperactivity disorder (ADHD), a clinically and pathophysiologically heterogeneous child psychiatric disorder. There is increasing evidence for specific effects of neurofeedback when applying 'standard' protocols (slow cortical potentials, theta/beta, sensorimotor rhythm). Knowledge about underlying mechanisms and moderating variables is increasing. Nevertheless, further well-controlled and conducted trials are needed to answer open questions concerning optimisation and individualisation of neurofeedback. Further improvements may develop with new methods and technical developments (e.g., tomographic neurofeedback) and new concepts (integrated ADHD treatment).

This Frontiers Research Topic comprising 14 articles intends to answer the following questions concerning neurofeedback in ADHD:

- How efficacious is neurofeedback?
- What is the rationale of applying a certain neurofeedback protocol in ADHD?
- What are central mechanisms and which moderating variables may affect training and treatment outcome?
- How to optimise treatment? What are new developments and which benefits may be expected?

Aspects of learning theory are also stressed dissociating 'neurofeedback as a treatment' and 'neurofeedback as entertainment'. In the Editorial, this crucial aspect is compared to the way you read (and study) a scientific book versus reading a thriller for leisure. In this respect: Enjoy this Research Topic, study and apply it in practice, unless you read it for entertainment purposes!

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EDITORIAL
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Editorial: Neurofeedback in ADHD

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Almost a century ago Ivan Pavlov laid the groundwork for what we now know as classical conditioning. Not long after this first description of classical conditioning, and the first description of the human EEG by Berger (1929), early observations were made that the human EEG (alpha blocking response) could be classically conditioned (Durup and Fessard, 1935; Loomis et al., 1936). This alpha blocking response consists of a desynchronization of the dominant alpha activity, present during an eyes closed (or dark) condition, into a desynchronized low voltage beta EEG (also see Ros et al., 2014, in this research topic). More systematic studies demonstrated that the alpha blocking response fulfilled all of the Pavlovian types of conditioning (Jasper and Shagass, 1941a) and could not be explained by sensitization (Knott and Henry, 1941). Jasper and Shagass took their experiments one step further, showing that using these principles of conditioning, subjects could be taught "voluntary control" over their alpha blocking response, by pairing the light-onset not to an auditory tone, but to a sub-vocal command ("block"; Jasper and Shagass, 1941b). In their most basic form, these can be considered the first demonstrations of "neurofeedback" or voluntary control over the EEG based on basic learning principles. Some years after these initial studies, the first reports employing operant learning principles to EEG were reported by Kamiya [voluntary control of alpha power and alpha peak frequency (Kamiya, 1968)], McAdam et al. [voluntary control of the contingent negative variation (CNV) or slow cortical potential (SCP) (McAdam et al., 1966)], and Sterman (operant conditioning of the so-called sensori-motor rhythm (SMR) in cats, Wyrwicka and Sterman, 1968). Interestingly, from a historical perspective, these EEG parameters are still the focus of intensive study in neurofeedback research, as this research topic nicely illustrates.

Neurofeedback as a therapeutic intervention has been most comprehensively investigated for the treatment of attention-deficit/hyperactivity disorder (ADHD), in line with the theme of this research topic. Leading from a review by Albrecht et al. (2015) on the neurophysiological background of this child psychiatric disorder, including its comorbidities, the efficacy of neurofeedback in the treatment of ADHD is discussed in great detail. The current controversy regarding the efficacy of neurofeedback in ADHD is centered on the fundamental question of how it should be evaluated: namely, in accordance with the APA guidelines (used to evaluate psychological treatments), or along the lines of drug treatments (requiring double-blind placebo controlled designs). In their perspective article, Vollebregt et al. (2014) review this issue in more detail, alongside Gevensleben and colleagues who investigated the feasibility of a double-blind placebo controlled design for SCP neurofeedback (Gevensleben et al., 2014a). A further interesting approach was undertaken by Micoulaud-Franchi and colleagues, who report an updated meta-analysis of neurofeedback studies in ADHD (Micoulaud-Franchi et al., 2014). Using a comparable approach as the European ADHD Guidelines group (Sonuga-Barke et al., 2013), they demonstrated significant small to medium effect sizes specifically for inattention, in line with an earlier meta-analysis that also revealed strongest effects for the same domain (Arns et al., 2009). In addition, Christiansen and colleagues report preliminary results of a randomized controlled trial comparing SCP neurofeedback to a self-management program (Christiansen et al., 2014).

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As is clear from the historical studies mentioned above, neurofeedback is built on the foundations of learning theory. Therefore, it is crucial to dissociate "neurofeedback as a treatment" from "neurofeedback as entertainment." The "neurofeedback as entertainment" is an approach popularized by many modern devices such as the Mattel Mindflex (keep a ball in the air using your brain activity) or consumer-grade EEG units such as the Emotiv Epoc which run brain-training "apps." In the same way as there is a difference between "reading a book" for entertainment purposes and "studying a book" to learn how to apply a specific technique it is no different for neurofeedback. Unfortunately in some clinical studies the goal has been to "entertain" children with "EEG-driven games," rather than really applying a learning procedure the children could benefit from for a longer period. In this respect, the contributions from Strehl (2014) and Zuberer et al. (2015) are important and valuable contributions covering aspects of learning theory. Gevensleben and colleagues additionally discuss different neurocognitive models of how neurofeedback works (Gevensleben et al., 2014b). Ros and colleagues go one step further by offering a firmly neurophysiological account, proposing a "systems neuroscience framework" for tuning pathological brain oscillations (Ros et al., 2014).

Up to now, most neurofeedback protocols in the treatment of ADHD (e.g., SMR, Theta/Beta, and SCP Feedback) have shown comparable effect sizes on ADHD domains such as inattention, impulsivity and hyperactivity (reviewed in Arns et al., 2014b). In this research topic further indications for specificity of various neurofeedback protocols emerge. Studer and colleagues originally report protocol specific effects on motor system excitability, as well as P3 amplitudes and CNV amplitudes for Theta/Beta and SCP neurofeedback (Studer et al., 2014). Arns and colleagues further reveal that although clinically both SMR and Theta/Beta neurofeedback have similar effects, only for SMR neurofeedback the clinical effects are mediated by a normalization of sleep-onset latency, suggesting the clinical effects of Theta/Beta neurofeedback are mediated via a different mechanism (Arns et al., 2014a).

Although the majority of current research has utilized neurofeedback protocols that stem from before the twenty-first century, it is also important to look ahead and acknowledge new developments. With respect to individualized treatment, it may be adequate to adapt protocols as suggested by an EEG study of attention in Heinrich et al. (2014), and the theoretical framework of Ros et al. (2014). Several contributions also introduce new and promising approaches to neurofeedback, such as the contribution by Marx and colleagues, who compared SCP neurofeedback with Near Infrared Spectroscopy (NIRS) neurofeedback in children with ADHD, providing feedback from a signal physiologically similar to the fMRI BOLD response (Marx et al., 2014). Also, the perspective article by Bauer and Pllana provides further insights and opportunities in the application of EEG-based tomographic neurofeedback, theoretically enabling feedback of more focal brain activity (Bauer and Pllana, 2014).

We hope that you will enjoy this research topic, study and apply it in practice, unless you read it only for entertainment purposes!

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REVIEW
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Pathophysiology of ADHD and associated problems—starting points for NF interventions?

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Attention deficit hyperactivity disorder (ADHD) is characterized by severe and age-inappropriate levels of hyperactivity, impulsivity and inattention. ADHD is a heterogeneous disorder, and the majority of patients show comorbid or associated problems from other psychiatric disorders. Also, ADHD is associated with cognitive and motivational problems as well as resting-state abnormalities, associated with impaired brain activity in distinct neuronal networks. This needs to be considered in a multimodal treatment, of which neurofeedback (NF) may be a promising component. During NF, specific brain activity is fed-back using visual or auditory signals, allowing the participants to gain control over these otherwise unaware neuronal processes. NF may be used to directly improve underlying neuronal deficits, and/or to establish more general self-regulatory skills that may be used to compensate behavioral difficulties. The current manuscript describes pathophysiological characteristics of ADHD, heterogeneity of ADHD subtypes and gender differences, as well as frequently associated behavioral problems such as oppositional defiant/conduct or tic disorder. It is discussed how NF may be helpful as a treatment approach within these contexts.

Keywords: Neurofeedback (NF), ADHD, ODD/CD, tic disorder, comorbidity, children, neurobiology

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Introduction

Difficulties with Inattention or Hyperactivity and Impulsivity as the core symptoms of Attention deficit Hyperactivity disorder (ADHD) are a frequent psychosocial burden. With an early onset during childhood, ADHD is often persisting throughout life. It is a heterogeneous disorder, and a challenge to treat. In light of this heterogeneity, the most promising treatment approach should be multimodal in nature (Taylor et al., 2004; Swanson et al., 2008). Pharmacological interventions particularly with stimulants such as methylphenidate and amphetamine sulfate, as well as non-stimulants like Atomoxetine are highly effective in reducing ADHD symptoms (Banaschewski et al., 2006; King et al., 2006), but long-term effectiveness is still questionable (Molina et al., 2009; van de Loo-Neus et al., 2011). In addition, side-effects, non-response and prejudice have raised interest in non-pharmacological treatment options (Sonuga-Barke et al., 2013; Daley et al., 2014).

Neurofeedback (NF) as a non-pharmacological intervention for ADHD utilizes cognitive-behavioral therapeutic elements to gain access on and practice brain activity (Arns et al., 2014). In an operant learning paradigm, specific neural activity is quantified by means of Electro-Encephalography (EEG) or functional Magnetic Resonance Imaging (fMRI) and fed back in real time with an easily accessible optical or acoustic signal. In general, the participants

learn to modulate their brain activity towards an *a priori* specified criterion (standard EEG-based NF protocols require the participants to increase beta (13–20 Hz) and to decrease theta (4–8 Hz) activity, or to train slow cortical potentials (SCP) in order to modulate cortical excitability); and successful trials are positively reinforced.

Gevensleben et al. provide two different frameworks, how NF may be effective in ADHD (Gevensleben et al., 2014c). On the one hand, following a "conditioning and repairing model", NF may be used to compensate specific neurophysiological deficits present in patients with ADHD, which in turn ameliorates impairments. On the other hand, the "skill-acquisition model" suggests that NF may be used to train and enhance self-regulation skills not necessarily impaired in ADHD, but may in turn, by means of active transfer and supportive coaching, be used to compensate existing deficits.

There are a number of studies indicating potential effectiveness of NF on ADHD symptom severity, but further evidence particularly from randomized controlled trials using more blinded assessments is required (Arns and Strehl, 2013; Sonuga-Barke et al., 2013; Micoulaud-Franchi et al., 2014). On the other hand, further double-blinding or particularly sham feedback may diminish motivation and the belief in self-efficacy in both participants receiving sham and NF interventions, and may thus question an important precondition for effective trainings (Logemann et al., 2010; Gevensleben et al., 2012). Further details about NF interventions can be found in a number of reviews and conceptual papers (Strehl et al., 2006; Heinrich et al., 2007; Arns et al., 2014; Gevensleben et al., 2014b), and recent advances in the field are described in this issue on "NF in ADHD".

The following selective overview describes pathophysiological characteristics of ADHD alongside their potential relevance for NF intervention. First, a brief overview of the clinical characteristics of ADHD is given. Second, pathophysiological characteristics of ADHD linked with difficulties in cognitive functions and motivation as well as during resting state are described, and third, a number of associated problems such as frequent comorbidities of ADHD with Conduct- and Tic-disorders are presented. Finally, perspectives for NF interventions will be considered within these contexts.

Characteristics of Attention Deficit Hyperactivity Disorder

ADHD is currently considered as a neurodevelopmental disorder. It is characterized by severe and age-inappropriate levels of inattention and hyperactivity/impulsivity that are present in at least two areas of life for over 6 months (WHO, 1993; APA, 2013). According to the fifth edition of the Diagnostic and Statistical Manual (DSM-V), subtypes with predominantly Inattentive or Hyperactive/Impulsive characteristics as well as a combined type are distinguished. In any case, the symptoms must already be manifest in childhood (before age of seven following the DSM-IV, and before age of 12 according to the recently revised DSM-V; Kieling et al., 2010), and must not be better explained by other disorders.

ADHD is one of the most frequent problems in psychiatry. The core symptoms of ADHD are present in approximately 5% of children and adolescents, irrespective of cultural background, and with a strong overrepresentation of boys (Polanczyk and Rohde, 2007). In about one or two out of three of children with ADHD, the symptom may persist with clinical significance into adulthood, leading to a slightly lower prevalence of more than 3% in adults (larger in higher income countries), which makes ADHD a life-long problem for many patients (Fayyad et al., 2007; Polanczyk and Rohde, 2007). Childhood ADHD may lead to lower educational, occupational, social and clinical outcomes in adulthood even if it remits early on, and may thus not be considered as a benign disorder (Klein et al., 2012).

ADHD and its Neuronal Background

ADHD is associated with a number of neurophysiological deficits. More recent theoretical approaches integrate clinical symptoms and neuropsychological difficulties within a framework of specific brain dysfunctions: cognitive deficits may emerge from dysfunctions particularly in fronto-striatal or meso-cortical brain networks, while problems with reward processing may be associated with dysfunctions in the mesolimbic dopaminergic system (Sagvolden et al., 2005; Sonuga-Barke, 2005). However, deficits in ADHD may already be seen in the resting brain, and a more fundamental neuronal network approach suggests that in ADHD particularly Default-Mode-Network (DMN) activity (usually prominent during rest) may interfere with activity in neuronal networks engaged in task processing, leading to difficulties in state regulation and periodic attentional lapses (Sonuga-Barke and Castellanos, 2007; Castellanos and Proal, 2012).

Cognitive Functions

There are a number of cognitive theories that describe impairments in executive functions as a central problem in ADHD (Pennington and Ozonoff, 1996; Tannock, 1998; Sergeant, 2000; Biederman, 2005). Several theoretical accounts propose a "top-down" executive system responsible for inhibition, working memory and cognitive flexibility, which is particularly active when more complex demands require adaptation and effortful control (Baddeley and Della Sala, 1996; Miller and Cohen, 2001; Diamond, 2013). Following Barkley, children with ADHD may show a core deficit in behavioral inhibition, which in turn leads to impairments in working memory, self-regulation, internalization of speech and reconstitution (Barkley, 1997). This account has been put forward in the more recent "multiple pathway" models of ADHD, which emphasize besides cognitive deficits also motivational or reward processing problems (Nigg et al., 2005; Sonuga-Barke, 2005).

Cognitive problems in ADHD are reported in numerous studies with different tasks. It was frequently found that children with ADHD display several deficits in tasks that demand

executive control, i.e., their reaction-times were slower and more variable, and more errors were made. This has been demonstrated for important aspects of executive functions such as set shifting assessed with the Wisconsin Card-Sorting Task or planning and problem solving as required in the Tower-of-Hanoi paradigms (Barkley et al., 1992; Klorman et al., 1999). On the other hand, interference control during Stroop- or Simon tasks yielded mixed or even negative results, particularly when confounders were controlled for (van Mourik et al., 2005, 2009; Albrecht et al., 2008b), but further improvements on how interference liability can be derived from performance data may clarify these findings (Lansbergen et al., 2007; Schwartz and Verhaeghen, 2008).

Thus, ADHD may be associated with a number of cognitive deficits, but these may not "causes" but rather consequences of the disorder, and may not provide causative therapy options: a recent meta-analysis suggests that cognitive trainings (e.g., on working memory) may improve performance and may ameliorate neuropsychological deficits found in ADHD, but direct effects on ADHD symptoms may be limited (Cortese et al., 2015).

Action Monitoring and Response Inhibition

Action monitoring as an important aspect of executive functioning comes into play when task demands raised response conflicts. There is a large body of evidence from electrophysiological studies elucidating some of the implicated mechanisms. For instance, if a task requires responding to a certain stimulus but to withhold the response to another one, the stimulus-locked event-related potentials (ERP) usually shows a fronto-central negativity peaking around 200–400 ms after onset of the stimulus which is larger for the Nogo than for the Go condition, particularly when the Nogo condition is rare. The same effect can be observed when the target is primed with either congruent or incongruent distractors. The so called N2 and the N2-enhancement were originally attributed to (response) inhibition (Kok, 1986, 1999; Falkenstein et al., 1999), but recent studies suggest that it reflects a more general action monitoring or cognitive control process that is also present if no response needs to be inhibited (Nieuwenhuis et al., 2003; Donkers and van Boxtel, 2004). Sources of N2 evoked by Go/Nogo- or Flanker-Tasks were found in medial frontal brain regions, namely the ACC (Van Veen and Carter, 2002; Nieuwenhuis et al., 2003; Bekker et al., 2005).

While several studies using Continous Performance Tests (CPT) or Go-Nogo-tasks in children did not find conflict-specific differences in N2 between ADHD and controls (Overtoom et al., 1998; Banaschewski et al., 2004; Fallgatter et al., 2004), some studies did, but variations were explained by comorbidity with other externalizing disorders (Lawrence et al., 2005; Wiersema et al., 2006) or appeared only with prolonged time-on-task (Yong-Liang et al., 2000). Thus, the detection of action monitoring deficits in ADHD may require tasks that are particularly demanding, e.g., that reveal a substantial number of performance errors, which is usually not realized in the CPT.

This may be achieved with the Flanker Task, requiring response to a central target flanked by either congruent or incongruent flanker stimuli (Eriksen and Eriksen, 1974) which was frequently used in ADHD research (Jonkman et al., 1999; Mullane et al., 2009). In a special variant of this task aimed maximizing the congruency effect, lower N2-enhancement and deficits during error processing in children and adults with ADHD, and moreover intermediate effects in first-degree relatives without a diagnosis of ADHD were found, indicating that action monitoring may be an important feature on the developmental pathway from genetical and environmental liability to ADHD (Albrecht et al., 2008a; McLoughlin et al., 2009).

Studies on brain activity more specifically related to response inhibition revealed mixed results, which may be explained by heterogeniety of the methods used. Studies with the Stop-Task, requiring a frequent and consequently predominant response which should be withold if a Stop-signal is presented, indicated that particularly the right inferior frontal gyrus is implicated in successful stopping of an ongoing response (Aron et al., 2003; Hughes et al., 2013). Several EEG and fMRI studies suggest impairments in Stop-Task performance and stop-signal related brain activity in ADHD (Brandeis et al., 1998; Pliszka et al., 2000; Albrecht et al., 2005; Rubia et al., 2008), but there are also some negative findings in treatment-naive children (Pliszka et al., 2006). Response inhibition problems in the Stop-Task may be significant in ADHD across the lifespan, and its specificity is particularly clear in adults with ADHD (Lijffijt et al., 2005).

Importantly, activity in the medial prefrontal cortex related to cognitive control (particularly the N2) and error processing (error negativity) may operate with theta (or maybe even lower delta) frequency (Yordanova et al., 2004; Cavanagh et al., 2012; Zavala et al., 2014).

Perspectives for NF

A number of recent studies with healthy adults indicate that NF training of frontal midline theta activity may improve attention and executive functions like working memory and cognitive flexibility (Wang and Hsieh, 2013; Enriquez-Geppert et al., 2014), and may lead to morphological changes in the cingulate cortex (Enriquez-Geppert et al., 2013). An application in ADHD may thus ameliorate cognitive deficits accordingly, but empirical evidence for improvement in executive functioning following NF in ADHD is weak (Vollebregt et al., 2014), and requires better controlled studies with sufficiently sized samples before definitive conclusions can be drawn.

A promising approach may be NF from dedicated brain regions that show diminished functional activity in ADHD. A recent study reported in this issue using near infrared spectroscopy (NIRS) NF of brain activity in the bilateral prefrontal cortex (implicated in executive functions and response inhibition) showed effectiveness in behavioral symptom ratings and executive functions, but may require fewer sessions than EEG or EMG NF (Marx et al., 2015). Activity in the ACC may be directly trained by tomographic NF (Bauer and Pllana, 2014). In a more recent study using tomographic NF from Theta/Beta or

SCP activity localized in the ACC, Liechti et al. (2012) reported clinical improvement as well as resting EEG normalization in participants, but it remains open whether these improvements were (region-) specific for tomographic NF training (Liechti et al., 2012).

Preparation

Preparation for an upcoming event may be of great importance not only for specialists like flight controller, carefully watching their radar equipment for cues indicating critical situations that demand intervention. Almost half a century ago, it was found by Walter et al. that cues (predicting a consecutive imperative stimulus requiring a response) evoke a centrally negative SCP that terminates with the presentation of the next stimulus (contingent negative variation, CNV; Walter et al., 1964). Originally interpreted as "sensorimotor association and expectancy", neuronal networks generating the CNV may be active if more general preparation for an upcoming event is required (Macar and Vidal, 2003).

Neurophysiological studies suggested that the CNV is generated in thalamo-cortical structures including the dorsal anterior cingulate cortex (ACC), frontal cortex, thalamus and midbrain dopaminergic nuclei (Gómez et al., 2003; Fan et al., 2007; Lütcke et al., 2008). Patients suffering from Parkinson's disease that goes along with neuronal cell death in these nuclei showed specific reductions in Cue- (or warning stimulus) CNV amplitude (Pulvermüller et al., 1996; Ikeda et al., 1997; Gerschlager et al., 1999) as well as deficits in performance and slow wave activity during a temporal anticipation paradigm (Praamstra and Pope, 2007). This confirms the role of midbrain dopaminergic neurons in anticipation, time estimation or temporal memory (Suri and Schultz, 2001; Macar and Vidal, 2003).

Dopaminergic deficits may also explain anticipation and preparation problems in patients with ADHD, which showed reduced activation in brain regions implicated in CNV generation (Rubia et al., 1999; Smith et al., 2008). In line with these considerations, CNV is probably reduced in ADHD (van Leeuwen et al., 1998; Hennighausen et al., 2000; Perchet et al., 2001; Banaschewski et al., 2003a, 2008) and may represent a persistent deficit in patients with ADHD throughout life (McLoughlin et al., 2010; Doehnert et al., 2013). Moreover, diminished Cue-CNV may be familially-driven in children and adults with ADHD (McLoughlin et al., 2011; Albrecht et al., 2013) and may be related to polymorphisms of the dopamine receptor D4 gene (Albrecht et al., 2014). It is further subject to dopaminergic manipulations used for treatment of ADHD, as performance and CNV amplitude may be enhanced by methylphenidate (Linssen et al., 2011; Kratz et al., 2012).

Perspectives for NF

Many psychiatric or neurologic disorders are associated with preparation problems or related difficulties NF training of SCP may be a direct compensatory approach, as it relies on phasic modulation of SCPs and probably consequent cortical excitability (Rockstroh et al., 1984; Mayer et al., 2013; Gevensleben et al., 2014b).

Change in CNV-activity after SCP training is often replicated in NF-ADHD research (Gevensleben et al., 2012), but the relation to task performance appear rather complex and requires further investigation (Gevensleben et al., 2014a).

Reward Processing

Deficient reward processing is a central aspect of several theories on ADHD. A model proposed by Sagvolden and colleagues claims that rewards have a shorter-term impact on learning and behavior in ADHD, e.g., characterized by a steeper gradient between the delay of a reinforcer and its effect on the probability that the reinforced action will be repeated (Sagvolden et al., 1998). Such a steeper delay of reinforcement gradient may be a consequence of lower tonic levels of dopaminergic activity in the mesolimbic system including the ventral tegmentum and the nucleus accumbens, while attention and response organization problems may originate from hypofunctioning of the mesocortical system also including the ventral tegmentum with projections to the prefrontal cortex (Sagvolden et al., 2005). Another model by Tripp and Wickens argues that phasic dopaminergic activity in the striatum related to cues indicating reinforcement may be impaired in ADHD (Tripp and Wickens, 2008).

A recent review by Plichta and Scheres summarizes consistent evidence from functional imaging studies on reward anticipation in ADHD: particularly the areas in the ventral striatum including nucleus caudatus, nucleus accumbens and the putamen show lower activation during reward anticipation in ADHD than controls, which may be rather related to hyperactive-impulsive symptom severity but perhaps not inattention (Plichta and Scheres, 2014).

Perspectives for NF

Immediate performance feedback may be beneficial for patients having problems with motivation or reinforcement anticipation. This would suggest that NF would be particularly applicable to such patients, but it may further modified to train brain activity associated with delayed reinforcement. As such, NF intervention may also help acquiring self-regulation skills useful for compensating motivational deficits and delay aversion in structured and potentially unattractive and boring situations.

Resting State Brain Activity

Brain activity at rest, recorded when individuals are awake, relaxed and not engaged in any particular task, is characterized by complex oscillations that may reflect important features of arousal and attention that may change with development. Important aspects of resting state brain activity can be obtained using recordings of the EEG (Banaschewski and Brandeis, 2007; Rothenberger, 2009). The resting EEG of a time interval can be decomposed by means of a Fourier-Transformation in frequency and power. Cross-sectional developmental studies suggest that from childhood to adolescence and early adulthood a decrease in power of slow Delta (1.3–3.5 Hz) and Theta (3.5–7.5 Hz), but at the same time an increase in faster Alpha (7.5–12.5 Hz) and

Beta (12.5 — ∼ 25 Hz) activity emerges (Matousek and Petersen, 1973; John et al., 1982).

Earlier studies suggest that children with learning disabilities (Harmony et al., 1995), dyslexia (Klimesch et al., 2001) and ADHD (Bresnahan et al., 1999) may be characterized by lower power in the faster Alpha and Beta frequency bands, and in case of ADHD also potentially increased Theta activity (Barry et al., 2003). This view has been challenged by recent studies that did not replicate increased theta or theta/beta ratios in ADHD under resting conditions (Barry and Clarke, 2013; Liechti et al., 2013), albeit reduced relative beta power may be characteristic for a subgroup of children and adults with ADHD inattentive subtype (Buyck and Wiersema, 2014). A recent meta-analysis concludes that Theta/Beta-Ratio may not be a reliable diagnostic parameter in ADHD (Arns et al., 2013). However, there is some evidence that aberrances in EEG-frequency bands exist during task processing (El-Sayed et al., 2002). In a recent trial, Heinrich et al. found higher theta and alpha activity during an attentive state in children with ADHD, most pronounced in the upper theta/lower alpha range (5, 5–10, 5 Hz; Heinrich et al., 2014). Taken together, elevated power in lower frequency bands during rest may not be generally associated with ADHD, but there is some evidence that abnormalities of brain activity oscillations at least during task processing (in the "active brain") might be part of the problem in children with ADHD.

Another view on resting state activity comes from a network perspective. MRI studies during rest (when participants were awake and rested quietly with eyes closed) revealed coherent activity fluctuations with low frequency (<0.1 Hz; Biswal et al., 1995) in a neuronal network including the medial prefrontal cortex, posterior cingulate cortex, precuneus and lateral parietal cortex (Gusnard et al., 2001a,b). This DMN activity is associated with a rather introspective and self-referential state (Gusnard et al., 2001a), which is attenuated during task performance when specific "task-positive" networks take over Fox et al., 2005; Fransson (2006). However, DMN activity may come back into play before performance errors or prolonged reaction times, possibly indicating attentional lapses (Weissman et al., 2006; Li et al., 2007; Eichele et al., 2008).

Misguided DMN activity may be important in several mental disorders (Broyd et al., 2009), and problems in ADHD may be particularly associated with attentional lapses due to DMN interference with activity in task-positive networks (Sonuga-Barke and Castellanos, 2007; Castellanos and Proal, 2012). Recent studies in adults with ADHD suggest lower anti-correlation between the posterior cingulate/precuneus (as an important part of the DMN) and the ACC often implicated in cognitive control and preparation (Castellanos et al., 2008; Uddin et al., 2008).

The association between DMN and electrical brain activity appears rather complex (Mantini et al., 2007) and may be unstable over time (Meyer et al., 2013). However, there are reports that very low frequency electrical brain activity (<1.5 Hz) may be altered in children and adults with ADHD, and particularly adults with higher ADHD symptom ratings show diminished deactivation in DMN regions during a flanker-task (Helps et al., 2010; Broyd et al., 2011).

Perspectives for NF

The theta/beta ratio during rest may not be generally impaired in patients with ADHD, but there is some evidence that problems may be present during task performance. Since NF targets the "active brain", it may act as a potentially ameliorating intervention. Training on theta/beta ratio was successfully applied in a series of intervention studies in ADHD children, but the precise mode of action is still under investigation (Heinrich et al., 2007; Gevensleben et al., 2009). NF training targets different variables on the neurophysiological (enhancement of regulation capability of different EEG parameters), neuropsychological (executive functions), and the cognitive-behavioral (e.g., enhanced self-regulation by positive reinforcement of goal-directed behavior) level. Until now, it remains open whether regulation capability on the neurophysiological, the neuropsychological (executive functions), or on the cognitive-behavioral level—targeting an initial deficit or activating compensatory mechanisms—account for NF training effects (Gevensleben et al., 2014b). Most likely, NF outcome in ADHD treatment results from a combination of several of these variables.

Further venues of NF interventions may consider DMN interference by training the interplay between and connectivity within in the DMN and task-relevant networks.

Heterogeniety in ADHD

ADHD is in many ways a heterogeneous disorder. This is reflected in the ADHD subtypes, overrepresentation of boys, and moreover in the fact that various comorbid conditions are not an exception, but the rule in patients with ADHD. For the presentation below, we consider comorbidities with a higher prevalence than the simple product of the prevalence of both disorders involved. As an example, the prevalence of oppositional defiant or conduct disorder (ODD/CD) in ADHD should be equal to the prevalence in the total population—in fact it is at least 20-times higher, and the reasons for this are still under debate. Research indicates that some comorbidities may in fact be a separate clinical entity (potentially like ADHD + ODD/CD, as discussed below), whilst others may in many ways an addition of difficulties present in either disorder (e.g., like ADHD + Tic). In any case, heterogeneity in ADHD may further complicate treatment.

Clinical Heterogeneity—Hyperactive/Impulsive and Inattentive Subtypes

The Diagnostic and Statistical Manual distinguishes Hyperactive/Impulsive (ADHD-H) and Inattention (ADHD-I) symptom clusters in the diagnosis of ADHD (APA, 2013), but it remains controversial whether these form separate clinical entities. On the one hand, developmental studies suggest that children initially diagnosed with ADHD-H may shift to Combined Type (ADHD-C) as attention demands increase in school, whilst diagnoses of attention problems alone may remain stable and form a separate clinical entity (Lahey et al., 2005). Compared to patients with ADHD combined type,

children with ADHD-I may be characterized by rather passive social interaction and more associated internalizing problems (Maedgen and Carlson, 2000). In the resting EEG, children and adults with ADHD-I may show lower power in the beta-band and increased theta/beta ratio (Buyck and Wiersema, 2014), which may have significance for compensatory NF intervention.

However, on the neuropsychological level children with ADHD-I show similar performance problems as ADHD-C in a wide range of demands (Nigg et al., 2002; Baeyens et al., 2006), albeit there is some evidence that ADHD-I may show particular preparation problems (Adams et al., 2008).

Perspectives for NF

Empirical evidence suggests that NF unfolds an impact on all three symptom clusters of ADHD (inattention, impulsivity, hyperactivity). In a large multicenter randomized controlled trial of a combination of theta-beta/SCP NF training for children with ADHD, we found comparable effects for symptoms of inattention as well as hyperactivity/impulsivity (Gevensleben et al., 2014b). No differences in efficacy concerning subtypes of ADHD were obtained. This result is supported by meta-analytic data, obtaining large effect sizes for inattention and medium to large effect sizes for hyperactivity/impulsivity symptom ratings (Arns et al., 2014). Latest evidence from a trial encompassing children with comorbidity of Tourette-disorder and ADHD suggested that specificity of outcome of NF training concerning patterns of inattention, hyperactivity and or impulsivity may rely on transfer tasks (homework) in the course of the training (Gevensleben et al., 2014b), which should be considered in the treatment of ADHD subtypes.

Similarities and Differences Between Boys and Girls with ADHD

Although overrepresentation of boys in ADHD is at least 3 to 1 in the population and much higher among clinical referrals (Tannock, 1998; APA, 2013), studies explicitly addressing the role of sex on cognitive parameters are rare. In an earlier meta-analysis, Gershon concluded that girls suffering from ADHD were lower-rated on ADHD symptoms and externalizing problems, but they were more impaired than boys on internalizing symptoms. Furthermore, females showed lower "crystallized" cognitive functioning as measured by full scale and verbal IQ, but "fluid" performance IQ did not differ between sexes. Regarding executive functions, girls with ADHD show in many ways similar impairments as boys (Gershon, 2002).

That has been demonstrated with several neuropsychological tests including the Stroop- (deHaas, 1986; Rucklidge and Tannock, 2002) and Wisconsin Card Sorting Test (Houghton et al., 1999; Seidman et al., 2005) as well as with various versions of the CPT (Breen, 1989; Schuerholz et al., 1998; Sharp et al., 1999; Yang et al., 2004; Seidman et al., 2006). An exception may be impulsivity, or consequent problems with response inhibition: a recent meta-analysis on CPT performance by Hasson and Fine indicated that girls may generally show less commission errors than boys, and beyond that case-control differences on impulsivity errors were also lower in girls (Hasson and Fine, 2012).

Studies on brain activity during preparation and response control yielded mixed results. Regarding cognitive control, Liotti et al. (2007) found no sex differences in Stop-Task performance and N2 amplitude (Liotti et al., 2007). This is in line with a more recent study with the Flanker-Task, detecting independently of sex also problems with N2-enhancement and error processing in nonaffected siblings of patients with ADHD (girls were outnumbered in our ADHD sample, not allowing a direct comparison in patients), albeit girls showed a generally more accurate response style and larger error positivity probably associated with affective error processing (Albrecht et al., 2010). In the CPT on familiarity, girls made less commission errors (particularly in a more demanding CPT with additional incompatible flanker stimuli) at the expense of slower response speed, and they also showed larger Cue-P3, but similar Cue-CNV (Albrecht et al. in preparation).

Taken together, girls with ADHD or nonaffected siblings may show a rather accurate response style and fewer problems with impulsivity, but they may share many problems with executive functions detected in studies mostly on boys. It remains an open question whether impulsivity explains the overrepresentation of boys among patients with ADHD as it may lead to more severe and probably clinically relevant psychosocial impairments.

Perspectives for NF

Since girls with ADHD may show similar impairments as boys, although they may be less impulsive, the current literature suggests that NF interventions need no sex-specific adaptations, but more research is needed before definitive recommendations can be given.

ADHD and Conduct Disorder

Children with conduct problems display a repetitive and persistent pattern of oppositional or dissocial behavior, aggression, or deliquency for more than 6 months that goes beyond childlike mischief or typical problems during puberty. The DSM distinguishes ODD, characterized by "negativistic, hostile, and defiant behavior" from CD including aggression, violation of "the basic rights of others", and delinquency (APA, 2013). Since ODD and CD often occur interrelated and the former may antecede the latter in child development, both are often considered together as ODD/CD (Loeber et al., 2000).

With a prevalence of approximately 2% in children and adolescents, it is one of the more frequent child psychiatric diagnoses. However, among patients with ADHD, ODD/CD is with a comorbidity rate of 40–70% much more frequent, and the reasons for this are still under investigation (Newcorn and Halperin, 2005). It was found that ADHD may be a predictor for ODD, and that ODD may predict CD (Burke et al., 2005).

ODD/CD is associated with a number of neurobiological abnormalities. At first, children with ODD/CD may show impaired stress reactivity, which is mediated by activity in the hypothalamic-pituitary-adrenal (HPA) axis and expressed in the

release of cortisol, which was moderately inverse associated with aggressive symptoms (van Goozen et al., 2007). This may result in low sensitivity to punishment that may in turn hamper learning from the consequences of inappropriate behavior (Matthys et al., 2013). Further, activity of the autonomic nervous system (ANS), via the interplay of its sympathetic and parasympathetic branches responsible for the regulation of arousal and energy generation, may be lower (as indicated by lower heart rate and skin conductance reactivity) in aggressive or antisocial individuals (Lorber, 2004), suggesting underarousal and consequently "fearlessness" (Raine, 2002) or risk taking and "sensation seeking" (Zuckerman, 1994). Moreover, there are also studies linking lower serotoninergic activity (5-HT) and monoamine-oxydases (MAO) to aggression, and selective serotonine reuptake inhibitors are frequently used for reducing aggression in patients (Carrillo et al., 2009).

In a series of neuroimaging experiments, Rubia et al. showed that children with ADHD may be characterized by "cool" cognitive deficits like inhibition, attention and timing related to abnormal activity in inferior frontal, striatal and parietotemporal brain regions, whereas ODD/CD was associated with "hot" deficits in the regulation of motivation and affect (related to emotional impulsivity) resulting from dysfunctions in the paralimbic system including orbito-frontal and superior-temporal areas and the ACC as well as the limbic system (Rubia et al., 2008, 2009a,b; Rubia, 2011). Particularly the latter may lead to a lack of self-control in emotional situations Matthys et al. (2013).

Besides these differences between ADHD and ODD/CD, there is an ongoing debate, whether children with comorbid ADHD + ODD/CD may form a separate clinical entity as diagnosed in the ICD-10 as "F90.1 Hypercinetic Conduct Disorder" (WHO, 1993), or whether the comorbidity of ADHD and ODD/CD may be considered separately as in the DSM-V (APA, 2013).

In earlier electrophysiological studies, Banaschewski et al. studied children with ADHD, ODD/CD, comorbid ADHD + ODD/CD and controls in a 2*2-factorial design assessing additive and non-additive effects of both disorders. During CPT performance, children with ADHD showed slower and more variable response speed, whilst children with comorbid ADHD + ODD/CD committed more dyscontrol errors. On the level of brain electrical activity, children with pure ADHD were characterized by lower Cue-CNV suggesting preparation problems. Both children with pure ADHD and ODD/CD but not comorbid ADHD + ODD/CD displayed diminished attentional orientation as indicated by impaired P3a to Cues and uncued targets (Banaschewski et al., 2003a). Children with comorbid ADHD + ODD/CD displayed diminished Nogo-P3 related to motor response control (Banaschewski et al., 2004). In the Stop-Task, response inhibition deficits in performance and associated brain activity of both children with pure ADHD and ODD/CD reached significance, whilst the yougsters with comorbid ADHD + ODD/CD did again show overall less severe problems (Albrecht et al., 2005). These findings are supported in a neuropsychological study by Luman et al showing that children with ADHD + ODD/CD were located in between children with ADHD and controls regarding response inhibition speed, timing performance and the impact of incentives or penalty on timing performance (Luman et al., 2009).

Taken together, children with ADHD and ODD/CD may have a broad deficit in performance and brain activity associated with several executive functions. Comorbid ADHD + ODD/CD may show elevated "hot" cognitive deficits in motivation, affect regulation and impulsivity (and accordingly response control problems), whilst problems with "cool" attentional orienting and response preparation may be less severe than expected from an additive model of impairments found in both pure ADHD and ODD/CD.

Perspectives for NF

There is evidence that children with comorbid ADHD + ODD/CD may show particularly problems with self-regulation, whilst cognitive deficits may be less severe than expected from typical findings from ADHD and ODD/CD, suggesting that NF interventions may use these cognitive resources and may dwell on the enhancement or compensation of diminished self-regulation skills accordingly. Since ADHD may precede ODD/CD in child development, early interventions may be particularly promising. Moreover, combined NF SCP and theta/beta training yielded, besides particular reductions of teacher and parent-rated ADHD symptoms, also effects on parent-rated oppositional behavior and conduct problems when compared to a standardized computer attention training (Gevensleben et al., 2009), indicating that NF may also be beneficial in treating ODD/CD.

ADHD and Tic Disorder

Tic disorders (TD) are characterized by involuntary, sudden, short, repetitive and non-rhythmic fragments of usual movements and/or vocal expressions. Tics are ranging from mild (e.g., eye blinking or sniffing) to severe (e.g., strong head or body jerking, shouting) intensity and simple (e.g., shoulder shrugging, grunting) to complex (e.g., turning, vocalizing complex words or sentences) extent that do not fulfil any subjective purpose (Leckman, 2002). TD are considered as "Neurodevelopmental Disorders" in the DSM-V (APA, 2013); more details about clinical assessment and treatment options may be found in the European Guidelines on TD (Cath et al., 2011; Muller-Vahl et al., 2011; Roessner et al., 2011; Verdellen et al., 2011).

Tics do often occur in bouts and are particularly present during stress or in positive or negative emotional situations. Particularly patients older than 10 years may realize sensory-motor phenomena (e.g., an urge to execute a tic) before and/or after tic, and are often able to suppress their tics for a limited period of time (Banaschewski et al., 2003b). Urges and uneasy sensory-motor feelings may be a part of the impairment (Swain et al., 2007).

The situation of patients with Tics is further complicated by frequent comorbidities with ADHD, anxiety, obsessive-compulsive disorder or mood disorder. ADHD + TD may be present in about half of children with TD, particularly in patients with Tourette's syndrome.

Assessment of the psychopathological profile revealed particularly mood, thought, attention and social problems as well as somatic complaints in children with TD, which do partly overlap with difficulties found in ADHD. Importantly, effects were (with the exception of somatic complaints) additive in ADHD and TD (Roessner et al., 2007).

TD is probably associated with disturbances in cortico-striato-thalamo-cortical neuronal networks which may be partly compensated by increased prefrontal activity instrumental in tic suppression (Leckman et al., 2006; Swain et al., 2007; Wang et al., 2011). Studies on structural imaging via voxel-based morphometry (VBM) or diffusion tensor imaging showed abnormalities in a number of brain regions including the basal ganglia, putamen, thalamus, corpus callosum and in the prefrontal cortex, which may reflect pathological as well as compensatory alterations (Peterson et al., 2003; Plessen et al., 2004; Jackson et al., 2011; Liu et al., 2013; Müller-Vahl et al., 2014). However, a recent VBM study with younger medication naïve boys with Tourette's syndrome without comorbid conditions did not replicate abnormalities in gray or White matter, (Roessner et al., 2009). Thus, it remains open whether the above mentioned structural abnormalities may be a consequence of long-term tic suppression or comorbidities in Tic disorders.

A recent imaging study in adults generally replicated an earlier study of Bohlhalter by further elucidating the progression of brain activity in the cortico-striato-thalamo-cortical circuit preceding a tic and additionally suggesting the role of DMN activity in tic generation (Bohlhalter et al., 2006; Neuner et al., 2014). Peterson found increased activity during tic suppression in the prefrontal cortex and basal ganglia, which were inversely related to tic severity in everyday life (Peterson et al., 1998).

Moreover, studies on excitability of the motor system using transcranial magnetic stimulation indicated reduced motor inhibition in individuals with TD (Ziemann et al., 1997), which improves with development (Moll et al., 2006). Reduced inhibition within the motor circuit was also seen in ADHD, and shows again additive effects in individuals with comorbid ADHD + TD (Moll et al., 2001; Orth and Rothwell, 2009; for a review see Orth, 2009).

Studies on higher order cognitive functions in TD suggest that patients may not show general impairments, but may at most be affected as a consequence of their tics or potential compensatory mechanisms; studies addressing the co-existence of TD + ADHD often found deficits explained by ADHD following an additive model (Schuerholz et al., 1998; Roessner et al., 2008; Greimel et al., 2011). However, this may not hold for electrophysiological parameters of preparation and self-regulation after decision making, as children with ADHD + Tic may be more similar to children with pure Tic disorder, following a sub-additive model (Yordanova et al., 1996, 1997). Diminished preparatory slow-wave CNV in children with Tics was furthermore associated with tic severity, suggesting a possible functional link with tic suppression (Siniatchkin and Kuppe, 2011).

Functional imaging studies particularly in adults with TD yielded mixed results, and the interpretation of functional data in TD may be complicated by the interplay of both activity reflecting pathophysiological mechanisms and potential compensatory activity required during tic control (Gerard and Peterson, 2003; Vloet et al., 2006). This is supported by a cross-sectional developmental study in children and adults with the Stroop-task, showing normal performance during interference control, but elevated fronto-striatal activity and deviant development of activity in prefrontal and posterior cingulate areas in patients with Tic disorder compared to healthy controls (Marsh et al., 2007).

Perspectives for NF

In sum, ADHD + TD is probably not a separate clinical entity as it is the case for ADHD + ODD/CD. Individuals with ADHD + TD may share difficulties associated with both disorders often following an additive model, which may however be a special challenge to treat. SCP-NF may be used to ameliorate diminished slow-wave activity during preparation, which may be a common psychopathological impairment in both ADHD and Tic disorders. Typical interventions used in the treatment of TD that rely on intact cognitive control mechanisms or executive functions such as habit reversal may be less effective when ADHD is associated.

Nevertheless, NF may be a promising component of a multi-modal therapy, as it combines training of potentially problematic brain activity with direct feedback and reward.

In previous intervention studies, Theta-SMR-protocols have been applied in Tic-/Tourette disorder, from a traditionally point of view aiming at inhibiting over-activity in senso-motor cortical regions (Tansey, 1986). There is some evidence for positive effects of NF in subjects with Tic-/Tourette disorder from several single-case trials (see Rothenberger and Gevensleben, 2013 for a short overview). Further promising results evolved from a pilot study comparing the impact of sensory motor rhythm (SMR; 12–15 Hz) vs. SCP-NF training on Tic-/Tourette symptoms (Gevensleben et al., 2014b). Under both conditions Tic-severity was reduced by about 25% after 24 units of NF. Interestingly, in those patients who additionally suffered from ADHD (about 50% of the sample) ADHD symptoms are reduced significantly only after SCP training (not after SMR), indicating a potentially specific effect of SCP training on ADHD (at least in patients suffering from comorbid ADHD + TD).

Conclusion

ADHD as a neurodevelopmental disorder is associated with pathophysiological problems during cognitive demands, reward processing and during rest. It is further complicated by a number of heterogeneities regarding clinical characteristics, sex differences, and frequent comorbid disorders. The current manuscript introduced associated pathophysiological characteristics and discussed their potential relevance for NF intervention in ADHD.

It is argued that cognitive deficits during preparation for an upcoming event and response inhibition problems associated with deficient activity in the prefrontal cortex and in the ACC, as well as impaired resting-state brain activity may be ameliorated

by respective NF trainings. Tomographic NF interventions using high density EEG recordings, fMRI or NIRS targeting specific brain areas may allow more direct training of brain activity impaired in ADHD. Motivational problems during reward processing may rather be compensated by the acquisition of self-regulation skills.

NF interventions may be used for hyperactive/impulsive and inattentive subtypes, and may not require sex-specific adaptations. It may in general be useful for children with comorbid ADHD and conduct disorders characterized in many ways by sub-additive cognitive deficits of both pure disorders but pronounced self-regulation deficits, as well as for ADHD and associated Tic disorder characterized largely by additive impairments.

Taken together, NF intervention in ADHD may be applied in order to ameliorate specific deficits, and/or to acquire self-regulation skills to use them for the compensation of difficulties in other domains.

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Neurofeedback in attention-deficit/hyperactivity disorder – different models, different ways of application

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In children with attention-deficit/hyperactivity disorder (ADHD), different neurofeedback (NF) protocols have been applied, with the most prominent differentiation between EEG frequency-band (e.g., theta/beta) training and training of slow cortical potentials (SCPs). However, beyond distinctions between such basic NF variables, there are also competing assumptions about mechanisms of action (e.g., acquisition of regulation capability, generalization to daily life behavior). In the present article, we provide a framework for NF models and suppose two hypothetical models, which we call "conditioning-and-repairing model" and "skill-acquisition model," reflecting extreme poles within this framework. We argue that the underlying model has an impact not only on how NF is applied but also on the selection of evaluation strategies and suggest using evaluation strategies beyond beaten paths of pharmacological research. Reflecting available studies, we address to what extent different views are supported by empirical data. We hypothesize that different models may hold true depending on the processes and behaviors to be addressed by a certain NF protocol. For example, the skill-acquisition model is supported by recent findings as an adequate explanatory framework for the mechanisms of action of SCP training in ADHD. In conclusion, evaluation and interpretation of NF trials in ADHD should be based on the underlying model and the way training is applied, which, in turn, should be stated explicitly in study reports.

Keywords: neurofeedback, attention-deficit/hyperactivity disorder (ADHD), model, learning, application, evaluation

INTRODUCTION

Overwhelming evidence exists for (1) the plasticity of the human brain, especially in childhood (Pascual-Leone et al., 2005), (2) distinct brain electrical patterns in cognitive and emotional processing (Banaschewski and Brandeis, 2007), and (3) the possibility to modulate brain electrical activity via neurofeedback (NF) in animals and humans (Banaschewski and Brandeis, 2007; Heinrich et al., 2007; Sherlin et al., 2011). Hence, there is growing interest in EEG-based NF as a treatment option for children with attention-deficit/hyperactivity disorder (ADHD) as documented for example by an increasing number of randomized controlled trials (RCTs) which have been conducted to study clinical efficacy and mechanisms of actions (for review see Arns et al., 2014; Gevensleben et al., 2014). However, diverging opinions exist how to interpret the results of the available studies regarding clinical efficacy (for example, Arns and Strehl, 2013 vs. Sonuga-Barke et al., 2013).

In a RCT of our group, NF comprised two "standard-protocols": theta/beta training [aiming to decrease theta (4–8 Hz) activity and to increase beta (13–20 Hz) activity] and training of slow cortical potential (SCP; associated with the bidirectional regulation of cortical excitability). Both protocols were trained in separate blocks and paralleled regarding the setting and demands upon the participants. For NF, we obtained a larger reduction of the severity of ADHD symptoms (medium effect size) compared to a computerized attention skills training ("active control group"; Gevensleben et al., 2009a, 2010). Further, while linking brain electrical measures to the clinical outcome protocol-specific associations provided further evidence for the specificity of effects of theta/beta training and SCP training (Gevensleben et al., 2009b; Wangler et al., 2011).

In clinical practice, so-called QEEG (quantitative EEG)-based NF is also applied in ADHD. Before starting QEEG-based NF, multichannel-EEG is recorded and compared to a database of typically developing children. Frequency band and electrode location showing the greatest deviance from the "norm" are targeted during training. Related to this individualized approach, a randomized double-blind placebo-controlled trial was conducted by van Dongen-Boomsma et al. (2013). For pre-selected patients, mainly theta and sensorimotor rhythm (12–15 Hz) activity at frontal, central, or parietal leads were addressed in the training. Regarding the overall severity of ADHD symptoms, NF was not superior to the placebo (sham) training though a medium effect size for the symptom domain hyperactivity/impulsivity indicated some advantage for NF.

From the short descriptions of these two RCTs, it becomes apparent that different NF protocols and different evaluation

strategies have been applied[1]. However, having a closer look beyond protocols and control conditions, it also turns out that there are different ways a NF training is realized depending on the different underlying model of action, i.e., assumptions regarding the underlying neuronal and psychological mechanisms as well as moderating and mediating factors affecting the effects of NF training (e.g., what are the mechanisms of learning and generalization in NF, how should supposed mechanisms underlying behavioral changes be addressed in the training?). So far, these aspects have not been considered adequately regarding NF in ADHD.

In the present article, we intend to provide a framework for defining NF models based on those above-mentioned aspects. To underline the relevance of the framework, which is suggested for theoretical and practical purposes, we reflect available studies and illustrate that different views are supported by empirical data.

MECHANISMS AND APPLICATIONS – MODELS OF NF IN CHILDREN WITH ADHD

COMPETING ASSUMPTIONS ABOUT NF

What is the indication for NF: repairing a neural dysfunction vs. strengthening resources/compensatory mechanisms on different levels

Application of NF in children with ADHD directly evolved from considerations about distinct neurophysiological dysfunctions (reviewed for example by Albrecht et al., submitted), encompassing different brain electrical activity parameters and electrode locations. Elevated theta/beta ratios in the resting EEG, reflecting reduced tonic cortical activation (Barry et al., 2003, 2009), and a reduced contingent negative variation (CNV; an event-related potential component associated with cognitive preparation) in cued attention tasks (Banaschewski and Brandeis, 2007), served as rationales to apply theta/beta training and SCP training, respectively.

Following a classical medical model of (psychiatric/neurodevelopmental) disorders, "repairing" the presumed cause (neurophysiological deficit) should "normalize" behavior: "The principle of NF is that over time, participants learn operant control of their EEG and change from an 'abnormal' state to one resembling that of typically developing children. This process is thought to eventually remediate the symptoms associated with ADHD" (Bakhshayesh et al., 2011, p. 482).

On the other hand, NF may simply be regarded as "a tool for enhancing specific cognitive or attentional states in certain situations" (Gevensleben et al., 2009a, p. 781), irrespective of presumed distinct neurophysiological deficits. The application of NF to improve "peak performances" in arts or sports is based on such an approach of "optimizing" rather than "repairing" (e.g., Landers et al., 1991; Egner and Gruzelier, 2003, for a review see Gruzelier, 2014b).

Nowadays, etiology of (psychiatric/neurodevelopmental) disorders is rather investigated on the basis of a bio-psycho-social model, considering the impact of different factors on different levels. Accordingly, regarding treatments, different areas of impact should also be taken into account. Therefore, NF does not necessarily need to address only a distinct neural dysfunction but may encompass (compensatory) mechanisms on different interacting levels, the strengthening of neural resources as well as changes of cognitive-behavioral and social variables[2].

The effect of NF: is there a change of "EEG trait[3]" or a change in "EEG state"?

Particularly traditional models of NF in child and adolescent psychiatric disorders consider a stable change in the EEG signature ("*EEG trait*") in terms of a durable change in protocol-specific EEG activity (Lubar and Shouse, 1976). Change of the "*EEG trait*" is typically assessed studying pre–post-changes in the *resting* EEG. Resting EEG in this case is considered to represent a kind of individual signature of the brain.

Others tend to expect an improved skill to change the "*EEG state*" in order to optimize performance temporarily (i.e., to improve attentional self-regulation; Heinrich et al., 2004). Regulation-skill refers to self-initiated effort of "activating and maintaining a state of cortical arousal" (Bakhshayesh et al., 2011) and is assessed during task performance. This perspective underlines the active part the subject plays in the allocation of attentional resources. From this point of view, changes after NF might not only be detectable by resting EEG assessment but should also be reflected in neurophysiological (and cognitive) patterns during task performance.

Neuro-regulation – implicit vs. explicit learning?

Concerning core mechanisms of NF, changes in within-session neuro-regulation (i.e., changes in EEG activity during treatment sessions) and improvements in neuro-regulation as the training proceeds are expected before changes in the clinical outcome result. Such systematic changes in EEG activity following positive reinforcement could be obtained in animals as well as in humans (e.g. Strehl, submitted). However, learning might evolve in an implicit (unconscious and automatic) and/or explicit (goal directed, controlled, and attention-demanding) way.

Implicit learning is defined as "the acquisition of knowledge that takes place largely independently of conscious attempts to learn and largely in the absence of explicit knowledge about what was acquired" (Reber, 1993, p. 5). Automatic processing and effortlessness of the procedure is postulated by some authors: "*Learning occurs as the child's brain adjusts and interprets the cause-and-effect relationship between its own activity and the resultant video game responses*" (Steinberg and Othmer, 2004, p. 34); "w*hen the children and adolescents played the video game or watched the films, they produced brainwave activity that was 'shaped' toward more regulated performance*" (Duric et al., 2012, p. 3). Therefore, NF

[1]There are also significant differences in the implementation of feedback protocols concerning aspects like fixed vs. variable thresholds, discrete vs. continuous feedback, discussed elaborately by Sherlin et al. (2011), Strehl (submitted).

[2]Changes of cognitive-behavioral and social variables are also reflected in changes of underlying neural networks.

[3]As "trait" we understand individual EEG patterns considered stable over time and situations, usually measured in resting conditions and representing an idiosyncratic EEG signature of a person. As "state" we define EEG activity based on the EEG trait, triggered by distinct situations and assessed during an active condition (typically during task performance).

in children with ADHD might be considered an intervention "*... which trains the brain, via operant conditioning, to improve its regulation of itself...*" (Arnold et al., 2012, p. 410). Referring to voluntary control of circumscribed brain regions using real-time functional MRI, Birbaumer et al. (2013, p. 298) suggest that "*brain responses are learned, stored, and retained in a manner that is comparable to a motor skill, following the rules of implicit learning. In contrast to explicit learning, implicit learning and memory do not require conscious and effortful search.*"

At least it seems plausible that learning of neuro-regulation is enhanced by precise monitoring of the EEG signals being fed back, searching for a link between internal regulation and the mirrored neuronal signals, intentional building, and testing of cognitive strategies to shift generated EEG activity pattern in the required direction (for an overview of learning mechanisms in NF see Strehl, submitted). Therefore, controlled cognitive processes may also be involved in the acquisition of neuro-regulation capability (and generalization of self-regulation ability to daily life; see following section), suggesting rather an active role for the participant.

A further, often neglected notion is the superior cognitive level of expectations and attributions of patients: how do the participants perceive the training and participate in the exercises, what is the role of motivational, attributional, and personality factors for the course and outcome of the training (Meichenbaum, 1976)? Are these factors and associated underlying networks (e.g., mesocorticolimbic dopaminergic system related to motivational aspects) also modulated by the training?

Generalization – does it occur automatically or is special effort needed to achieve transfer into daily life?

Training effects should not be restricted to the environment where the NF training is conducted. NF strives for behavioral changes in daily life. If NF repairs an underlying neural dysfunction and/or learning happens automatically and unconsciously then generalization should occur automatically: "*... when brain behavior is normalized, the child's behavior follows*" (Steinberg and Othmer, 2004, p. 35).

If NF relies on controlled learning and acquisition of skills and outcome depends on attributions and motivation, additional effort to transfer novel skills into daily life appears necessary in order to improve efficacy and clinical value.

IMPLICATIONS FOR THE APPLICATION OF NF

The assumptions reflected in the previous section impact the way NF training is applied.

Indication – "Repairing" a neural dysfunction vs. strengthening neural resources

Assuming a distinct neurophysiological dysfunction to be addressed in NF training in children with ADHD has implications for the indication of NF. Primarily, subjects with a manifest neurophysiological dysfunction (e.g., enhanced theta and/or reduced beta activity) are expected to improve behavior after NF training addressing this particular dysfunction (e.g., Monastra et al., 2002). Consequently, in a trial proposal by a collaborative NF group only children with significantly enhanced theta/beta ratios will be included (Kerson and Collaborative Neurofeedback Group, 2013). Treatment solely targets the distinct neurophysiological dysfunction.

If, on the other hand, NF is expected to exert its effects via (compensatory) mechanisms on different (neurophysiological and cognitive-behavioral) levels pre-selection based on distinct neurophysiological profiles does not play an essential role. Room for improvement in self-regulation on the neurophysiological and cognitive-behavioral level provides rough indication criteria, hopefully in the future differentiated and optimized by knowledge about moderators of outcome (neurophysiological, cognitive, and social predictors of improvement such as distinct EEG parameters, personality variables, and supporting social conditions). Treatment focuses on neurophysiological functioning during the treatment sessions but also targets further variables on the cognitive-behavioral (self-efficacy, achievement motivation) and social level (social reinforcement), interacting with the achievement in neuro-regulation capability. Further effort (via cognitive-behavioral interventions such as education/instructions, positive/social reinforcement, transfer tasks/home work and parent/teacher counseling) is spent to ensure enhancement of general behavioral self-regulation capability (Gevensleben et al., 2012), i.e., the goal may be a personalized combination of machine-guided and trainer-guided learning.

Acquisition of (neuro-)regulation: mechanisms of learning, mechanisms of change

Mechanisms of the acquisition of neuro-regulation capability beyond basic operant mechanisms (reaction-consequence-contingency; positive reinforcement; for an overview see Sherlin et al., 2011) are not elucidated satisfactorily. Assumptions about the mechanisms of learning (e.g., how to achieve EEG changes during sessions) affect further aspects of the application of NF (e.g., via the attitude of the trainer, the introduction of the training, the level of ambition, and the instructions before and during treatment; Meichenbaum, 1976). If one expects NF to work in an automatic and unconscious manner, participants are instructed accordingly: "*the participant was instructed that the brightening of the movie screen and the audio clicks are good signs and that the learning process is mostly unconscious so no specific effort is needed*" (Logemann et al., 2010, p. 51). NF systems are considered to work autonomous, a "NF coach" to guide trainees is not required (e.g. Arnold et al., 2012).

In concurring approaches the need for active and effortful engagement is emphasized: "*Children were only advised to be attentive to the feedback and to find the most successful mental strategy to move the ball into the required goal. Because there is no unique cognitive strategy for the task, examples were given that have been shown to be successful in at least some children. Between runs, therapists asked the subjects to verbalize strategies and encouraged them to try new strategies or stick to the successful ones*" (Strehl et al., 2006, p. e1533).

How to assure generalization?

To assume that generalization of effects occurs automatically (via change of "EEG trait") makes further efforts obsolete. Enduring and general change in significant EEG pattern after NF training

should lead to enduring and general change in daily behavior automatically.

On the other hand, if NF is interpreted as a neuro-behavioral treatment aimed at developing skills not only for self-regulation of brain activity but also for general behavior in daily life, additional elements are introduced in the training (Heinrich et al., 2007). To support transfer into daily life, some authors established transfer trials where no contingent feedback is provided (see, e.g., Strehl et al., 2006) and force participants to practice regulation skills in daily life. Parents are instructed to spend support: "*the trainer encouraged the child to develop an appropriate strategy . . . to work out a plan how and where to use the strategy in daily life, discussed problems encountered with transfer and introduced a training diary.*" "*Parents were invited to participate at training sessions and to supervise transfer training with cards at home*" (Drechsler et al., 2007, p. 5).

"CONDITIONING-AND-REPAIRING" vs. "SKILL-ACQUISITION" MODEL

Table 1 summarizes and contrasts different assumptions concerning models and applications of NF underlying different NF approaches. Assumptions are contrasted by two hypothetical models. Both models are proposed only for didactic reasons and represent extreme poles of concurring assumptions. Models comprising assumptions from either side or combining elements from both sides (e.g., interaction of implicit and explicit learning processes) can be developed.

The so called "*conditioning-and-repairing model*" encompasses a somehow more traditional view of NF and follows a mono-causal medical model as treatment targets a distinct causal deficit. Key assumptions are that NF repairs an initial neural dysfunction by implicit operant conditioning processes. Attenuation of this deficit leads to attenuation of the symptoms.

Alternatively the so called "*skill-acquisition model*" is based on a biopsychosocial model, taking different possible conditions and levels in the development and maintenance of symptoms into account. It underlines effortful, controlled (explicit) learning and the necessity to support generalization of acquired skills directly by cognitive-behavioral strategies. NF training targets self-regulation on a neurophysiological and a cognitive-behavioral level, both representing two sides of the same coin, targeted from both directions, on the neurophysiological and the cognitive-behavioral level. In contrast to the conditioning-and repairing-model, improved neuroregulation and clinical outcome (reduction of the severity of ADHD symptoms) are not necessarily strongly correlated.

Annotations about specificity of treatments

The distinction of specific vs. non-specific variables of a treatment also relies on the underlying model. Continuous monitoring of behavior, contingent feedback, and positive reinforcement might be considered powerful variables of NF. During NF, monitoring, feedback, and reinforcement impact the neurophysiological as well as the cognitive-behavioral level. In view of a conditioning-and-repairing model, reinforcement on the cognitive-behavioral level

Table 1 | Concurring assumptions and resulting ways of application regarding NF (in attention-deficit/hyperactivity disorder, ADHD).

	"Conditioning-and-repairing model"	"Skill-acquisition model"
Assumptions		
Indication	Specific neurophysiological deficit	No specific deficit
Mechanisms of learning (EEG regulation acquisition)	Automatic, unconscious (implicit) learning (operant conditioning of EEG pattern)	Controlled, effortful acquisition of regulation skills (explicit learning)
Significance of psychological and social variables and personality traits as moderators/mediators	Susceptibility to basic learning mechanisms (operant conditioning), no higher-order cognitive processes involved.	Effects moderated/mediated by cognitive-attributional variables; generalization of effects moderated by social support, positive reinforcement of target behavior
Effects of the treatment	Automatic change in EEG-trait (tonic change).	Change in EEG-state (phasic changes), acquisition of self-regulation skills, enhancement of neurophysiological functioning
Ways of application		
Instructions, acquisition of self-regulation	No active trainer, no specific instructions/no effort needed, passive participant	Active coaching, support in the search for regulation strategies, active participant, effort to enhance self-regulation skills
Generalization	Automatic transfer to daily life → no effort necessary to support generalization	Transfer-trials; tasks for generalization of effects (e.g., homework)
Setting	Unimodal treatment (Repairing the EEG deficit "normalizes" behavior.)	Module in a multimodal treatment, involvement of parents/teachers

(praise by the trainer, pride about a good score, both leading to enhanced self-efficacy) constitutes an unspecific variable. On the background of a "skill acquisition model," these are basic variables and essential prerequisites of further treatment variables (neuroregulation).

IMPLICATIONS FOR THE EVALUATION OF NF

HOW TO EVALUATE EFFICACY OF NF? WHICH VARIABLES ACCOUNT FOR THE EFFICACY OF NF? WHICH VARIABLES SHOULD BE CONSIDERED "SPECIFIC" OR "UNSPECIFIC"? CAN THE FIDELITY OF THE NF TREATMENT BE ENSURED UNDER PLACEBO-CONTROL CONDITIONS?

There is no doubt that RCT are necessary to evaluate efficacy of NF in the treatment of children with ADHD. In pharmacological research, double-blind, placebo-controlled trials are considered the gold standard in the evaluation of efficacy. Concerning the mechanisms of action of pharmacological treatment, placebo conditions should allow a valid separation of specific from non-specific effects. Blindness to the treatment condition and placebo-control are meant to level the expectations of the participants about the treatments. This is reasonable in the evaluation of efficacy of treatments, if a treatment does not rely on the participant's expectations and active engagement.

Larger effects of NF compared to placebo training would indicate efficacy and specificity of NF. Unfortunately, previous placebo-controlled trials found no superiority of NF in children with ADHD (see Vollebregt et al., 2014b)[4]. However, as stated by Vollebregt et al. (2014b, p. 02): "absence of evidence does not equate with evidence of absence." If NF does not turn out to be superior to placebo training in certain trials (e.g., Logemann et al., 2010; van Dongen-Boomsma et al., 2013) different reasons come into account – first and foremost treatment fidelity. In NF trials confirming the null-hypothesis, it should be obligatory to analyze pre- and post-training EEG data and especially the course of regulation-data to ensure that the training was accompanied by corresponding changes in the resting EEG and, most important, that regulation capability evolved adequately in the NF group (and, if at all, increased to a smaller extent in the placebo group). If participants fail to acquire regulation capability during the treatment (as reported, e.g., in Vollebregt et al., 2014a related to the report of van Dongen-Boomsma et al., 2013), fidelity of the training must be considered seriously impaired and the most likely explanation for the results of hitherto existing placebo-controlled trials is that the key mechanism of NF, the operant learning to alter EEG patterns, was knocked out (for detailed comments to previous placebo-NF-trials, see Arns et al., 2014). Other aspects can also impair fidelity of the application of NF (Sherlin et al., 2011). In this manuscript, we primarily consider feasibility of placebo-controlled trials on the background of different NF models.

Following a "*conditioning and repairing model*," placebo-controlled trials constitute a valid strategy for the evaluation of NF. The efficacy of the treatment is assumed to rely on changes of EEG patterns, automatically achieved by operant conditioning via NF by implicit learning mechanisms. Expectations of the participants carry no weight and no effort for further generalization of the treatment effects must be spent.

Following the "*skill acquisition model*" evaluation should follow criteria employed in the evaluation of cognitive-behavioral interventions. According to a "*skill acquisition model*" efficacy of NF treatment in ADHD does not (solely) rely on implicit and tonic changes in EEG but improved skills of self-regulation, acquired during treatment sessions and furthermore during transfer-tasks at home (Gevensleben et al., 2012) – and probably also touching other neuronal circuits than those primarily addressed by the feedback protocol. Variables like treatment credibility, outcome expectation, self-efficacy, achievement motivation, or locus of control are assumed to be basic moderators of treatment (Borkovec and Sibrava, 2005; Gevensleben et al., 2012). In other words, specific variables are thought to depend on those essential "unspecific" but basic variables. Participant's estimation of practicing placebo training may impair treatment credibility, outcome expectation, self-efficacy, effort spent in skill acquisition, and transfer into daily life. Following the "*skill acquisition model*," fidelity of the treatment may be seriously impaired in placebo-controlled NF trials[5].

Though no NF study in the fields of ADHD to date directly investigated the moderating effects of those basic variables, the results of latest placebo-controlled trials (as reported above) are in line with the aforementioned assumption.

Active control conditions may be preferable (e.g., computerized attention training, EMG biofeedback training including a feedback of artifacts derived from the EEG; Heinrich et al., 2007; Holtmann et al., 2014; Maurizio et al., 2014), paralleled with respect to the setting and the demands upon the participants as well as to the expectations and attributions. In addition, basic ("unspecific") factors (e.g., expectations) can either be controlled for by using appropriate questionnaires (Kotchoubey et al., 2001; Gevensleben et al., 2009a) or could be systematically manipulated via instructions to assess their influence on treatment outcome (Goldberg et al., 1982; Holroyd et al., 1984).

A comparison of different NF protocols can be regarded as another evaluation strategy which may be applied irrespective of the underlying model. Larger clinical improvements for one NF protocol than another provides clear evidence for specific effects (e.g., Gevensleben et al., 2014). Moreover, distinct effects at the neurophysiological level (associated with the clinical outcome) may further indicate specificity of effects.

EMPIRICAL EVIDENCE

In the "Mechanisms and Applications – Models of NF in Children with ADHD" section, we assembled concurring assumptions about the indication, mechanisms of change, and effects of NF. In the following we will highlight some empirical evidence concerning each of the above mentioned notions. Empirical evidence concerning certain aspects of NF is rare and contradictory. Most studies evaluated outcome of NF rather than treatment processes. Hence, valid data concerning prerequisites and predictors of outcome as well as mechanisms of change (learning, generalization) often is missing. We will focus on standard protocols of NF in

[4]In other areas, placebo-controlled designs were applied successfully (Gruzelier, 2014c).

[5]Ethical aspects also argue against the use of a placebo condition (Gevensleben et al., 2014).

children with ADHD (theta/beta and SCP training) and lend some findings from trials with healthy adults if indicated. Our aim is not to give an exhaustive review of the existing literature but to substantiate our aforementioned considerations and to elucidate the eligibility of the presented models of NF in order to encourage further research elucidating mechanisms of NF. A comprehensive overview concerning the empirical validation of NF in healthy adults is provided by Gruzelier (2014a,b,c).

INDICATION FOR NF AND EFFECTS/RESULTS OF NF

What is the evidence for distinct neurophysiological deficits in ADHD?

An elevated theta/beta ratio (enhanced theta activity, reduced beta activity) has been considered a neurophysiological marker of children with ADHD (Snyder and Hall, 2006) and represents the background for the application of theta/beta-NF in children with ADHD. In the light of latest empirical findings, at least the general assumption of a neurophysiological deviation in case of an elevated theta/beta ratio at rest in children with ADHD is arguable. Recent studies (e.g., meta-analysis by Arns et al., 2012; Liechti et al., 2012) conclude that, at most, only a subgroup of children with ADHD exhibit this feature. Regarding an elevated theta/beta ratio as an indication criterion for theta/beta treatment therefore would limit the target population to only a small subgroup of children with ADHD.

On the other hand, Heinrich et al. (2014) reported inter alia increased theta activity in children with ADHD during an attentive state in a cognitive task though an increased theta/beta ratio only characterized children of the predominantly inattentive subtype of ADHD. Children of the combined type showed the largest deviation in the upper-theta/lower-alpha (5.5–10.5 Hz) range.

A reduced CNV has been reported in the major part of studies in children with ADHD (for review see Albrecht et al., submitted) though complexity (Bruckmann et al., 2012), age of the participants (Kratz et al., 2011), and aspects of comorbidity (Banaschewski et al., 2003) may affect results.

Generally it should be kept in mind that the mentioned "neuronal deficits" represent only some neuronal correlates of disturbed behavior but do not give a full explanation of the complex ADHD picture. Hence, the thinking of "just repairing" appears to be rather simplistic. Moreover, as ADHD is considered a clinically and pathophysiologically heterogeneous condition, it appears rather likely that a deviant neurophysiological pattern is not shared by all children with ADHD.

Does NF repair this neurophysiological deficit or strengthen compensatory mechanisms? Is there a change of "EEG trait" or a change in "EEG state"?

Frequency band training. In children with ADHD reliable evidence indicating post-treatment protocol-specific lasting change in resting EEG ("trait") is lacking. Several previous trials abstained from assessing pre–post-change of resting EEG after NF.

We found a decrease in theta activity (no change of beta activity) in the resting EEG after NF, irrespective of the treatment protocol (SCP- vs. theta/beta training; Gevensleben et al., 2009b). There is some evidence that enhanced theta activity predicts superior outcome after theta/beta training. After 18 sessions of theta/beta training, larger improvements were related to higher baseline theta activity, as well as to a larger reduction of theta activity, mainly at parietal-midline sites (Gevensleben et al., 2009b). These results would indicate that the "worst cases" (high baseline-theta) improve the most. So, this result may be considered in line with the assumption that the more the initial deficit is "repaired," the more improvement in behavior can be observed.

On the other hand, it has to be considered that, during training, children practiced to get into an "active," attentive state (in contrast to the resting condition) and that no effects were observed for beta activity and the theta/beta ratio, respectively, which were also targeted during training.

Monastra et al. (2002) reported a decrease of the theta/beta ratio after theta/beta training in children with ADHD characterized by a high baseline theta/beta ratio. Effect sizes of EEG changes as well as regarding behavioral measures in this study including pre-selected children with ADHD outperform all other controlled NF trials. However, among other differences, pre- and post-training EEG assessment encompassed several conditions (resting and active conditions) and might therefore also display enhanced regulation-skills, changing task-specific "EEG state" rather than general "EEG trait."

In healthy adults, associations between distinct NF protocols and changes in the spectral topography of the resting EEG do not support the change of EEG trait notion (Egner et al., 2004) or are at least inconclusive (Gruzelier, 2014c). For example, Doppelmayr et al. (2009) obtained no significant increase of sensorimotor rhythm (SMR, 12–15 Hz) activity in the resting EEG after 25 units of SMR training, although there were solid increases of SMR amplitudes during training.

Evidence for protocol-specific general and lasting change in resting EEG activity (that we would consider a change of EEG trait) is inconclusive. However, sustainability of NF induced tonic resting EEG changes might depend on the number of treatment sessions. Maybe more sessions than conducted in previous trials would be necessary to achieve enduring change[6].

SCP training. SCP training was associated with CNV effects in a number of trials in children with ADHD (Heinrich et al., 2004; Doehnert et al., 2008; Wangler et al., 2011) representing a change in the short-term mobilization of cortical resources reflecting a change in EEG state. It has to be noted that not children with an initially more reduced CNV (pronounced deficit) but those children with a higher CNV (less pronounced deficit) improved more after SCP training (Wangler et al., 2011). Thus, outcome of treatment may rather rely on the better access to basic neurophysiological resources: the more resources are available at baseline, the better the outcome of the NF treatment ("the best cases improve the most").

All in all, there is valid evidence that SCP training attenuates an initial deficit in regulation of cortical excitability in children with ADHD. There is also evidence that a link between the neurophysiological and the cognitive-behavioral level contributed to improved clinical outcome.

[6]Increases in gamma activity in the resting EEG of Buddhist practitioners doing meditation training for 10.000–50.000 h over 15–40 years (Lutz et al., 2004) may reflect an extreme example.

ACQUISITION OF NEURO-REGULATION CAPABILITY – LEARNING DURING NF SESSIONS

Implicit or explicit learning of neuro-regulation?

Investigation of implicit learning mechanisms relies on dissociation paradigms to prevent awareness of the learning process. No serious attempt has been practice in neuro-regulation until now in order to assess, in how far neuro-regulation might evolve implicitly in first and foremost.

In a recent summary of their efforts to elucidate the acquisition of regulation capability Birbaumer et al. (2013) "*...propose that self-regulation of brain activity is akin to skill learning and thus may depend on an intact subcortical motor system...*" as well as "*... that brain-self-regulation need not be an explicit and conscious process...*" (Birbaumer et al., 2013, p. 295). Concerning regulation capability, activity of the basal ganglia and cortical motor structures appeared to play a significant role in the differentiation of good against poor learners (Hinterberger et al., 2005; Birbaumer et al., 2013) and the deletion of striatal NMDA receptors in rodents eliminated the ability to develop neuro-regulation skills (Koralek et al., 2012). This finding indicates that acquisition of neuro-regulation relies on similar neuronal structures and might develop similar to motor skill acquisition (though it has to be kept in mind that cognitive and motor circuits are functionally segregated within these structures; Alexander et al., 1986).

However, the forced acquisition of neuro-regulation skills during scientific trials or clinical applications in humans and even in rodents proceeds not implicitly (out of awareness) but intentional and goal-directed (Kübler and Birbaumer, 2008; Koralek et al., 2012). Philippens and Vanwersch (2010) trained marmoset monkeys to voluntary control their SMR brain activity (11–14 Hz) and omitted the reinforcement after a successful trial: "*it was clearly seen that this monkey was expecting a reward immediately after the successful EEG pattern. This indicates that the monkey was aware that his mood or behavior expressed by the brain activity was related to the reward*" (Philippens and Vanwersch, 2010, p. 330). Furthermore, Ninaus et al. (2013) obtained that regulation effort during NF is accompanied by activity in frontoparietal and cingulo-opercular networks involved in cognitive control.

Therefore, although acquisition of neuro-regulation encompasses mechanisms of procedural learning, there is no clear evidence until now, that neuro-regulation primarily results from implicit learning (automatic, out of conscience, not goal-directed).

Acquisition of neuro-regulation seems to depend on attention (Daum et al., 1993) and motivation (Kathner et al., 2013), is distracted by parallel/concurring information (Johnson et al., 2012), and influenced by affect, attribution, and personality (Hardman et al., 1997; Witte et al., 2013; Kotzias, unpublished). Furthermore, there is a large variability in the success of acquiring neuro-regulation between subjects with a significant rate of non-learners (Drechsler et al., 2007). These findings do not support the notion of pure implicit learning of neuro-regulation. However, sometimes explicit, controlled processing may disrupt implicit learning, e.g. if exceeding verbalization induces an explicit learning mode in the performance of a (procedural) task which is not suitable for predominant explicit processing (Reber, 1993; Sun et al., 2005; Drechsler et al., 2007)

Due to the fact that implicit and explicit processes usually interact in skill learning (Sun et al., 2005; Goujon et al., 2014), it is reasonable to assume that different learning mechanisms interact in neuro-regulation. Acquisition of skills in complex tasks is considered a "*vital interplay that occurs between automatic and controlled processes throughout skill development*" (Shebilske et al., 1999, p. 402). The acquisition of (motor) skills evolves at different stages, initially requiring controlled and effortful processing (e.g. trial and error) developing to more automated and effortless skills (e.g. from declarative to procedural knowledge, Anderson, 1983). In clinical settings (as for the application of NF in children with ADHD), the acquisition of neuro-regulation is a goal directed, self-referential procedural learning process, presumably encompassing interacting implicit as well as explicit learning mechanisms. However, controlled experimental trials disentangling learning mechanisms, including analysis of the relevant cortical and subcortical neural structures, are still outstanding.

GENERALIZATION

Automatic generalization

After a single session of NF (voluntary alpha-attenuation), Ros et al. (2013) obtained an enduring increase of salience network activity (at least 30 min after treatment) in healthy adults reflecting a neuroplastic effect. Furthermore, a single session of NF facilitated performance in a procedural learning task, also without explicit instruction to transfer a regulation "strategy" to the upcoming task (Ros et al., 2014).

In Hoedlmoser et al. (2008) and Schabus et al. (2014), 10 sessions of SMR enhancement led to enhanced expression of 12–15 Hz spindle oscillations during sleep and improved sleep quality, indicating even longer automatic changes in EEG activity associated with a better outcome. However, this trials were goal-directed (reducing sleep problems) and did not exclude that participants transferred strategies from treatment on their own effort.

Effortful transfer

On the other hand, the finding of Schafer and Moore (2011) obtained in monkeys who gained voluntary control over the activity of neurons within the frontal eye field indicates the necessity of an explicit transfer to take place since, after training, selective attention correlated only with voluntary fluctuations of frontal eye field activity.

Concerning ADHD, the outcome of SCP training may differ depending on whether transfer tasks rather address attentional or motor aspects. In several studies, SCP training induced comparable reductions of inattentive and hyperactive/impulsive behavior (e.g., Leins et al., 2006; Gevensleben et al., 2009a) or larger effects regarding inattention (Drechsler et al., 2007). However, the same SCP protocol only had a significant effect on hyperactivity/impulsivity but not inattention in our recent study (Gevensleben et al., 2014) investigating ADHD-related behavior in children with tic disorders. Application differed from previous ADHD trials with regard to treatment goals (improvement of motor inhibition in tic disorders), instructions, and transfer tasks/homework, probably accounting for the differential outcome pattern. It may be inferred that SCP regulation builds the basis for behavioral change and transfer tasks guide the direction.

CONCLUSION AND IMPLICATIONS

There is strong evidence for the efficacy and specificity of certain NF approaches in ADHD, particularly SCP training applied as a neuro-behavioral treatment. Evidence results from trials using active control conditions, comparing different NF protocols and also by taking changes on the neurophysiological level into account. Hence, we argue that the guiding question today is, how to optimally use NF techniques to enhance efficacy of NF and how to optimize training for a certain participant ("personalized medicine").

In the present article, we outlined that different models exist how NF may work (with the "conditioning-and-repairing model" and the "skill-acquisition model" representing two extreme poles) and that the underlying model unfolds implications for the application of the training as well as for the evaluation design of a RCT. These aspects may contribute to the divergent findings and interpretations regarding NF in ADHD. We recommend the following points for (future) NF trials in ADHD:

- As long as there is no detailed knowledge about the mechanisms of NF (in circumscribed fields of application) the assumptions about the mechanisms on which the application of NF is based shall be expatiated according to the framework proposed.
- It has to be checked that potential operators and moderators of efficacy are not attenuated by the design of the trial or the application of the NF protocol.
- Evaluation and interpretation of NF trials shall be based on the underlying model and the way training is applied.

Besides these aspects related to our framework, it is important that the application of NF follows the principles of learning theory (Sherlin et al., 2011). Moreover, particularly if the NF approach does not turn out to be superior to a control condition it is essential to document treatment fidelity in the way that successful neuro-regulation actually took place.

Reflecting the available literature, we suppose that

- NF is indicated whenever self-regulation ability should be enhanced and there is valid knowledge about neurophysiological target patterns.
- The acquisition of regulation capabilities advances in a goal-directed manner with implicit and explicit learning mechanisms interacting closely.
- Learning of neuro-regulation does not solely rely on neurophysiological preconditions but is significantly moderated by attributions, personality, and motivational factors and relies on personal effort.
- exhaustive rehearsal presumably leads to improved and automated regulation skills accompanied by changes in functional and structural brain "*trait*" in the long run.

Concerning the aspect of generalization, empirical findings indicate that different models may be valid depending on the NF protocol and mechanisms to be addressed by the training. We hypothesize:

- Distinct and circumscribed bottom-up mechanisms are enhanced by improved neurophysiological functioning alone (e.g., related to encoding or procedural learning in an experimental task).
- Complex attentional and social behaviors (encompassing different top–down and bottom–up mechanisms) rely to a larger extent on self-regulation skills and will not change to a clinically significant level due to distinct neurophysiological changes alone but have to be addressed on different levels. Neurophysiological changes must spread out beyond NF-trained neuronal circuits and be accompanied by changes in cognitive-behavioral patterns to achieve enhanced self-regulation in complex environments.

We are aware that evidence for these propositions is weak, However, they may serve as a clue for future studies that should target possible moderators (e.g., neurophysiological profile, comorbidity, social support, treatment setting) and mediators of change (e.g., neuro-regulation, changes in attributions, and behavioral skills) as well as obligatory vs. optional variables of a specific NF approach and model, respectively.

The scope should be widened from outcome to process evaluation to study an interplay of variables on different levels. This may not only comprise behavioral (e.g., severity of ADHD core symptoms and associated domains) and neurophysiological factors (neuro-regulation data over the course of the training; brain electrical activity at rest and during task performance in the lab) but also psychological and environmental aspects. In this context, we suggest to consider appropriate evaluation scales and to manipulate factors systematically as part of the research protocol (e.g., enhancing or diminishing treatment credibility or self-efficacy by specific instructions).

Conducting such studies would allow to fill gaps in current models of NF in ADHD gradually and to judge which model is suitable for which application (under which conditions).

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What learning theories can teach us in designing neurofeedback treatments

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Popular definitions of neurofeedback point out that neurofeedback is a process of operant conditioning which leads to self-regulation of brain activity. Self-regulation of brain activity is considered to be a skill. The aim of this paper is to clarify that not only operant conditioning plays a role in the acquisition of this skill. In order to design the learning process additional references have to be derived from classical conditioning, two-process-theory and in particular from skill learning and research into motivational aspects. The impact of learning by trial and error, cueing of behavior, feedback, reinforcement, and knowledge of results as well as transfer of self-regulation skills into everyday life will be analyzed in this paper. In addition to these learning theory basics this paper tries to summarize the knowledge about acquisition of self-regulation from neurofeedback studies with a main emphasis on clinical populations. As a conclusion it is hypothesized that learning to self-regulate has to be offered in a psychotherapeutic, i.e., behavior therapy framework.

Keywords: neurofeedback, learning theories, psychotherapy

INTRODUCTION

"Monkeys meditate for marshmallows"—this is the headline of a report published in the NewScientist in September 2011[1]. Philippens and Vanwersch (2010) had trained marmorset monkeys to increase the sensorimotor rhythm (SMR) of their brains. This was the first time after the famous study of Wyrwicka and Sterman (1968) that it was shown that (even) animals are able to learn self-regulation of brain activity. The very latest neurofeedback studies with animals by Schafer and Moore (2011) and Koralek et al. (2012) will be mentioned below. In humans operant conditioning of electrophysiological brain activity was demonstrated by Kamiya (1966, 2011) who successfully taught subjects to increase and decrease the amount of alpha activity. The success of these trials is attributed to the principles of operant conditioning.

If we consider self-regulation as a skill as it is acknowledged in the brain-computer-interface (BCI) research (Lotte et al., 2013) not only operant conditioning but also classical conditioning, the 2 Process-Theory (Lacroix and Gowen, 1981; Lacroix, 1986) and motivational factors have to be taken into account. **Table 1** depicts these paradigms, the involved mechanisms and important variables in skill learning. Section "Basics from Learning Theories to be Considered in Designing a Neurofeedback Protocol" refers to the important variables derived from learning theories and their use in designing neurofeedback protocols. If available, corresponding results from neurofeedback studies with clinical populations will be reported. The paper ends with a short glance at studies regarding the neuronal basis and the therapeutic framework of neurofeedback.

While the focus of this hypothesis and theory paper is on theoretical basics and clinical studies it has to be pointed to the growing amount of EEG-neurofeedback studies for optimizing performance. Three consecutive reviews report on the cognitive and affective outcomes in healthy adults (Gruzelier, 2014a), creativity (Gruzelier, 2014b) and on methodological and theoretical considerations (Gruzelier, 2014c).

BASICS FROM LEARNING THEORIES TO BE CONSIDERED IN DESIGNING A NEUROFEEDBACK PROTOCOL

This section will examine the "mechanisms" and "important variables" as depicted in **Table 1** and describe their impact on the design of learning processes with the aim of self-regulation of physiological variables.

FEEDBACK, REINFORCEMENT AND KNOWLEDGE OF RESULTS

Biofeedback in general is based on real-time feedback of voluntarily induced changes of certain physiological signals. A successful change according to the task is positively reinforced, while failure to change is punished. These basic operant conditioning aspects of biofeedback are harder to access in neurofeedback as there are no receptors to perceive the electrophysiological activity of the brain. The state of the brain can at best be reconstructed by cognitions and emotions. Therefore external feedback is indispensable and it is worth questioning whether self-regulation of brain activity will ever work without any external feedback. The answer can be derived from the animal studies mentioned above. One monkey who increased his SMR activity

[1]http://www.newscientist.com/article/dn20989-monkeys-meditate-for-marshmallows.html

Table 1 | Factors involved in acquisition of a skill (after Neumann, 2001, extended and modified).

Paradigms	Mechanisms	Important variables
Operant conditioning: **Learning the outcome of a certain behavior**	Trial and error	Reinforcement, reinforcer, shaping
Classical conditioning: **Learning to predict important events**	Target behavior is associated with (elicited by) conditioned stimuli	Transfer
2 Process theory	1. Phase: operant conditioning of adequate behavior. 2. Phase: association of feedback with interoceptive stimuli.	Instruction; strategies Knowledge of results; feedback; practice
Motivation	Intrinsic / extrinsic	individual differences

within 4 sessions of 30 min duration did not receive the reward in the last session. The video shows that he is expecting (and then missing) the marshmallow. He has developed an association between a certain brain activity and its consequences (Philippens and Vanwersch, 2010). Koralek et al. (2012) trained rodents to increase or decrease the pitch of an auditory cursor by 2 different cell assemblies in the primary motor cortex (M1) to either approach sugared water or a food pellet. The tone delivered a continuous feedback of brain activity, which could be rewarded either by food or by sugared water. The rate of correct responses decreased significantly when the feedback was not contingent or when the animals had had free access to the reinforcers before a training session. It was concluded that those "neuroprosthetic skills" were intentionally acquired and goal oriented. The animals changed their behavior (i.e., the activity of certain, distinct cell assemblies) dependent on the reinforcement value of its consequences. The importance of the reinforcement is underlined by Siniatchkin et al. (2000). Children were trained to regulate slow cortical potentials (SCP) and received online wrong feedback but were verbally praised if the trial was successful. From this study as well as from the animal study by Koralek et al. (2012) it may be concluded that positive reinforcement is more important than the operant component of the feedback given!

Contrary to this is what we can derive from the studies regarding the "knowledge of results" by Trowbridge and Cason (1932). Participants were asked to estimate the length of lines. The best results were obtained if quantitative feedback was given, followed by qualitative ("good", "bad") feedback. No feedback or senseless syllables yielded the worst results. The best solution is probably the combination of correct feedback and reinforcement. To prevent misunderstandings, the terms "feedback" and "reinforcement" should be differentiated from each other, knowing that feedback is reinforcing in itself. As a consequence a neurofeedback protocol should deliver continuous feedback as regards to the brain activity in question and a positive reinforcement in addition. By scheduling a feedback trial and the subsequent reinforcement the so-called "post-reinforcement synchronization" (PRS) has to be considered. PRS refers to a synchronization of the EEG that was observed in animals (see Sherlin et al., 2011) and in humans (Hallschmid et al., 2002) and is positively correlated with the outcome of learning. With regards to this mechanism, a neurofeedback training session should be discontinuous with many little breaks allowing PRS to take place. According to this, videos or games as feedback seem to be rather unfavorable.

A couple of basic studies, mostly for SCP-Feedback, tried to assess which modality (visual, auditory) and which timing promote learning and whether proportional or binary feedback are preferred. The evidence is rather clear: visual feedback is superior to auditory feedback (Kisil, 1992; Hinterberger et al., 2004), proportional feedback is superior to binary (Travis et al., 1974; Kisil, 1992) and feedback should be as immediate as possible (Kisil and Birbaumer, 1992).

Any of the abovementioned aspects refer not only to the development of the desired behavior but also for undesired behavior. If the system picks up and feeds back behaviors like breathing, eye movements or muscle activity then the patient will learn to demonstrate those behaviors! The outcome is even worse if non-physiological artifacts are fed back. In this case the patient will learn nothing at all because he cannot influence a signal produced e.g., by a faulty electrode. Even worse he will experience loss of control and may develop feelings and cognitions of learned helplessness. As a consequence a proper online artifact-control is mandatory for any equipment.

SHAPING AND THE QUESTION OF THRESHOLD REGULATION

Shaping in the operant conditioning paradigm refers to the successive approximation to a new behavior, especially skills. Although claimed by authors the automatic threshold regulation in feedback protocols does not correspond to the prerequisites of a shaping process. Automatic threshold regulation was introduced to make sure that a patient is rewarded at least in 60% or 70% of trials (e.g., Lansbergen et al., 2011). By this in a session a performance may be rewarded that is worse than the performance the day before. From a patient's perspective whatever he does, in 70% of the time or trials he gets positive reinforcement for sure, even if he is doing nothing. In order to establish a shaping process the final goals as well as the breakpoints on the way to the goal have to be defined. Finally a prognosis whether the achievement of the final goal will be enduring and generalize to similar albeit different situations in life. As an example learning to swim will be broken down in steps like overcoming any water fears, being able to imitate certain movements with help, being able to swim in deep water, being able to swim in deep water for at least 10 min. . .After this goal is reached parents may allow children to

swim without their surveillance expecting that the child will not drown. Neither breakpoints nor final goals nor a prognosis are known for neurofeedback. At best norms are available regarding the amount of activity in a certain frequency band as it is assumed for the theta/beta ratio (Montgomery et al. in Demos 1998) but they were assessed during spontaneous EEG measurements, which cannot be simply transferred to brain activity in a (probably demanding) neurofeedback session. Finally, to date there is no knowledge available regarding change in amplitudes during the treatment and its relation to symptom change. Studies that have found a correlation of performance during so called transfer trials will be mentioned in the next section.

The argument brought forward against automatic threshold regulation partly holds for manual and/or individual regulation of thresholds, too. Whenever the participant "earns" too much or not enough reward, the threshold is adjusted, i.e., is set higher or lower. Again, the idea is to guarantee a certain amount of reward to keep the participant motivated. The motivation becomes more important than the quality of the performance. This is a questionable strategy which should be taken into consideration in future studies.

A few cognitive neuroscience studies with healthy subjects have shown a positive correlation with the amount of changes in amplitudes and cognitive performance (for a review see Gruzelier, 2014a). The open question then is the reference for determining "improvement": pre-training baseline, first session, last session, pre-session baseline. . .? The nature of the brain signal that is feedback should make a difference. More stationary activity as in the frequency bands may not need a continuous update of the baseline whereas because of their phasic nature SCP should be continuously (i.e., after each trial) updated. Here it might be more adequate to reinforce any change compared to baseline (see Sherlin et al., 2011).

Again only a few studies have assessed the nature of learning in EEG-feedback (for a review see Gruzelier, 2014c). More knowledge as regards to this issue will help to deal with the question of shaping and threshold regulation.

TRANSFER

The transfer of a skill from the setting in which it was acquired to any situation in life where the skill is needed is an important issue. Delivering feedback after every trial compared to intermittent feedback leads to the fastest learning success in motor learning. In the long run however retaining feedback is more successful. Following this observation, Winstein and Schmidt (1990, cited after Mazur, 2002) developed the "guidance hypothesis". From the very beginning of training, participants experience the same situation they will be confronted with after the training has ended. In addition, they assume that withholding feedback elicits more efforts in memorizing and supports intrinsic motivation.

In 1901, Thorndike and Woodworth put forward the theory of "context specifity" (Thorndike and Woodworth, 1901). They proposed that the degree to which skills transfer to novel situations depends on the number of elements that are identical between the learning context and the novel situation. From animal research, Cartoni et al. (2013) derived the "Pavlovian-Instrumental Transfer Hypothesis" (PIT). They conclude that a conditioned stimulus that is associated to a reward can affect the operant conditioned behavior in different ways. Firstly, an action directed to a goal needs the right context. This is given, if there are cues (in the novel situation) that indicate (from the old context) higher chances to get a reward. This can be realized if the cues from the lab or practitioner's office are transferred to the everyday life environment (e.g., classroom) and vice versa if cues from everyday life are transferred to the environment where the training takes place. Secondly, an action may have more or less chances to achieve a goal. Successful actions outside the training environment should be rewarded. Finally, the utility of a behavior in a certain situation is evaluated. According to this, cues should help to discriminate situations in which a certain behavior would be useful or not. An increase of theta e.g., might be useful in order to fall asleep while a decrease might be useful to be concentrated and awake. Cue dependent learning constricts learning to the learning environment as long as the cues are not transferred to everyday life situations. The same holds not only for the newly acquired behavior but also for the old, dysfunctional behaviors. Unfavorable stimulus (classroom)—response (inattentive brain states)—reinforcement (punishment, bad marks) associations have to be changed to favorable ones (classroom-attentive brain states-praise, good marks) by associating cues from the classroom with the acquired behavior. This can be done e.g., by simulation class room situations during the training and by bringing cues from the lab to the classroom. Of course the best place for neurofeedback exercises is the classroom—therefore the development of neurofeedback equipment that can be reliably, validly and safely used in real life situations would help a lot!

If the skill is to be transferred with the help of cues these have to be known. A systematic and thorough behavior analysis will help the patient as well the therapist to become aware of eliciting antecedents, be they environmental, emotional, cognitive, behavioral or physiological variables.

Children with Attention Deficit-/Hyperactivity Disorder (ADHD) may have additional problems transferring newly acquired behavior to everyday life. According to Abikoff (2009) this may be caused by the shortened delay gradient and the inability to anticipate consequences, which in turn affect the perception of cues. Being less able to generalize and to discriminate may compromise the transfer. There are two ways out of this dilemma: if neurofeedback is offered in a cognitive behavior therapy context the therapist can take care of disease specific issues (see Disease), and if the self-regulation is automatized and elicited independently of voluntary action (see next section).

AUTOMATION: PRACTICE MAKES PERFECT

If the self-regulation of brain activity is regarded as a skill automating should be expected as the final aim. The skill is stored in the implicit memory and can be unconsciously retrieved. According to Fitts (1964, cited after Fitts and Posner, 1967) motor learning takes place in three consecutive steps. The "cognitive phase" at the beginning of the process demands a high amount of attentiveness while basis sequences are being learned. The learner will identify by trial and error the correct behavior. During the subsequent "associative" phase the new behavior is practiced, wrong reactions are inhibited if possible. In the end the

performance is executed reliably and less attentiveness is needed in this "autonomous, automatic phase".

The "Two-Process-Theory" (see **Table 1**) of the acquisition of autonomic control substantiates Fitts' model. During the cognitive phase the participant tries to identify strategies (see next section) that lead to successful behavior. Thereafter the repeated matching of a reaction and feedback that signals success interoceptive stimuli form an image of a correct reaction, just as shown in the above mentioned monkey meditating for marshmallows. According to Lacroix (1981) biofeedback training leads to autonomic control through a process primarily consisting of the identification of efferent behavioral programs already within the subjects' repertoire.

In patients with epilepsy who took part in a neurofeedback training of SCP Kotchoubey et al. (2002) showed that self-perception of self-regulation performance developed after patients were successfully able to self-regulate SCPs. Patients who failed in developing self-regulation skills could not correctly estimate their performance. As already mentioned, unlike peripheral motor behavior, electrophysiological activity of the brain is not perceivable. This leads to the question what are the interoceptive stimuli that had been associated with the feedback? Kotchoubey et al. (2002) suggest that changes in the cerebral blood flow, i.e., the extension of receptors of the arterial walls during cortical activation and deactivation might be responsible. Results of a functional imaging study proved an increase of blood flow in different areas of the cortex, depending on the task which was either to produce electrically negative or positive slow potential shifts (Hinterberger et al., 2003). Kotchoubey et al. (2002) provide an alternative explanation by referring to the general control theory. According to this theory subjects perceive operations that are connected with successful control of the cursor (i.e., feedback object) and by this may develop percepts.

Results from long-term studies support the model of skill learning for neurofeedback treatments. After neurofeedback of slow cortical potential patients with ADHD are still able to self-regulate the brain activity 6 months (Leins et al., 2007) and 2 years (Gani et al., 2008) after the end of treatment. In patients with epilepsy successful self-regulation was observed after 1 year (Kotchoubey et al., 2001) and 9 years (Strehl et al., 2014) after the end of treatment. As the activity during activation is more and more concentrated in the area below the sensor this is seen as a further proof for the automation of the skill (Neumann, 2001).

Strategies and instructions

If the self-control is achieved through perception of operations as may be derived from the above mentioned control theory the use of a certain strategy seems to be a possible operation. These strategies are rather easy to choose in the case of feedback of spontaneous EEG activity. The correlation between activation and arousal seem to allow easy access to a certain strategy. Very often participants in a theta-/beta-feedback training are instructed to be relaxed and attentive but there is no systematic data available. The use of strategies for SCPs feedback was investigated by Roberts et al. (1989). It was concluded that there are no valid interindividual strategies known. In SCP feedback participants are asked to self-regulate thresholds of cortical excitation. The slow negative potential shift resembles the contingent negative variation (CNV) which can be observed e.g., in a Go/No go experiment. Here the negative shift is provoked by a warning stimulus in expectation of an imperative stimulus after which the subject has to execute a motor reaction as quickly as possible. Therefore Roberts et al. (1989) expected that the imagination of movement preparation would work as a strategy. This was not confirmed by their study; instead strategies differed from subject to subject and even within the subject in the course of the experiment. Today it is thought that the analogy to the CNV does not work because during the feedback trials no imperative stimulus is given. It was concluded that a strategy is the individually developed percept during the associative phase of successful SCP-regulation Neumann (2001). As a consequence it is recommended not to indicate strategies at all. In a study with healthy participants who had to self-regulate the SMR those subjects who reported to use no specific strategy improved best (Kober et al., 2013). Better within session learning of lateralized SCP regulation was observed in a group with healthy participants who did not receive guidance compared to the group who was told to use emotional strategies. A group by session by block by trial analysis showed no performance differences between the groups (Hardman et al., 1997). The authors assume that vivid strategies might overload cognitive resources and that not being able to name the strategy may indicate a more automatic regulation.

Practice schedules, how much practice and skill decay?

The seemingly simple question regarding the number of sessions comprises several aspects. How many sessions are necessary until the skill is acquired? How many sessions are needed until reduction of symptoms will be observed? How many sessions will be paid (if at all) by the health insurances? Closely connected is the question regarding the training schedule.

Following the theory of reactive inhibition of Hull (1943) spaced practice yields better retention than massed practice. Accordingly Wang et al. (2014) reported significant improvement after 20 sessions spaced working memory training in healthy children compared to massed training (20 sessions in 2, 5 or 10 days). In the absence of any systematic research on these issues for neurofeedback trainings the bridging from basic theory to encompass cognitive training research and neurofeedback protocols is not easy. Considering that neurofeedback sessions normally last 20 to 60 min more than one session per day does not seem to be possible simply for practical reasons. There are two more aspects to consider. Firstly, how big does the interval between 2 sessions has to be in order to declare a training to be spaced—e.g., 1 day or 1 week? Secondly, does it make a difference which system is being trained—cognition, contingencies between behavior and its reinforcement, or a physiological parameter? Arnold et al. (2013) observed no difference in outcome and parents' satisfaction after two vs. three weekly sessions, although parents preferred the schedule with three sessions a week.

The question regarding the number of sessions refers to the prognosis of learning success. Basically a positive correlation between successful self-regulation and clinical outcome is subsumed. From clinical practice it is well-known that the picture is more complicated. One patient may have succeeded

in self-regulation without improving clinically, the other may have improved clinically without being able to self-regulate in a reliable manner, or self-regulation and outcome may correlate. From research it is only known that in neurofeedback protocols including transfer trials where no feedback is given, the performance during transfer trial predicts the clinical outcome (Strehl et al., 2005 for epilepsy patients; Strehl et al., 2006; Drechsler et al., 2007 for children with ADHD). These studies used SCP-protocols. Drechsler et al. (2007) as well as Strehl et al. (2005) used a significant differentiation between tasks (cortical negativation and cortical positivation) as a marker for learning success, while Strehl et al. (2006) chose a significant negative shift from baseline as criterion. A significant correlation between the number of sessions and decrease of symptoms of inattention was reported as a result of a meta-analysis by Arns et al. (2009). The relation between number of sessions and schedule has not been investigated so far.

Blume (2012) showed in her thesis that different studies used diverse criteria such as significant shifts of potentials compared to baseline, a differentiation between parameters (if more than one was trained), number of correct shifts, and duration of the correct shifts as well as a ratio between certain criteria. If "correct" shifts are to be chosen again criteria are needed. Finally it has to be decided which time points should be included as the amount of data produced in any of N sessions is huge. In her analysis of SCP-FB sessions she decided to classify participants as a "learner" if an a- priori defined differentiation and a reliable negativation was shown in the last session. As a result at the follow-up session 6 months after the end of training some children could now be labeled as a "learner" who were previously classified as a "non-learner". It was concluded that the learning is ongoing and learning success cannot be predicted from the performance during the sessions. If these results can be replicated and proven to be clinically valid other criteria have to be developed in order to allow an early prognosis. For a small sample of children with ADHD it was demonstrated that the reduction of symptoms of inattention correlated positively with the change of mean amplitudes of negative shifts during training session 5 and 9, but not in session 13, due to an increase in negativities in children with poor outcome (Gevensleben et al., 2014). The authors hypothesize that these children might have needed a prolonged training. Searching for predictors within the training performance would help to individually tailor the treatment.

According to Singer (1980) learning curves in motor learning show that the task, its difficulty, duration and number of repetitions as well as individual variables influence the learning progress. The impact of individual variables is demonstrated in the so-called "overtraining" (Kreider et al., 1998, cited after Blume, 2012). The extent to which practice can lead to further improvement decreases with the extent of practice. Too many sessions may be disadvantageous if a participant is a quick learner. Blume (2012) observed participants who fulfilled the criteria as "learner" rather early after 12 sessions and fell off in quality after the second training phase containing 13 more sessions. In the follow-up evaluation they showed a good performance again. It is concluded that speed of learning differs in individuals possibly according to age, maturation of brain, stress vulnerability and / or cortical functioning (see below—individual factors).

Although skills can last a lifetime they do deteriorate with non-use. As mentioned above according to follow-up studies after SCP-feedback in epilepsy and ADHD, patients not only continued to improve clinically after the end of treatment, self-regulation of brain activity was improved or sustained. It may be concluded that learning does not stop with the last session. By using the self-regulation skill in everyday life patients are being reinforced to be less hyperactive, impulsive and inattentive. This in turn consolidates the behavior while unfavorable brain activity is being extinguished. The skill is used automatically whenever it is needed—in the end it can be assumed that the functioning of the brain has changed.

INDIVIDUAL VARIABLES

The acquisition of the skill to self-regulate brain activity is not only based on certain rules or laws of learning. As already mentioned in the last section, individual variables have to be taken into account, too.

Motivation

According to Hofmann et al. (2012) participants need sufficient motivation to invest effort to overcome the discrepancy between the gap between actual and potential performance and obstacles and temptations along the way. Achievement motivation as hope for success or fear of failure and attribution styles are individual variables that might influence the intrinsic as well as the extrinsic motivation. There is limited data on the impact of these variables from neurofeedback and BCI-research available. Witte et al. (2013) observed in healthy participants that control beliefs as regards to technology correlated negatively with the ability to self-regulate SMR. It is assumed that a locus of control might lead to emotional or cognitive overload, which negatively influences the performance.

Intrinsic motivation can be spoiled by inflated praise (Brummelman et al., 2014) and may be enhanced by feedback, which draws attention to a skill without making a judgment about the individual or reporting on feelings. As a general rule an inherently interesting or enjoyable task promotes intrinsic motivation. Therefore it is discussed how to offer feedback sessions to be as interesting as possible. The succession of repeated trials seems to be contraindicated. Trainer or therapists sometimes ask for protocols that use different levels of expertise, similar to computer games. This analogy does not work because self-regulation of brain activity does not improve in a linear manner. As in any motor learning it is not the animation that leads to an improved technique. Instead the execution of the correct behavior (guided by the trainer) is reinforcing in itself. For patients with ADHD it is known that they may perform very well if the task is entertaining, however when facing monotonous tasks the symptoms become obvious. As a consequence a boring training would simulate difficult situations in everyday life. On the other hand loss of motivation has to be avoided—a difficult tightrope walk. Again the therapist is responsible in guiding the treatment and helping the patient to overcome frustration and moments of boredom.

Cognition

Results on the impact of cognitive variables as memory or attention are not consistent (Daum et al., 1993; Holzapfel, 1998). Intelligence did not turn out to be a prerequisite of successful self-regulation in Holzapfel et al. (1998) who treated a patient with an IQ below 80.

With regards to brain resources, Wangler et al. (2011) showed that in children with ADHD a larger CNV before training predicted a bigger improvement after training.

Disease

Factors being correlated with a disease might influence the performance, too. In locked-in patients with Amyothrophic Lateral Sclerosis (ALS) e.g., moods, bodily complaints, and quality of care influence the performance (Neumann, 2001).

For many years it was assumed that patients with an impairment of executive functions would not be able to learn self-regulation. Maintenance and updating of relevant information, inhibition of irrelevant impulses and mental set shifting are features of the working memory which are necessary for self-regulation (Hofmann et al., 2012). Although they are impaired e.g., in patients with ADHD, results from neurofeedback treatments show, that these patients nevertheless successfully complete the training (e.g., Strehl et al., 2006; Mayer et al., 2012).

In some diseases the typical symptoms may prevent taking part in neurofeedback training. For example an autistic child will not allow being touched or to having electrodes fixed on head and face. In this case a well-trained therapist will implement a shaping program in order to establish trust and compliance.

NEURONAL BASIS OF NEUROFEEDBACK LEARNING

Due to the use of intracranial electrodes, the latest animal studies deliver insight into the neuronal basis of neurofeedback learning. According to Koralek et al. (2012) striatal neurons change their firing rates and build strong connections with motor cortex neurons. If by experimental manipulations these connections cannot develop the animal is not able to learn the skill. The authors conclude that corticostriatal plasticity is the basis not only for abstract skill learning but also for learning intentional neuroprosthetic skills in the absence of movements.

The specificity of neurofeedback was proven by Schafer and Moore (2011). Rhesus monkeys learned to voluntary reduce or enhance the activity of neurons within the frontal eye field. The pitch of a tone was used as feedback and juice was given as reinforcement. This operant conditioned behavior was associated with improved selective visual attention. The authors suggest that the specific association of self-regulated neural activity with top-down attention may constitute a basis for the observed improvements in patients with ADHD after neurofeedback.

CONCLUSION: NEUROFEEDBACK AND PSYCHOTHERAPY

Neurofeedback is not a magic box easily delivered to the patient. Neurofeedback as well as biofeedback for patients will always take place within a patient—therapist interaction. "My experience with years of biofeedback training with various physiological modalities leaves me with the conviction that a very large portion of the total influences on learning is bio-social in nature, testifying to the evolution of the species as a social species. Though seldom discussed in the scientific literature, the nature of interpersonal relations between trainer and trainee are often decisive for learning progress." (Kamiya, unpublished, retrieved in Neumann, 2001, p. 32).

The *equipment is a tool* within this interaction, *neurofeedback is a method* of behavior therapy. As in any other behavior therapy the therapist initiates and helps through a process during which the patient may learn a new behavior that helps to overcome his symptoms. Different from the usual bottom-up targets in behavior therapy, which are overt behavior, cognitions and emotions, neurofeedback tries to directly change cortical activity. But with the help of the equipment brain activity becomes overt, too. The therapist will need to know the laws of learning as well as how to applicate neurofeedback training in order to be a competent partner in this top-down behavior therapy approach.

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Are treatment effects of neurofeedback training in children with ADHD related to the successful regulation of brain activity? A review on the learning of regulation of brain activity and a contribution to the discussion on specificity

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While issues of efficacy and specificity are crucial for the future of neurofeedback training, there may be alternative designs and control analyses to circumvent the methodological and ethical problems associated with double-blind placebo studies. Surprisingly, most NF studies do not report the most immediate result of their NF training, i.e., whether or not children with ADHD gain control over their brain activity during the training sessions. For the investigation of specificity, however, it seems essential to analyze the learning and adaptation processes that take place in the course of the training and to relate improvements in self-regulated brain activity across training sessions to behavioral, neuropsychological and electrophysiological outcomes. To this aim, a review of studies on neurofeedback training with ADHD patients which include the analysis of learning across training sessions or relate training performance to outcome is presented. Methods on how to evaluate and quantify learning of EEG regulation over time are discussed. "Non-learning" has been reported in a small number of ADHD-studies, but has not been a focus of general methodological discussion so far. For this reason, selected results from the brain-computer interface (BCI) research on the so-called "brain-computer illiteracy", the inability to gain control over one's brain activity, are also included. It is concluded that in the discussion on specificity, more attention should be devoted to the analysis of EEG regulation performance in the course of the training and its impact on clinical outcome. It is necessary to improve the knowledge on characteristic cross-session and within-session learning trajectories in ADHD and to provide the best conditions for learning.

Keywords: neurofeedback, ADHD, specificity, self-regulated brain activity, learning curves, learning indices

Recent meta-analyses and reviews have evaluated the efficacy of neurofeedback training in children and have concluded that there is a need for more placebo-controlled studies in ADHD research with better blinding of raters and possibly also of trainers (Lofthouse et al., 2012; Sonuga-Barke et al., 2013). Placebo control, often used interchangeably with sham (e.g., Heywood and Beale, 2003; van Dongen-Boomsma et al., 2013) or mock (e.g., Egner et al., 2002) feedback in this context, lacks only the active core component, namely the consistent feedback contingent upon specific EEG patterns, and appears indistinguishable from the neurofeedback condition. This typically implies that non-contingent sham feedback is provided to the participant during the training, either by frequently changing contingencies with real data (e.g., Heywood and Beale, 2003), by using simulated EEG-like data or feedback (e.g., Logemann et al., 2010; van Dongen-Boomsma et al., 2013), or pre-recorded data, which all may be combined with contingent feedback of real artifacts (Kerson and Collaborative Neurofeedback Group, 2013). While placebo control and pre-post analyses of change on clinical, neuropsychological and electrophysiological levels would appear to be the first choice with regard to efficacy, it may be questioned whether they constitute the best method for investigating the specificity of NF. Although placebo control aims to control for all non-specific influences of the training setting, such as learning to sit still, improved personal well-being due to the positive relation to the therapist, or positive expectations, it entails methodological limitations. Sham feedback fails to control for generic and non-specific learning effects, i.e., by the experience of improvement and progressive mastery, of self-efficacy, and increase of control which may be induced by any kind of biofeedback. Although sham neurofeedback using slowly alternating contingencies with different frequencies may allow at least piecewise learning (Hoedlmoser et al., 2008; Doppelmayr et al., 2009), alternative placebo-type control conditions such as EMG biofeedback (Bakhshayesh et al., 2011; Maurizio et al., 2014), or feedback from a distinct control region as in neuroimaging (Caria et al., 2007) provide better control for progressive learning.

More importantly, with regard to specificity, neither placebo control nor any other type of control condition can provide positive proof that successful learning of EEG regulation in the active condition is responsible for clinical improvements. To that aim, it would be necessary to demonstrate that learning of EEG-regulation occurred during the training and that the NF-training success, in the sense of successfully learned self-regulation of brain activity across time, is related to positive outcome on the clinical, neuropsychological or electrophysiological level (see Holtmann et al., 2014a). Adequate control for the generic effects of learning would then require successful learning at a similar rate in the control condition.

In addition, for the time being, the effects which might be induced by sham feedback remain poorly understood. This may be particularly relevant for individuals with ADHD, who according to the ADHD literature may display problems with self-perception in various different ways: A sizable portion of children with ADHD show an inappropriate overestimation of self-efficacy and ability, the so-called illusory positive bias (see Owens et al., 2007). Other studies have demonstrated feelings of low self-efficacy and low self-esteem in patients with ADHD (Newark and Stieglitz, 2010; Mazzone et al., 2013) which usually leads to a negative bias in self-perception. In addition, patients with ADHD seem to display problems with the self-perception of internal states (Donfrancesco et al., 2013). Many children with ADHD may be unaware of how it feels to be in an alert and focussed state of mind. Thus, providing ADHD patients with sham feedback could prevent them from developing a more adequate self-perception or lead them to mistrust their intuition. Although the findings from sham neurofeedback control conditions suggest no detrimental effects regarding core ADHD symptoms, effects on self-perception remain to be tested directly. Also from this perspective, NF studies which use genuine neurofeedback and which examine whether learning of self-regulated EEG activity actually occurred during the training, may present a better alternative in order to investigate the specificity of NF than placebo controlled studies.

In this paper, we will present a short review of NF-studies with ADHD patients in which learning of EEG regulation was analyzed and we will discuss methods how to evaluate and quantify learning of EEG regulation over time. Among the many varieties of NF protocols with ADHD (e.g., Hurt et al., 2014), the training of frequency bands (NF-FB) and the training of slow cortical potentials (NF-SCP) are the best scientifically evaluated and will therefore be the focus of the following review (**Table 1**). We will additionally refer to studies with Q-EEG-training and with healthy participants or clinical groups other than ADHD in order to illustrate a respective method (**Figure 1**).

ADHD Neurofeedback Protocols and Learning of EEG Self-Regulation

We identified 15 published NF group studies with ADHD children which include the analysis of EEG regulation learning across training sessions (**Table 1**). The majority of these studies used NF training of the frequency bands (NF-FR) and central electrodes. During NF-FR, subjects are provided with continuous (visual or/and audio) feedback and are positively reinforced as long as the spectral activity of the targeted EEG-frequency band or the ratio of specific frequency bands stays below (or above, respectively) a pre-defined threshold. As soon as the threshold is passed, the feedback stimulus changes, announcing that the subject has reached an undesired state. A classic ADHD study protocol aims to decrease theta activity and increase beta activity (Lubar et al., 1995; Leins et al., 2007; Bakhshayesh et al., 2011). Another characteristic protocol for ADHD aims at increasing the sensorimotor rhythm (SMR; Kropotov et al., 2005; Russell-Chapin et al., 2013), which is known to play an important role for motor excitability (Sterman et al., 1970; Pfurtscheller et al., 1996). While these frequency specific protocols are usually employed with the aim of obtaining "normalization" of characteristic spectral EEG abnormalities in ADHD, a more recent rationale is to train "regulation" of spectral EEG activity instead (Holtmann et al., 2009, 2014a). This change

TABLE 1 | ADHD Neurofeedback studies analyzing learning of EEG regulation.

Study, NF-participants	Protocol, electrode sites, no. of sessions	Learning parameter/criterion for good performance	Learner rates/ learning outcome	Association between NF-learning and outcome gains
Lubar et al. (1995) *N* = 17	Theta↓/Beta↑ (bipolar electrodes situated halfway between Cz and Pz and halfway between Fz and Pz); 40 sessions	MP Theta/Beta/significant positive correlation between sessional learning parameter and session number	65% learners	Stronger improvement in attentional test (TOVA) in learners than non-learners
Kropotov et al. (2005) *N* = 86	Beta↑ (C3-Fz); SMR↑ (C4-Pz); 15–22 sessions	At least 25 % increase of within sessional Beta- or SMR-power relative to resting-BL at the 1st session/of at least 60 % of successful sessions	82.5% learners	Improvements of ADHD symptoms and of Go/Nogo response-time and Go/Nogo SD
Strehl et al. (2006) *N* = 25 (Gani et al., 2008: 2-years-follow up)	SCP ↑↓ (Cz); 30 sessions (3 blocks of 10); follow-up sessions 31–33 (after 6 months)	MA of negativity trials during FB and TF, difference in MA between positivity and negativity trials/Good and poor learners based on median split of mean difference between MA of positivity and negativity trials at 3rd training phase	*MA negativity trials*: 2nd session < last session 2nd session < follow-up *Difference between MA of positivity and negativity trials*: at follow-up↑	Good TF-performance (difference between MA of positive and negative trials, sessions 21–30) is associated with clinical improvement only in good learners
Drechsler et al. (2007) *N* = 17 (Doehnert et al., 2008)	SCP ↑↓ (Cz); 30 sessions	MA of negativity trials during FB and TF/good and poor learners based on median split of mean difference between MA of positivity and negativity trials during TF-sessions 14–28	*MA negativity trials*: FB: session 3–6 < session 25–28 TF: session 3–6 < session 25–28	Difference between MA of positive and negative trials during TF (sessions 14–28) correlates with clinical improvements (hyperactivity/impulsivity) in good learners
Leins et al. (2007) Group 1 *N* = 16, Group 2 *N* = 16	Group 1: Theta↓(↑), Beta↑(↓) (C3f, C4f); Group 2: SCP↑↓ (Cz); 30 sessions, 31–33 follow-up sessions (after 6 months)	Group 1: MP Theta/Beta Group 2: MA of negativity trials. Both: difference between up- und down-regulation	EEG learning both groups: 2nd session < last session 2nd session < follow up	
Bakhshayesh et al. (2011) *N* = 18	Theta↓/Beta↑ (Cz); session BL; 30 sessions	MP Theta/Beta across sessions (section 1, 2, 3)	Theta/Beta ↓ in 2 out of 3 training conditions; BL ↓	
DeBeus and Kaiser (2011) *N* = 42	Beta↑/(Theta + Alpha)↓ (Fz); 20 sessions	[Beta/(Theta + Alpha)] ↑ (= Engagement Index) of sessions 1–3 compared to 18–20/Increase of Engagement Index by $\frac{1}{2}$ SD	74% learners	Teacher rated improvements correlate with change in Engagement Index in learners
Liechti et al. (2012) Maurizio et al. (2014) *N* = 13	Theta↓(↑)/Beta↑(↓); SCP↑↓; tomographic NF of anterior cingulate cortex activity; Pre-session QEEG ; 36 sessions	MP of Beta/Theta or MA across sessions	Only partial learning for a simple SCP variant, otherwise no cross-sessional learning; decrease of pre-session QEEG within-NF-group variability across sessions (normalization)	No association between EEG learning and behavioral outcome, except between SCP delayed feedback regulation and hyperactivity/impulsivity
Hillard et al. (2013) *N* = 18	Undisclosed protocol (wide band spectrum regulation) (Fpz); 12 sessions	MP frequency analysis at FPz within (minute 1 to 25) and across sessions (session 1 to 12)	*Across sessions*: Alpha↑ and Beta↓, all other frequency bands↓; *Within session*: Theta/Beta ↓, Theta/Alpha ↓	
Russell-Chapin et al. (2013) *N* = 12	SMR↑ (Cz); 40 sessions	MP of SMR	SMR↑ (session 1 < session 40)	

(Continued)

TABLE 1 | Continued

Study, NF-participants	Protocol, electrode sites, no. of sessions	Learning parameter/criterion for good performance	Learner rates/ learning outcome	Association between NF-learning and outcome gains
Bink et al. (2014) *N* = 45 (adolescents)	Theta↓/SMR↑ (Cz); Session mean 37 (± 5)	MP of Theta/SMR (Alpha, high Beta) of sessions 1–5 compared to 31–35; Within session first 15 min. compared to last 15 min.	*Across session*: no change of overall MP; *Within-session*: Theta↓ larger at sessions 31–35 than 1–5.	
Escolano et al. (2014) *N* = 20	Individual upper Alpha↑ (AFz, F3, Fz, F4, FCz and Cz); Pre- and post-session active and passive BL; 18 sessions	MP of individual upper Alpha across sessions and within sessions	Pre-session task-related MP ↑ (= active BL) across sessions; Pre-post MP ↓ within sessions; absolute and relative Alpha MP ↓ within sessions	No association between learning/training response and behavioral improvements
Gevensleben et al. (2014) *N* = 10	SCP ↑↓ (Cz); 13 double sessions	MA during positivity or negativity trials/MA↑ across sessions 1, 5, 9 and 13	Cross sessional increase of negative MA during negativity trials	Association between negativity MA of session 5 and 9 and inattention symptoms↓
Takahashi et al. (2014) *N* = 10	SCP ↑↓ (Cz); 16 (20) sessions	Peak amplitude during positivity or negativity trials across sessions	Positive shift amplitude ↑ in session 9, 13; negative shift amplitude ↑ in session 11, 12	
Vollebregt et al. (2014) EEG learning analyzed: *N* = 10	Individualized protocols; most often SMR↑/Theta↓; 30 sessions	MP per trained frequency-band across sessions	No systematic improvement on target frequencies	

SCP = slow cortical potentials, MA = mean amplitude, MP = mean power, ↓ = decrease, ↑ = increase, TF = transfer condition, FB = feedback condition, BL = baseline, SD = standard deviation.

in perspective is based on research that failed to find consistently abnormal or characteristic EEG frequency patterns in children with ADHD at group level (Liechti et al., 2013). Consequently, some NF-FR protocols alternate between phases of up- and down-regulation which is consistent with the typical approach in SCP regulation (Leins et al., 2007; Liechti et al., 2012; Maurizio et al., 2014). In contrast, QEEG NF training (and/or z-score training) and other individualized NF protocols assume EEG abnormalities compared to normative data, which are trained in order to reach normalization (Hillard et al., 2013; Vollebregt et al., 2014).

In six out of 15 studies, NF of the slow cortical potentials (NF-SCP) was used (Strehl et al., 2006; Drechsler et al., 2007; Gevensleben et al., 2014; Takahashi et al., 2014), sometimes in combination (Liechti et al., 2012; Maurizio et al., 2014) or contrasted with NF-FR (Leins et al., 2007). SCPs are shifts in electro-cortical potentials which are thought to index the regulation of cortical excitability. NF-SCP trials are short, at about 8 s, and participants are instructed to enhance activation (negativity trials) or reduce activation (positivity trials) relative to the baseline measured at the beginning of each trial. The magnitude of a produced negative amplitude reflects the amount of resources allocated to prepare a motor or cognitive response while a shift towards the positive polarity reflects a decrease in cortical excitability, which is in turn associated with a reduced responsiveness (Birbaumer et al., 1990).

In these NF-SCP studies, learning progress was mostly confined to negativity trials (i.e., to activation), while no or only moderate learning seemed to occur in positivity trials (i.e., deactivation) (Strehl et al., 2006; Drechsler et al., 2007; Leins et al., 2007; Gevensleben et al., 2014; for NF-SCP with healthy adults see Studer et al., 2014). In the initial training sessions, subjects seemed to spontaneously produce positive amplitudes (Strehl et al., 2006; Drechsler et al., 2007), but failed to do so in the subsequent sessions, possibly because they took recourse to more intentional strategies. According to Strehl et al. (2006), children report that the positivity trials are more difficult and exhausting. Alternatively, considering the already high performance in positivity trials during the initial training phase, the lack of improvement in positivity trials might be attributed to a possible ceiling effect (Strehl et al., 2006; Leins et al., 2007). Only one recent study (Takahashi et al., 2014) found comparable increase of positive as well as negative shift amplitudes across training, based on peak amplitudes.

Very few ADHD-studies examined learning of EEG regulation in transfer conditions (Strehl et al., 2006; Drechsler et al., 2007; Leins et al., 2007; Liechti et al., 2012) which is hypothesized to be a more ecologically valid learning measure than performance in feedback trials. In transfer trials, participants regulate their brain activity without feedback or while feedback is delayed. The ability to follow the instructions during transfer trials without the aid of immediate feedback should reflect the child's ability to regulate his/her brain activity independently of external triggers. This ability is considered a necessary precondition for applying the acquired skill in situations outside the laboratory. NF-studies in ADHD reporting learning progress for both transfer and feedback trials are rare (Leins et al., 2007; **Table 1**). There is evidence that ADHD-subjects are less effective in transfer trials than in feedback trials

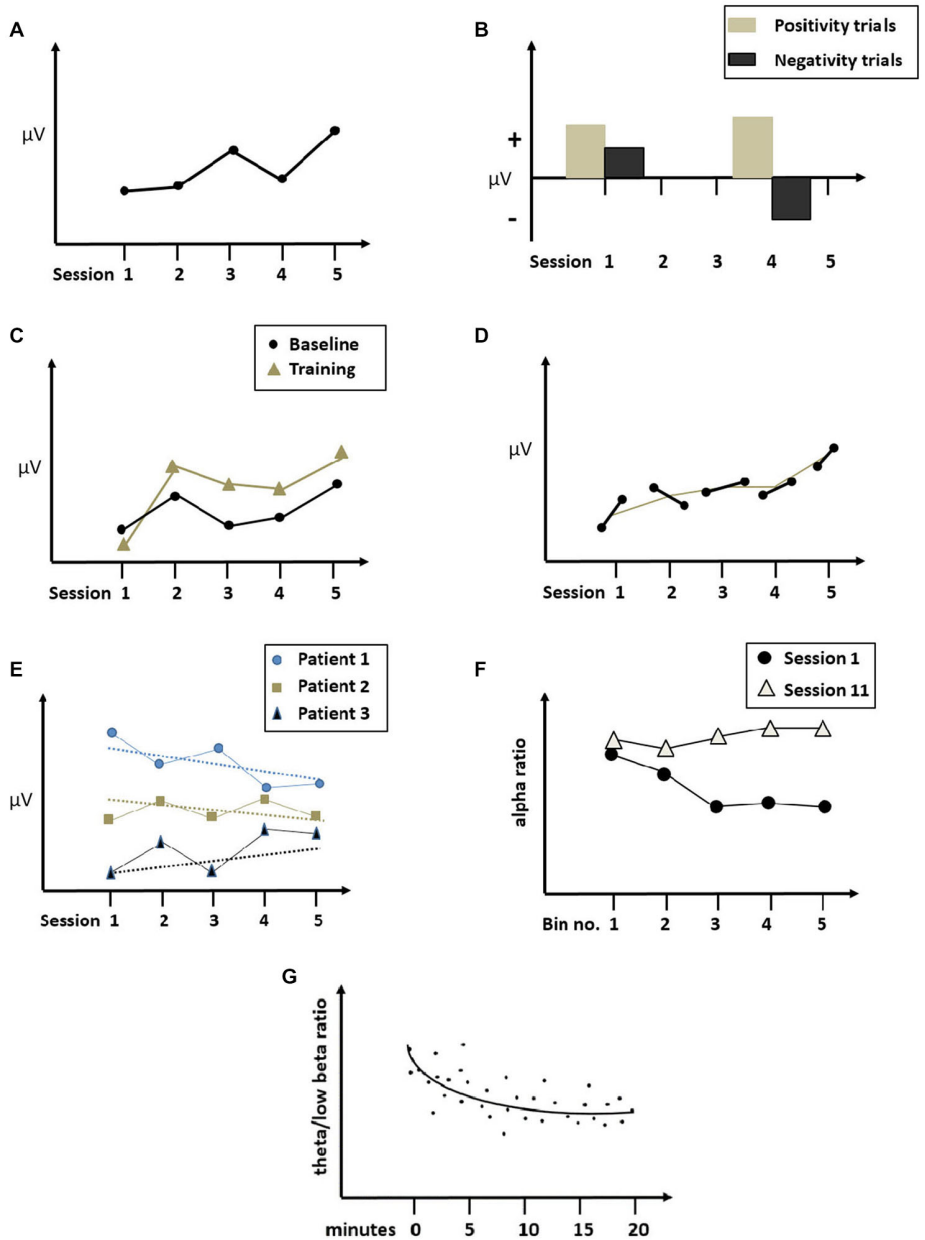

FIGURE 1 | Illustration of across and within session learning curves. **(A)** Across sessions comparison of single sessions (SCP mean amplitude during positivity and negativity trials; adapted from Gevensleben et al., 2014; modified). **(B)** Learning curve across sessions of mean training performance (e.g., Cho et al., 2008; modified). **(C)** Pre-session baseline and mean training performance across sessions (adapted from Dempster and Vernon, 2009, modified), **(D)** Pre- and post- session baselines across sessions (adapted from Escolano et al., 2011, modified). **(E)** Individual pre-session baselines across sessions (adapted from Liechti et al., 2012, modified). **(F)** Within session learning curves of training performance during session 1 and session 11, segmented into bins of time (adapted from Cho et al., 2008, modified). **(G)** Within session learning curve collapsed across sessions, indicating mean theta/beta ratio per minute (adapted from Hillard et al., 2013, modified). The figures illustrate the methods used in the studies; all data have been modified.

(Strehl et al., 2006; Drechsler et al., 2007; Leins et al., 2007), which also appears to be the case in patients suffering from epilepsy (Kotchoubey et al., 1999). In healthy adults, EEG regulation performances were also less effective during transfer (Rockstroh et al., 1990) or comparable in both types of trials (Lutzenberger et al., 1982).

Several ADHD-studies compared NF-learning to learning progress in other biofeedback modalities, such as muscle relaxation (Bakhshayesh et al., 2011; for a recently published study design see Holtmann et al., 2014b) or biofeedback-guided learning of fine motor skills (Maurizio et al., 2014), with the latter showing better learning with motor than with

EEG feedback. Liechti et al. (2012) reported that children with ADHD did not display learning of EEG regulation across sessions in a tomographic EEG NF training. However, they did show progressive learning in muscular artifact control, thus demonstrating a significantly improved ability to sit still.

Measuring Learning of EEG Self-Regulation

As indicated in **Table 1** and illustrated in **Figure 1**, the methods used for determining the learning of self-regulation with NF-training are heterogeneous. By "learning" (or "EEG-learning") we will refer to an improvement in a targeted electrophysiological parameter measuring self-regulated brain activity across time, while "EEG training response" implies more generally any training-related change of an electrophysiological parameter (see Section Baseline increments). We will present a brief overview over different methods and learning indices used in the reviewed studies, discuss possible problems and present additional approaches from studies with other groups than ADHD.

Units of Measurement

The most commonly used units of measurement are the mean level of *amplitude* and the *percentage of time* beyond a predefined threshold of EEG activity. The amount of decrease or increase of amplitude in the desired direction or the increased amount of time spent in the desired range of frequencies should reflect the participant's improved regulation efficiency across time. Often, regulation success is dichotomized (yes or no) on each trial, and hit rates are computed online and presented as reinforcers (bonus points) after a block of trials. Such hit rates may be used to represent the EEG learning success across time (e.g., hits above threshold per minute, for children with high functioning autism see Pineda et al., 2014). This requires, however, that criteria for hits/reward are kept stable, which is not the case with adaptive programs or shaping. Moreover, the use of time units above threshold as criterion is not sensitive to smaller improvements in the regulation of amplitudes just below the threshold.

When considering SCP-NF, the observation of only the change in mean amplitude provides no direct evidence about the participant's ability to differentiate between a state of activation (reflected by a negative amplitude) or deactivation (reflected by a positive amplitude). Nevertheless this skill is hypothesized to be the main training goal in SCP-NF. For the evaluation of progress in learning to differentiate between polarities, it has been common to compute the difference between the means of positive or negative amplitudes and then compare these across sessions (Strehl et al., 2006; Drechsler et al., 2007; Doehnert et al., 2008). However, this method alone fails to account for cases in which regulation has only been achieved in one direction. To illustrate this, it might be the case that the participant mistakenly produces an amplitude of moderate negative polarity during the positivity trial, while the performance in the negativity trial is correct (i.e., strong negative polarity) (see Blume, 2012). This objection especially accounts for ADHD-patients, as in several studies cross-sessional learning has been reported only for negativity, but not for positivity trials (Strehl et al., 2006; Drechsler et al., 2007; Leins et al., 2007; Gani et al., 2008).

Cross-Session Learning

In the ADHD studies reviewed, the calculation of cross-session learning was based on different samplings of time periods: Several studies used two time periods (session 1 and session 40; Russell-Chapin et al., 2013) or a small number of selected sessions, usually consisting of one from the beginning, one or two in the middle and one from the end of the training course (1st, 5th, 9th, 13th session: Gevensleben et al., 2014; 1st, 10th, 20th, 30th session: Vollebregt et al., 2014; **Figure 1A**). However, sampling only a small number of single sessions for the calculation of learning is often problematic as the performance of a single session may be biased due to external variables unrelated to the training (i.e., motivation in the final sessions might be lower, day-to-day events, sleep patterns, etc.). In addition, several studies reported large variability in intra-individual learning performance (Strehl et al., 2006; Drechsler et al., 2007; Leins et al., 2007; for healthy participants e.g., Gruzelier et al., 2014a; Wan et al., 2014). To reduce this large variability throughout the course of the training, some researchers clustered groups of sessions into blocks for analysis, e.g., two sessions into one block (sessions 2/3, sessions 29/30 and follow-up: Strehl et al., 2006; Leins et al., 2007; Gani et al., 2008) or all sessions into three blocks of 10 sessions (Bakhshayesh et al., 2011). Alternately, only the second half of the sessions was incorporated into the (sub-) analysis, as this later phase was thought to be more indicative of learning progress than the first half (Drechsler et al., 2007; epileptic patients: Kotchoubey et al., 1999).

In other studies, training performance has been considered across all sessions, which allows for a more fine-grained analysis of the course of learning also including non-linear changes (**Figure 1B**; ADHD patients: Lubar et al., 1995; Hillard et al., 2013; for NF learning curves in studies with other clinical groups see e.g., Kouijzer et al., 2013; Enriquez-Geppert et al., 2014; Pineda et al., 2014; Wan et al., 2014). Strehl et al. (2005) argue that a steady learning curve across sessions is not necessary to qualify as a learner, as some subjects might find an optimal strategy only at the end of training.

Large intra-individual variability in cross-sessional EEG regulation performance has also been reported in studies with healthy adults and has been attributed to fluctuating arousal levels. Gruzelier et al. (2014a) refer to healthy participants' self-reported irregularities in night sleep. Indeed, there is evidence that ADHD patients in particular suffer from sleep irregularities (Spruyt and Gozal, 2011). However, the variability of performance due to fluctuations in motivation and arousal is a major feature of ADHD. In order to account for the intra-individual variability of learning performance, Strehl et al. (2006) normalized the data by dividing the individual mean NF-parameters by the individual standard error. This procedure reduces the likelihood of a bias towards subjects with high amplitudes in group analyses of learning. To illustrate this bias, one can imagine a subject with a slow gradual increase in amplitude and thus a small standard deviation. Without

normalization, this subject is less likely to reach a predefined criterion of good learning than another subject with a fluctuating pattern.

Within-Session Learning

Both within- and cross-session EEG-learning (decrease in theta/low beta and theta/alpha ratios) was reported in ADHD-patients by Hillard et al. (2013), using a wide band EEG regulation training at a prefrontal site. Within-session analyses for theta/low beta ration and theta/alpha ratio resulted in significant decrease in the shape of a logarithmic curve over the 25 min of training (for illustration see **Figure 1G**). In addition, significant progressive changes in the expected direction across sessions were found for all analyzed frequencies. Bink et al. (2014) found larger within-session decrease of theta activity during the last sessions of a NF-FR theta/SMR training compared to the first ones, but no significant change of mean power across sessions. Escolano et al. (2014) analyzed within-session learning in an individualized upper alpha training for children with ADHD. Before and after each session QEEGs were recorded with eyes closed (resting EEG, passive baseline) and with eyes open while performing a visual counting task (active baseline). An unexpected pre-post session decrease was found for counting task related EEG activity (alpha "rebound" effect), in contrast to findings by the authors with healthy adults (Escolano et al., 2011).

Different approaches exist to measure within-session learning, e.g., by relating the mean NF-parameters of each period within a session to the first (Wan et al., 2014) or preceding period (Egner and Gruzelier, 2001), collapsed across sessions. Alternatively, a period or a complete session may be divided into very short segments and collapses across sessions (Dempster and Vernon, 2009) or the change of within-session mean parameters may be analyzed across sessions (Cho et al., 2008; **Figure 1F**). Although it might initially seem counterintuitive to examine within-session learning regarding long-term outcome and specificity, there is evidence from NF-studies with healthy individuals that within-session learning collapsed across sessions may be correlated with outcome (Ros et al., 2009). Gruzelier (2014b) argues that the consideration of within-session learning would result in a more robust measure of learning than cross-session learning alone, because the overall error variance might be smoothed by a smaller sampling rate of the data within one session averaged over multiple sessions. Several studies with healthy individuals which included both within- and cross-session learning either failed to show cross-sessional NF-learning at all (Hardman et al., 1997; Cho et al., 2008) or only found a trend (Gruzelier et al., 2014b). By contrast, within-session learning was often evident, i.e., participants improved throughout the session. These findings suggest that it might be interesting to include within-session analyses—or cross-session changes of within-session learning, respectively—more systematically in future NF studies with ADHD.

Baseline Increments

There is increasing evidence from NF studies with healthy adults, that NF may have a strong impact on baseline QEEG, sometimes stronger than on the targeted electrophysiological parameter fed back during the training (Hanslmayr et al., 2005; Ros et al., 2009). As a consequence, EEG-learning should be reflected by a change in pre-session EEG baselines throughout the training course (Gruzelier, 2014b). However, only very few NF-studies with ADHD children examined pre-session or pre-post-session changes in EEG spectra. Bakhshayesh et al. (2011) compared session baselines of the first, second and third section of the training and found larger effects for baseline than for feedback parameters. Maurizio et al. (2014, see also Liechti et al., 2013) reported that after combined NF-SCP and NF-FR with tomographic EEG, individual pre-session baseline values gradually converged towards the group mean across sessions, which was interpreted as normalization (**Figure 1E**). In an individualized upper alpha-NF for children with ADHD, Escolano et al. (2014) recorded pre- and post-session QEEG and found a significant increase in power across sessions in the targeted parameter in an active pre-session QEEG condition, i.e., when children performed a counting task, while no significant increase in alpha power was obtained either during training or pre-session eyes closed resting EEG.

Several other NF-alpha studies with healthy subjects have shown that by recording a resting-baseline both before and after the training session, the incremental curves constructed from these data provided a more complete picture of the EEG training response over time (**Figure 1D**; Cho et al., 2008; Escolano et al., 2011; Zoefel et al., 2011; Kouijzer et al., 2013). First, within a training session, the post-session baseline was usually larger than the pre-session baseline. This could be interpreted as a measure of improvement within the session. Second, the overall learning progress achieved during one session was built upon the progress achieved in the previous session. In other words, the baseline measured at the beginning of a session was on the same level as the post-sessional baseline of the previous session. This ratchet-like linear increase in resting baseline seems to indicate that regulation skills are improving throughout the course of the training (Escolano et al., 2011; **Figure 1D**). A possible consequence from this finding is that EEG learning across sessions may be masked by progressive increments in resting baseline if these increments are not taken into account in the analysis of change. Compared to the training performance at the first session, target amplitudes may show a cross-sessional increase, even when no increase can be found when considering within-sessional mean amplitudes relative to their respective pre-session baselines (**Figure 1C**). Although this remains to be demonstrated for NF with ADHD, NF-alpha-studies with healthy adults lend support to this hypothesis (Dempster and Vernon, 2009). Incorporating a baseline measure might also enhance the comparability of learning performance on group level. For instance, in a NF-study with insomnia patients, (Schabus et al., 2014; also see Hoedlmoser et al., 2008) divided the session mean amplitude of a subject by the corresponding pre-session baseline. As a result, transforming the data into a relative instead of an absolute value may smooth out the high inter-subject variability of baseline measures.

Classification of Good and Poor Learning

Whereas most of the reviewed ADHD-studies analyse learning improvements of EEG regulation with regard to the full treatment group (Bakhshayesh et al., 2011; Russell-Chapin et al., 2013; Escolano et al., 2014; Gevensleben et al., 2014) some studies report the rate of learners (or responder rate) (Lubar et al., 1995; Kropotov et al., 2005; DeBeus and Kaiser, 2011), or distinguish between good and poor performers (Drechsler et al., 2007) (or successful and unsuccessful regulators; Strehl et al., 2006), in order to analyse learning outcome. However, in several NF-ADHD studies which do not include the analysis of EEG learning, the term "responder rate" is used with regard to the clinical outcome, which is usually defined by the reduction in ADHD symptoms (e.g., Gevensleben et al., 2009).

In studies which report the rate of learners, training success may be defined by a fixed criterion, e.g., a *percentage cut-off* in order to classify participants as learners if they have reached a predefined criterion in a fixed percentage of sessions. These cut-off values for successful learning often appear to be chosen *ad hoc* (e.g., Kropotov et al., 2005), or may be taken from previous studies (e.g., Weber et al., 2011, for NF with healthy adults). In a theta/beta training, Kropotov et al. (2005) defined successful learning by an increase in amplitudes of at least 25% during feedback periods compared to resting periods in at least 60% of all sessions. This definition resulted in 82% participants being classified as "good performers". The number of training sessions for each patient varied from 15 to 22, depending on several factors such as age, type of ADHD, learning curves, and parent reports. The termination criteria were (1) stabilization of training performance assessed by the dynamics of the trained parameter during the last three to five sessions; and (2) stabilization of patient's behavior according to parent reports. Lubar et al. (1995) and DeBeus and Kaiser (2011) used a relative change of NF-parameters as a criterion for categorizing performance. In this approach, subjects are classified as good performers when performance in the final training sessions is significantly superior to that in the first ones or when NF parameters increased across all sessions. Lubar et al. (1995) reported a responder rate of 65% in theta/beta NF-FR training, defined by significant negative correlation of theta by session number. DeBeus and Kaiser (2011) found 74% of responders in NF-FR training, defined as an increase of half a standard deviation in the Engagement Index (beta/theta + alpha) from session 1–3 to 18–20. (For studies with healthy participants see Vernon et al., 2003; Weber et al., 2011; Zoefel et al., 2011; Dekker et al., 2014).

A different approach is to employ a cut-off value defined by the median split of the learning parameter (Strehl et al., 2006; Drechsler et al., 2007; Doehnert et al., 2008) which allocates the participants into a group of good and a group of poor learners. Naturally, in this case no meaningful responder rate can be given. Moreover, learners and non-learners do not have to be equally distributed, contrary to what the use of median split may lead one to presume. As a consequence, the variability of learning performances may vary considerably in both groups. Evidently, given these methodological differences in the calculation of good learning in the aforementioned studies, it is difficult to draw meaningful conclusions about the average responder rate in ADHD NF. According to a study by Monastra et al. (2002), EEG learning essentially appears to be a matter of time. Only children with predefined QEEG abnormalities were included in their study and treatment was continued until the criterion for EEG learning had been obtained in each individual case ("normalization", i.e., a degree of cortical slowing within 1.0 SD of age peers). Therefore all participants reached the criterion, which is equivalent to a responder rate of 100%, but the number of sessions varied considerably among the participants. Further evidence that time may matter with regard to the classification of good and poor learning of EEG self-regulation comes from studies indicating that regulation skills might continue to develop and consolidate long after the end of the training (Blume, 2012; for NF with epilepsy see Strehl et al., 2005).

Failing to Learn

Some studies on NF in ADHD which investigated EEG learning performance failed to find the expected significant changes on group level. In a double blind placebo controlled study using Q-EEG feedback with individualized protocols, Vollebregt et al. (2014) compared mean power of the trained frequency bands of the first, tenth, twentieth and final session. The authors report that seven out of ten children showed changes in power toward the directed target, but no child showed changes in more than one frequency band, and that all children also presented changes away from a training target in some bands. Clinical responders (defined by behavioral improvements) showed EEG changes in both desired and non-desired directions. In a study using tomographic NF, including both NF-SCP and NF-FR, the authors failed to find significant EEG learning on group level (Liechti et al., 2012; Maurizio et al., 2014). Besides methodological aspects, the fact that the regulation of a brain area which is known to be underactivated in ADHD, the anterior cingulate cortex, was fed back, may have presented a special difficulty for the participants. However, in this study patients displayed individual changes towards normalization of pre-session baselines across sessions (**Figure 1E**).

Whether or why individual children might fail to learn self-regulation of brain activity has not been the central focus of ADHD-NF research. These questions have been tackled more comprehensively in the Brain Computer Interface (BCI) research, which aims at training individuals to control technical devices via the regulation of brain activity, e.g., to use a communication computer or to navigate a wheelchair controlled by the modulation of brain waves (Guger et al., 2003; Blankertz et al., 2010; Vidaurre and Blankertz, 2010). While neurofeedback is based on operant conditioning with a fixed-target EEG signal, BCI most often uses a machine learning approach. This means that the EEG signal is optimized according to the participant's brain activity during the task (Lotte et al., 2013). Nevertheless, a substantial portion of participants, 10–30%, fail to gain control, which has been referred to as BCI "illiteracy"

(Dickhaus et al., 2009) or "inefficiency" (Kübler and Müller, 2007). Allison and Neuper (2010) presume that a small number of probands may display individual brain structures, which, although not pathological, may not allow the recording of a target EEG parameter by normal surface electrodes (see also Halder et al., 2013). If proper calibration does not help in adapting to individual morphology, the solution is to switch to a different EEG parameter or neuroimaging technology. It is possible, however, that the patient will not be able to use BCI at all. Otherwise, one should try to improve the accuracy of the BCI procedure, e.g., by improving the selection of the existing brain signals through approved algorithms or by incorporating better error correction (Allison and Neuper, 2010). The authors hypothesize that BCI illiteracy might be confined to certain techniques or tasks in a particular individual while the same person may possibly perform better in another paradigm. All of these points are concerned with methodological and technical aspects, while, as the authors state, variables such as mood, motivation, distraction, and test setting may also play a role. In patients with Amyotrophic Lateral Sclerosis (ALS), motivational factors such as challenge and mastery confidence were positively correlated with BCI performance (Nijboer et al., 2008). However, an exaggerated feeling of self-efficacy may constitute an impediment rather than a help for good NF performance. Witte et al. (2013) reported that SMR-learning performance was negatively correlated with the attribution of locus of control. Participants whose confidence in control over a technical device was low performed better than those with a high belief of control. This effect was explained by a possible cognitive overload when controlling a technological device, which in turn might adversely affect the relaxation states which SMR-training aims to achieve. In a study on psychological predictors of SMR learning, the best predictor of SMR performance were objective measures for the accuracy of fine motor skills and the ability to concentrate on the task (Hammer et al., 2012), whereas subjective factors, such as well-being, did not predict performance. This was explained by the fact that only healthy individuals, consisting mostly of students, participated in the study.

To which extent these results from BCI research also apply to NF with ADHD and whether a proportion of children might be unable to learn EEG regulation with one protocol but might gain control with another, is unknown. In future studies, more attention should be paid to the question of whether and why children with ADHD might fail to learn self-regulation of brain activity.

Learning Patterns of Self-Regulated Brain Activity

One crucial question is how to interpret patterns of learning curves in terms of learning performance, and whether it is possible to distinguish characteristic learning patterns in ADHD. For the time being, the extent to which the learning of EEG regulation in ADHD may be expected to be progressive and regular remains unclear. Differences in the training administration of ADHD-NF studies (session frequency, time intervals between sessions, number or duration of trials per session, training breaks etc.) and the small number of patients in many studies make it difficult to draw conclusions. For theta/beta-NF, Lubar et al. (1995) (40 sessions) as well as Bakhshayesh et al. (2011) (30 sessions) observed an increment in performance during the first training phase, followed by a stagnation phase in the middle of the training and a subsequent increase in performance in the final third of training sessions. In an SCP-training (Blume, 2012; 25 sessions; 4 weeks-break between session 12 and 13), children with ADHD displayed a stagnation in the second compared to the first training phase, while performance was enhanced again at the 6-months follow-up. Interestingly, some of the children who had been classified as non-learners after the second training phase, showed good EEG performance at follow-up (see Strehl, 2014). These learning patterns—stagnation and subsequent increased performance after a break or in the final part of the training—have been discussed in terms of the individual speed of learning and a related overtraining-effect which might occur earlier for fast learners than for slow learners (Blume, 2012). In several studies with healthy participants, NF-FR learning has been reported to reach a plateau after 4–6 sessions with a subsequent stagnation (total session number 8–10) (Ros et al., 2009; Gruzelier et al., 2010; Keizer et al., 2010; Dekker et al., 2014; Enriquez-Geppert et al., 2014). These plateaus have been hypothesized to reflect training fatigue or over-learning. Patients' learning curve patterns might differ from those of healthy subjects. For instance, Kübler et al. (2004) found that healthy subjects reached a learning plateau after 3 sessions, whereas in patients with ALS, no learning plateau was reached after 12 sessions. In an NF-study with primary insomnia patients, participants displayed fluctuating learning, which, intercepted by sessions of stagnation, increased across sessions (Schabus et al., 2014). In anxiety patients, Hardt and Kamiya (1978) postulated a fifth-order learning curve, starting with an initial increase, and followed by a dip, a second increase, and a final exponential increase for alpha-NF learning.

In healthy individuals, learning curve patterns have been shown to distinguish non-learners from good learners, showing not only a plateau, but also a decrease of performance: Poor SMR performance was associated with a highly significant 10% decrease in NF-parameters during the second training phase when compared to the first (Ros et al., 2009). A further finding of this study was that smaller intervals between sessions seemed to lead to better EEG learning than longer intervals, indicating that an intense training rhythm may be advantageous.

It should be kept in mind that learning patterns in ADHD besides being extremely individual in nature, may also substantially depend on factors of the setting, such as the relation to the therapist, motivation, external support (Monastra et al., 2002; Drechsler et al., 2007; Strehl, 2014). For the time being, there is a lack of studies that describe characteristic learning patterns and possible subgroups of learners in ADHD which would allow to select the training protocol or to systematically adapt the program according to the learning type of the child.

The Association between Self-Regulated Brain Activity and Clinical Outcome Gains

The few studies that examined the association between NF-learning and the clinical outcome in ADHD (see **Table 1**) used heterogeneous methods. Participants may be categorized in poor and good learners for subsequent data analysis or classified according to good and poor clinical outcome, while in other studies no such distinctions are drawn.

For instance, Strehl et al. (2006) defined criteria for good SCP-learning (negativity learning, calculated by median split) as well as for good clinical outcome in ADHD (at least a 2-point reduction in either hyperactivity or inattention according to DSM-IV) and reported a statistically significant association between the two measures at the end of the training. At the 6-months follow-up, the association between clinical outcome and NF-learning still almost reached significance, indicating a long lasting effect of the training. Drechsler et al. (2007) reported a positive correlation between the pre-post decrease in parent-rated ADHD symptoms and the ability to differentiate between SCP positivity and negativity trials. This association was confined to the group of good performers, defined by median split, whereas in poor learners, ADHD symptomatic improvements were uncorrelated with SCP performance. In NF-FR training, DeBeus and Kaiser (2011) reported a significant correlation between improved EEG regulation and teacher ratings of ADHD symptoms, which was also confined to the group of good performers. Recently, Gevensleben et al. (2014) conducted an SCP-NF study with ADHD children, and found a correlation between the pre-post change in parent-rated inattention symptoms and the increase in negativity from the first to the fifth session and from the first to the ninth session. This study was based on a small sample (n = 10) and the authors did not distinguish between good and poor performers.

Several studies have analyzed the association between EEG learning and neuropsychological outcome. Kropotov et al. (2005) reported that learning to enhance beta and SMR in ADHD correlated with a significant decrease in response time and variability of response time in a Go/No-Go task only for good performers. Lubar et al. (1995) reported stronger improvements on a computerized attention test for learners than for non-learners after NF-FR training.

The relationship between positive clinical outcome and successful NF learning has been confirmed in a number of NF studies with other clinical groups, such as patients with epilepsy (Daum et al., 1993; Kotchoubey et al., 1997; Strehl et al., 2005) or sleep disorder (Schabus et al., 2014). In healthy subjects, NF-learning correlated positively with improvement in short-term memory (Nan et al., 2012), mental rotation (Hanslmayr et al., 2005), microsurgical skills (Ros et al., 2009) and enhancement in cognitive creativity (Gruzelier, 2014a).

However it should be kept in mind, that the relationship between successful regulation of an individual's brain activity and positive clinical outcome is not reciprocal: Improvements in parent-rated ADHD symptoms are not confined to learners (Drechsler et al., 2007), indicating that non-specific treatment effects also contribute to the clinical outcome.

Electrophysiological Pre-Post Changes, Protocol Specific Effects and Prediction

In NF research with ADHD patients, to date no study has directly related pre-post electrophysiological changes to increments in NF performance across sessions.

However, several studies have reported pre-post effects on electrophysiological levels, although most of them did not analyse EEG learning across sessions. Often, these studies focus in a hypothesis-driven manner on electrophysiological measures related to the feedback protocol used, examining pre-post Q-EEG changes after NF-FR with special emphasis on the trained frequency (e.g., Thompson and Thompson, 1998; Pop-Jordanova et al., 2005) and pre-post contingent negative variation CNV or other ERPs after NF-SCP (e.g., Heinrich et al., 2004; Mayer et al., 2012). There is evidence that training protocols may result in specific effects which, at least indirectly, supports the importance of successful and differential learning of EEG regulation with regard to pre-post EEG changes. Wangler et al. (2011) and Gevensleben et al. (2009) compared NF-SCP and FR-NF training in a crossover design and examined electrophysiological effects of both protocols. They reported pre-post increase in the CNV after NF-SCP but not after NF-FR. According to pre-post QEEG analyses, both protocols resulted in a decrease in theta bands activity. Despite this evidence of protocol-specific effects on EEG, it might be advisable to explore the full frequency spectrum or to include additional measures in the pre-post EEG analyses. Several studies, mostly with healthy participants, demonstrate that electrophysiological pre-post effects are not necessarily confined to the targeted training parameter (for a detailed review, see Gruzelier, 2014b). An example with ADHD patients is provided by Doehnert et al. (2008) who conducted SCP training and reported a pre/post QEEG theta decrease at Oz, while they did not find the expected effects on the CNV. Another evidence for extended effects comes from a study by Escolano et al. (2014) who in an alpha-NF analyzed the course of pre- and post-session QEEG in resting and in task-related states, though with a focus on the target frequencies. Cross sessional changes in the expected direction were limited to task-related pre-session QEEG while changes in pre-session resting EEG were not significant. Liechti et al. (2012) were unable to find any significant association between changes in ADHD symptoms and cross-session NF-learning. However, they reported specific associations between cross-session changes in baseline-frequencies and outcome gains, such as a positive correlation between theta/beta increases in specific regions and frontal beta decreases with reductions in hyperactivity/impulsivity. The extent to which in the case of generalized and extended EEG training response the electrophysiological outcome should still be considered the result of a specific training effect should be the subject of a more refined methodological debate.

Electrophysiological pre-post changes have been related to clinical outcome, which indicates that electrophysiological change is reflected by behavioral improvement (Doehnert et al., 2008; Gevensleben et al., 2009; Wangler et al., 2011; Arns et al., 2012). Still, electrophysiological pre-post measures do not

directly reflect EEG regulation performance during feedback trials. Pre-post changes in electrophysiological markers have also been reported after mindfulness training (Moore et al., 2012; Schoenberg et al., 2014), which shares several therapeutic characteristics with the NF setting, and thus results based on these measures do not provide the best indication of NF specificity.

Studies that analyze initial EEG learning patterns across or within sessions with regard to overall EEG learning performance, are rare. However, the identification of early predictors of Nf learning would be very helpful in terms of providing a better basis for therapeutic decision-making or adapting the training protocol accordingly. In an unpublished doctoral thesis by Goth (2006) on NF training in children with ADHD, the mean amplitudes of negativity trials in session 1 and 2 were the best predictors of subsequent improvements in SCP-NF-regulation performance, whereas a large number of inattention symptoms predicted poor EEG learning. In NF-FR training, a similar trend was found for successful regulation in early sessions. The best predictor of EEG learning success in NF-FR, however, was a high IQ.

In patients with ALS, good performance at an early training stage of SCP regulation was correlated with subsequent good learning (Neumann and Birbaumer, 2003). In a study with healthy adults, it could be shown that certain morphological parameters may have a beneficial effect on training success: Frontal-midline theta NF-learning was predicted by the volume of the mid-cingulate cortex and the white matter concentration of underlying brain structures (Enriquez-Geppert et al., 2013).

Is it Possible to Promote EEG Self-Regulation Performance?

It has been suggested that children with ADHD might require explicit rather than implicit learning (Lansbergen et al., 2011). According to several authors in the field, children with ADHD need to actively practice mental strategies to self-regulate brain activity and have to be instructed on how to translate the newly learned skill into everyday life (Gevensleben et al., 2009; Heinrich and Gevensleben, 2013; see Strehl, 2014). They suggest that during the first lessons of training, the trainer should encourage the child to find an appropriate strategy ("I imagine I'm waiting for the starting signal in a race"). This initial strategy should be gradually reduced and finally abandoned in the course of the training, when regulation becomes automatized (Heinrich and Gevensleben, 2013). To the best of our knowledge the impact of instruction and explicit strategy training on EEG training performance has not been systematically investigated in ADHD. Gevensleben et al. (2014) hypothesize that the use of different transfer instructions for children with Tic disorder than for children with ADHD may have resulted in specific clinical outcome gains in inhibitory control. However, these setting differences did not apply to the self—regulation during feedback trials, but to the transfer outside the laboratory. Whether self-regulation of brain activity may be helped or exacerbated by the use of conscious top-down strategies is unclear and probably also depends on specific protocols. As SCP training aims at quick changes in polarity, it may be expected that top-down regulation plays a more prominent role here than in NF-FR (see Loo and Makeig, 2012). Arguments both for and against the promotion of conscious strategy use and the importance of self-awareness for NF performance come from research with healthy subjects and other clinical groups. Neurofeedback has been hypothesized by several researchers to involve an increased awareness of the physiological states underlying the feedback (Plotkin, 1981; Congedo, 2007). Recent evidence for this hypothesis is provided by a study on EEG discrimination training with healthy adults (Frederick, 2012). After a baseline recording (150 s), subjects had to respond to a prompt asking whether in that moment they were in a low (<30th percentile of the baseline) or high alpha state (>70th percentile). They immediately received feedback about their guess. 75% of participants showed a significant learning curve and were successful in discriminating their brain activity states. There might be a reciprocal relationship between discrimination of brain states and the training of brain state regulation, as Cinciripini (1984) showed for SMR and Kotchoubey et al. (2002) demonstrated for SCP-training. Moreover, successful regulation skills might also have a positive impact on the discrimination ability of brain regulation states. Gruzelier (2014a) reports that the subjects' first positive self-judgment about their ability to regulate SMR ratios occurred close to the time, when their learning curve reached a plateau.

A further question concerns whether and how mental strategies might affect NF-learning. Nan et al. (2012) reported that their (healthy adult) alpha-NF subjects favored positive mental strategies (e.g., friends, love, family) which they estimated the most successful. However, these subjective judgments were not related to the actual NF-performance. The effects of strategy use might also depend on the frequency band: in NF-SMR training with healthy adults, participants who used no mental strategy at the end of the training performed better than those who did, thus indicating a possibly counterproductive effect of strategy use on SMR learning. In contrast, strategy use had no influence on gamma learning (Kober et al., 2013). Neumann and Birbaumer (2003) argue that providing patients with initial strategies may promote self-regulation at the beginning of training but would prevent subjects from trying out other potentially more effective strategies with training progress. This argument is in line with Witte et al. (2013) who emphasize the importance of the initial trial-and-error learning, which due to "immediate closed-loop feedback" could ameliorate the subjects' regulation skills. This unconscious adapting to the desired state might thereby become automated.

To conclude, the literature provides arguments both against and in favor of a more systematic approach to foster EEG learning and self-awareness of EEG activity states in children with ADHD. It might be worthwhile to devote more attention to the question of whether and how the learning of EEG self-regulation can be systematically promoted in children with ADHD.

Conclusion

Discussions about NF specificity need to include analyses of EEG regulation performance and its impact on clinical outcome. Besides its effects on ADHD primary symptoms, associations with factors usually regarded as "generic effects", such as improved self-perception or self-efficacy should also be considered. To provide optimal conditions for learning, it is necessary to improve our knowledge regarding characteristic cross-session learning trajectories and within-session performance in ADHD and to adapt training schedules accordingly. This also includes possible therapeutic strategies which might promote EEG self-regulation in children with ADHD. In the future, NF devices used for NF research with ADHD should adhere to more rigorous scientific standards, allowing for qualitatively acceptable EEG recording during treatment sessions, including artifact control, in order to document learning of EEG self-regulation. From a scientific point of view, the current practice, which allows the use of NF devices of uncertain quality or protocols based on undisclosed algorithms for NF research, is unsatisfactory. It is bewildering that, with regard to the evaluation of efficacy and specificity of NF, strictest methodological standards are demanded for the study design, while no scientific standards need to be applied to the treatment. Several meta-studies (Arns et al., 2009; Hodgson et al., 2014) have demonstrated the efficacy of NF with regard to the improvement of ADHD symptoms. Whether NF is efficacious AND specific still needs further investigation, which should go beyond analyzing pre-post changes and include analyses of the treatment process and the learning of EEG self-regulation.

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Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework

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Neurofeedback (NFB) is emerging as a promising technique that enables self-regulation of ongoing brain oscillations. However, despite a rise in empirical evidence attesting to its clinical benefits, a solid theoretical basis is still lacking on the manner in which NFB is able to achieve these outcomes. The present work attempts to bring together various concepts from neurobiology, engineering, and dynamical systems so as to propose a contemporary theoretical framework for the mechanistic effects of NFB. The objective is to provide a firmly neurophysiological account of NFB, which goes beyond traditional *behaviorist* interpretations that attempt to explain psychological processes solely from a descriptive standpoint whilst treating the brain as a "black box". To this end, we interlink evidence from experimental findings that encompass a broad range of intrinsic brain phenomena: starting from "bottom-up" mechanisms of neural synchronization, followed by "top-down" regulation of internal brain states, moving to dynamical systems plus control-theoretic principles, and concluding with activity-dependent as well as homeostatic forms of brain plasticity. In support of our framework, we examine the effects of NFB in several brain disorders, including attention-deficit hyperactivity (ADHD) and post-traumatic stress disorder (PTSD). In sum, it is argued that pathological oscillations emerge from an abnormal formation of brain-state attractor landscape(s). The central thesis put forward is that NFB tunes brain oscillations toward a homeostatic set-point which affords an optimal balance between network flexibility and stability (i.e., self-organised criticality (SOC)).

Keywords: neurofeedback, brain computer interface (BCI), electroencephalography (EEG), magnetoencephalography (MEG), brain plasticity, brain disorders, neuromodulation, criticality

> *"While we can conceive of a sum being composed gradually, a system as total of parts. . .has to be conceived of as being composed instantly"*
> – Von Bertalanffy, General System Theory (1969)

(De)SYNCHRONIZED BRAIN STATES

In 1934, a few years after the initial discovery of the electroencephalogram (EEG) by Hans Berger, the British magazine Spectator reported on a remarkable public demonstration (Walter, 1934, p. 479):

> *"Adrian and Matthews recently gave an elegant demonstration of these cortical potentials. [. . .] when the subject's eyes were open the line was irregular, but when his eyes were shut it showed a regular series of large waves occurring at about ten a second. [. . .] then came the surprise. When the subject shut his eyes and was given a simple problem in mental arithmetic, as long as he was working it out the waves were absent and the line was irregular, as when his eyes were open. When he had solved the problem, the waves reappeared. [. . .] so, with this technique, thought would seem to be a negative sort of thing: a breaking of the synchronized activity of enormous numbers of cells into an individualized working."*

A basic ingredient sufficient for producing neuronal oscillations is the mutual coupling between excitatory (E) and inhibitory (I) neurons (Wang, 2010). Here, as the E-neurons fire they activate the I-neurons, which after some delay retroactively silence the E-neurons, and so *ad perpetuum*. In essence, this E-I connectivity serves to keep neuronal activity within a restricted range, as purely E-E or I-I coupling would risk producing run-away excitation or inhibition (although such connections naturally also exist). This recurrent feedback mechanism, scaled-up to contain an intricate web of millions of excitatory and inhibitory neurons (as well as glia), ultimately contributes to what are commonly known as brain oscillations or "brainwaves" (Buzsáki and Watson, 2012). Brain oscillations may be recorded via invasive or non-invasive electrodes, given that neuronal activity is reflected in the minute fluctuations of electromagnetic field potentials, which are themselves generated by ionic exchanges at the cell-membrane and the synapse during neuronal communication (Nunez, 2000; Buzsáki et al., 2012). As seen in **Figure 1**, when neuronal activities occur in a spatially circumscribed region and become temporally synchronized, their local field potentials (LFPs) are then strongly

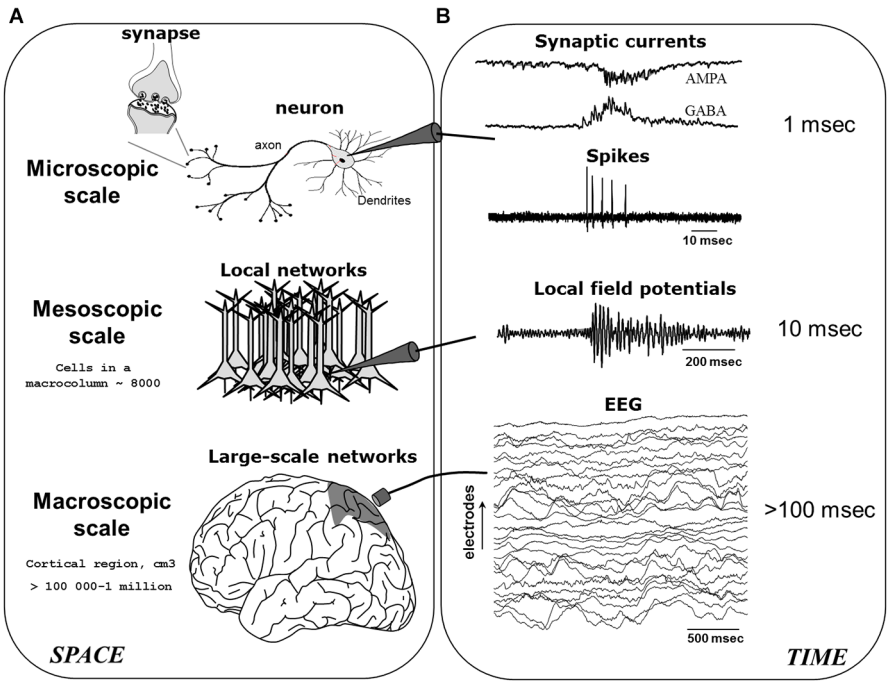

FIGURE 1 | The generation of electroencephalogram (EEG) network oscillations. EEG signals are generated by the integration of neural activity at multiple spatial **(A)** and temporal **(B)** scales. After Le Van Quyen (2011).

summated giving rise to large amplitude electroencephalogram (EEG) or magnetoencephalogram (MEG) rhythms. In what follows, we will mainly focus on the modulation of low-frequency M/EEG oscillations (typically <60 Hz), which represent the largest part of neuroelectric activity generated by the brain and which can be recorded noninvasively. Specifically, studies have established that the *amplitude* of M/EEG oscillations varies primarily as a function of the number, strength and phase-locking ("synchronization") of cortical synaptic activities (Nunez, 2000).

Hence, metaphorically akin to a "standing-waves" generated by a crowd of spectators, the size (amplitude) of an oscillation is proportional to the degree to which a group of persons (neurons) temporally stay "in sync" (synchronize) with each other. Conversely, reductions in amplitude result from a breakdown of such synchronization, in accordance with the historical expression: *desynchronization*. Likewise, the speed (frequency) of the wave will be determined by how quickly the individual elements rise and decay (Nunez, 2000), and this will depend on the intrinsic nature (resonance) of the person (neuron). Here, a greater (lower) number of oscillations occurring in the same period of time will equate to faster (slower) frequencies. The M/EEG may therefore be considered as an accurate non-invasive indicator of coordinated synaptic activity across cortical networks. In general, the M/EEG frequency spectrum has been traditionally divided into the following bands: infraslow (<1 Hz), delta (1–4 Hz), theta (4–7 Hz), alpha (7–12 Hz), spindle (12–15 Hz), beta (15–30 Hz), and gamma (>30 Hz).

Historically, EEG synchronization patterns were discovered to differentiate levels of psychological arousal in the progression from deep sleep to wakefulness, to high alertness (Jasper and Droogleever-Fortuyn, 1948). Low-frequency delta (1–4 Hz) waves were found to dominate deeper sleep states, while during lighter or more activated (REM) sleep the frequencies are more accelerated, but slower than in waking states. In relaxed wakefulness there was an emergence of the alpha (7–12 Hz) rhythm that gave rise to faster beta (15–30 Hz) and gamma (>30 Hz) frequencies upon activation of cognitive or attentional resources (Steriade et al., 1993; Gervasoni et al., 2004). In parallel to this acceleration of frequencies during arousal, there was also a more desynchronized or "activated" tracing of reduced amplitudes (as reported by Walter above). With the discovery that the ascending reticular activating system (ARAS; Moruzzi and Magoun, 1949) was responsible for consciousness and the sleep-wake cycle, some of the most important findings were that lesions in the ARAS abolished the aforementioned "activation" of the EEG whilst increasing episodes of sleep and motor inactivity (Lindsley et al., 1950). Interestingly, progressively greater degrees of EEG activation could be provoked by simple electrical stimulation of the brainstem (Moruzzi and Magoun, 1949), enhancing the precision and speed of visual discrimination in monkeys (Fuster, 1958). Consequently, EEG activation is widely regarded to be necessary for the emergence as well as the characteristic nature of consciousness (Villablanca, 2004), which once established, invites a fascinating question: how is intrinsic brain activity regulated further to give rise to volitional control of cognition? Here, synchronization patterns of neural activity suggest distinct "intrinsic states" that are modulated endogenously (e.g., via neuromodulation, plasticity), independently of external influences

(e.g., sensory, pharmacological or electromagnetic stimuli). This has been unequivocally demonstrated by Poulet and Petersen who, upon severing rats' sensory pathways, showed that internal state transitions during active vs. quiet behavior were uniquely reflected in cortical (de)synchronization patterns (Poulet and Petersen, 2008). On the other hand, a large body of evidence in humans points to the key role of cortical oscillations in top-down processing during attention and cognition (Palva and Palva, 2012). Thus, during waking consciousness, there is a critical involvement of higher-order cortical regions in orchestrating the phasic (i.e., sub-second) shifts between intrinsic brain states, either *cortico-cortically* or *cortico-subcortically* (Harris and Thiele, 2011). A good example of the former is the way motor cortex is able to concurrently trigger desynchronization of somatosensory cortex (Zagha et al., 2013). Similarly, there is evidence of a direct cortico-subcortical dialog during maintenance of wakefulness (in a novel environment), since destruction of either anterior cingulate cortex or locus coeruleus is sufficient to block exploratory activity and associated EEG activation (Gompf et al., 2010). Moreover, when major anatomical routes are severed, as with targeted lesions to the lateral prefrontal cortex plus corpus callosum, it leads to increased distractibility coupled with abnormally high neural synchronization in visual areas during attention (Gregoriou et al., 2014).

In parallel and at the molecular level, investigations indicate that tonic and phasic activation of the cortex is dependent on a family of neuromodulators released by the brainstem and/or basal forebrain, including dopamine, acetylcholine, and noradrenaline. It has become evident that both the (tonic) sleep-wake cycle and (phasic) top-down shifts in brain-state are regulated by an intricate interplay of neuromodulators (for a detailed review see Lee and Dan, 2012). Accordingly, attentional behavior and distinct EEG rhythms have been reported to be affected by the lesion and pharmacological blockade of noradrenergic pathways (Delagrange et al., 1993) and enhanced by cholinergic agonists (Bauer et al., 2012). Moreover, local application of acetylcholine in the monkey primary visual cortex is able to enhance the behavioral modulation of neuronal firing rates (Herrero et al., 2008). Such effects have been verified directly *in vitro*, as for example, dopaminergic antagonists are found to increase EEG spectral power (0–20 Hz) while agonists decrease it (Sebban et al., 1999), and this has been specifically linked to activation of dopamine receptors (Chen et al., 2013). Similarly, optogenetic studies report EEG desynchronization following selective activation of cholinergic (Kalmbach and Waters, 2014) or noradrenergic (Carter et al., 2010) neurons. In sum, the studies above reveal that in addition to the tonic sleep-wake cycle, cortical-subcortical neuromodulatory circuits are able to control brain oscillations phasically (i.e., on a sub-second time scale) in a top-down manner, which is illustrated schematically in **Figure 2**.

However, the observations above invite the inevitable question: what is the functional significance of such synchronized

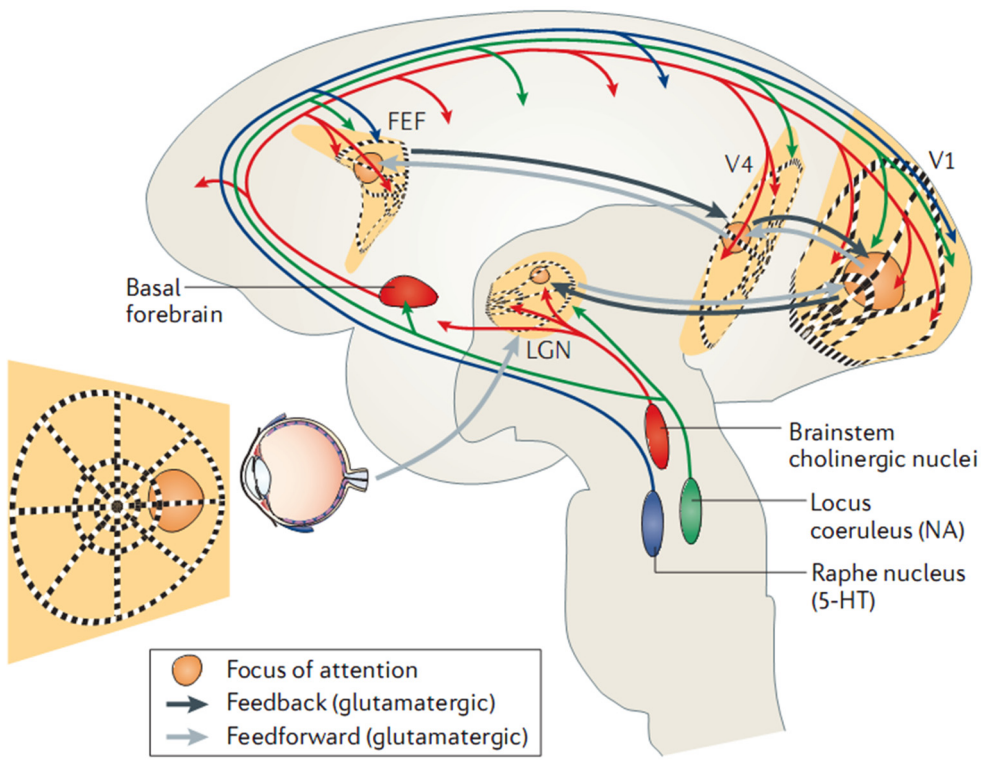

FIGURE 2 | Control of EEG (de)synchronization via shifts in intrinsic brain state. Here, a recurrent functional circuit subserving top-down attention is triggered by neocortical structures (black lines; frontal-eye fields (FEF); visual cortices (V1/V4), and reinforced by ascending neuromodulatory pathways (blue/green/red). Adapted with permission from Harris and Thiele (2011).

and desynchronized states? Why does the cortex, for example, display highly-synchronous low-frequency states during unconsciousness, and what necessitates the desynchronized, higher-frequency oscillations of wakefulness (Gervasoni et al., 2004)? Neuroscience is of course still answering these questions, and there is no encompassing theory as yet. However, several emerging perspectives are beginning to shed light on these phenomena.

The first perspective involves the observation that upon intracellular recording of corticothalamic (Contreras and Steriade, 1995) as well as corticospinal (Ezure and Oshima, 1981) neurons, cell-membrane depolarization (excitation) is found to be greater during desynchronized EEG states. Conversely, during sleep, membrane potentials are more hyperpolarized (inhibited) leading to slower oscillations which are characterized by large alternating cortical up (higher excitability) and down (lower excitability) states (Castro-Alamancos, 2009). Thus, in the simplest scenario, desynchronization stems from a rise in neuromodulators which elevate (depolarize) membrane potentials and their voltage-gated-ion channels closer to their firing threshold, enhancing their sensitivity to incoming sensory inputs (Castro-Alamancos, 2004; Wang et al., 2014). This is the case, for example, for the dominant low-frequency rhythm of sensory cortex ("alpha" rhythm), where trial-by-trial variations in detection performance (Ergenoglu et al., 2004; Haegens et al., 2011) and attentional state (Fries et al., 2001; Fan et al., 2007; Macdonald et al., 2011) are predicted by greater degrees of desynchronization. Similarly, desynchronized states are reported to sharpen visual receptive fields (Wörgötter et al., 1998) whilst shortening their response latencies (Wang et al., 2014), concomitant with increases in excitability (Romei et al., 2008) and neuronal spike rate (Haegens et al., 2011). In this way, neuronal synchronization may perform functional "gating" of sensory input by opening or closing neuronal excitability windows (Jensen and Mazaheri, 2010; Luczak et al., 2013). The second perspective involves the fact that desynchronized states have been attributed to larger background synaptic activity, which leads to higher resting membrane conductance (Wang et al., 2014). Such high-conductance states result in enhanced neuronal responsiveness, by boosting signal-to-noise ratios via "stochastic resonance" mechanisms (Destexhe, 2007). From yet another perspective, desynchronized patterns may be seen to minimize functional correlations of synaptic activities, thus maximizing their informational complexity (called *entropy*). Several studies report reduced inter-neuronal correlations during attention (Cohen and Maunsell, 2009) and memory formation (Bermudez Contreras et al., 2013) that imply mechanisms of active decorrelation (Ecker et al., 2010; Renart et al., 2010). According to this perspective, states of synchronized/desynchronized low-frequency activity have been proposed to coincide with decreased/increased information content (Hanslmayr et al., 2012). This notion has received direct experimental support during perceptual-decision making (Werkle-Bergner et al., 2014). As a corollary, extremes of too much or too little synchronization would both have negative consequences for population coding, as this would lead to abnormal redundancy of information, reflective of a highly ordered or chaotic system (Hanslmayr et al., 2012), respectively.

In general, the covered evidence suggests that low-frequency oscillations appear to limit the complexity of available computational states, so why should they feature so prominently in the brain? A potential biological compromise may be that oscillations enable segregated communication channels to be established in the brain, which would prevent a disorganized mixing of processing streams. Thus far, we have mainly considered the features of locally synchronized activities (i.e., arising within circumscribed anatomical regions), yet there is equally evidence of long-range synchronization phenomena, spanning distributed regions? Although this complex topic is beyond the scope of this paper, we touch upon it briefly in light of its relevance to pathological states. In essence, distributed brain regions have been observed to functionally co-activate on a variety of measures, including synchronization of phase, frequency, or amplitude (Engel et al., 2013). Recent studies indicate that these mechanisms enable the collective binding of neural assemblies to form functional networks independent of inter-neuron distance (Canolty et al., 2010), governing diverse processes such as attention (Doesburg et al., 2009a), memory retrieval (Foster et al., 2013; Watrous et al., 2013), and learning (Koralek et al., 2013). A putative mechanism by which this occurs involves the well-known "communication through coherence" theory (Fries, 2005), which posits that distributed neuronal assemblies are bound together by alignment of their oscillatory phases (i.e., phase-locking), thus enabling neuronal spiking to be transmitted through temporally-distinct excitability windows (e.g., low/high excitability states would respectively correspond to oscillation peaks/troughs). Mathematical modeling indicates that such inter-neuronal communication channels can become degraded if the sender-receiver populations become "out-of-tune" with each other in amplitude, phase, or frequency (Akam and Kullmann, 2012; Shin and Cho, 2013), echoing the relationship between broadcasting stations and radios. Moreover, it has become evident that such "synchrony" patterns of spontaneous brain activity frequently form well-defined, reproducible topographies across individuals, known as resting-state networks (Chu et al., 2012; Baker et al., 2014). It is now well-established that the intrinsic dynamics of these networks strongly influence "ongoing" processing of stimuli (Mayhew et al., 2013), as well as a wide-range of cognitive-behavioral functions (Sadaghiani and Kleinschmidt, 2013). Hence, it is not difficult to envisage the emergence of a dynamic interplay between local- and network-oscillation states, as the former would influence the latter via long-range connections (Zemankovics et al., 2013; Cabral et al., 2014), and vice versa (Doesburg et al., 2009a; Shin and Cho, 2013). Likewise, depending on behavioral state, distributed neurons may combine to form distinct functional connectivity networks by reorganizing their oscillatory modes (Quilichini and Bernard, 2012), given that neuromodulators released during different behaviors can preferentially activate neural populations by varying their "resonant frequencies" (Tseng et al., 2014). The general purpose of such synchronization patterns is to enable the simultaneous segregation/integration of distributed functional pathways (Varela et al., 2001; Buzsáki and Watson, 2012) in support of adaptive behavior (Krichmar, 2008). As we will see in the next section, adaptive behavior and consciousness can be altered when this delicate oscillatory balance is disturbed.

In summary, this introductory section highlights several important points: (i) neuronal synchronization is regulated by neuromodulators that govern behavioral states; (ii) both neuronal synchronization and behavioral state remain under top-down control during wakefulness; and (iii) neuronal synchronization modulates the excitability and functional segregation/integration of cerebral circuits.

NORMAL AND PATHOLOGICAL OSCILLATIONS

The notion of *pathological oscillations* is by definition predicated on the existence of "normal" oscillatory activity. Thus, a science of (ab)normal oscillations should also be supported by observations that quantitative measures (e.g., amplitude, frequency, phase-locking) of low-frequency oscillations exhibit a stable and reproducible distribution in neurologically-healthy populations, i.e., occur in a typical physiological range. Accordingly, studies report good reliability of conventional EEG measures in healthy populations within task/resting conditions and across time (Fingelkurts et al., 2006; Gudmundsson et al., 2007; Näpflin et al., 2007, 2008). This is qualified by a proviso that EEG parameters are not static from birth, but follow an established developmental trajectory consisting of a frequency acceleration of the dominant resting rhythm, and a decrease of the overall spectral power until adulthood (Dustman et al., 1999), reputedly due to synaptic pruning (Whitford et al., 2007). Such age-matched measures from healthy reference populations are implicitly used by neuroscience studies that seek to uncover meaningful differences with pathophysiological conditions. The literature on this topic is vast, but we provide a few representative examples of low-frequency EEG abnormalities prevalent in brain disorders. For instance, slower-waves (e.g., theta 4–8 Hz) are reported to be globally elevated in attentional deficit hyperactivity disorder (Clarke et al., 2007) which may in part be mediated by a slowed frequency of the dominant resting ("alpha") rhythm (Arns et al., 2008). Similarly, obsessive-compulsive disorder (OCD) patients demonstrate low-frequency power excess (2–6 Hz) in the resting state, which appears to be relatively localized to the subgenual anterior cingulate gyrus and adjacent limbic structures (Kopřivová et al., 2011). Another example is post-traumatic stress disorder (PTSD), which is observed to have both decreased power and accelerated frequency of the alpha rhythm, potentially reflecting cortical hyperarousal (Jokić-Begić and Begić, 2003; Wahbeh and Oken, 2013). In contrast, schizophrenia is distinguished by synchronization deficits of faster gamma (>30 Hz) rhythms during active processing (Grützner et al., 2013; Ramyead et al., 2014) that are found to inversely correlate with levels of the inhibitory neurotransmitter GABA (Ramyead et al., 2014). Alzheimer's patients display a pronounced lack of alpha-rhythms which positively correlates with hippocampal volume (Babiloni et al., 2009). The list is virtually endless given the plethora as well as complexity of disorders, and the interested reader is referred to comprehensive reviews on the subject (Coburn et al., 2006; Uhlhaas and Singer, 2006). Importantly, EEG can also be employed to assess recovery or response to treatment. For example, reduced delta (2–4 Hz) rhythm amplitude can be used as a biomarker of long-term recovery from ischemic cerebral stroke (Cuspineda et al., 2007), positively correlating with perfusion of cortical lesions (Finnigan et al., 2004). Faster beta band hyper-synchronization is related to motor impairment in Parkinson's patients, and its disappearance is associated with successful treatment with both medication (Silberstein et al., 2005) or deep brain stimulation (DBS; Little and Brown, 2014). Interestingly, administration of psychostimulants improves behavior in attention-deficit hyperactivity disorder (ADHD) and is found to normalize slow-wave patterns of EEG activity (Clarke et al., 2007). However a non-trivial caveat is that the notion of EEG abnormality (and its normalization following treatment) appears to be state-dependent (Arns et al., 2009), meaning that an appropriate behavioral task(s) may be necessary to uncover disorder-specific patterns, thereby evolving on the passive resting-state recording. For example, oscillatory and topographical differences between ADHD and healthy subjects manifest distinctly (or not at all) depending on the attentional task used (Sohn et al., 2010; Buyck and Wiersema, 2014).

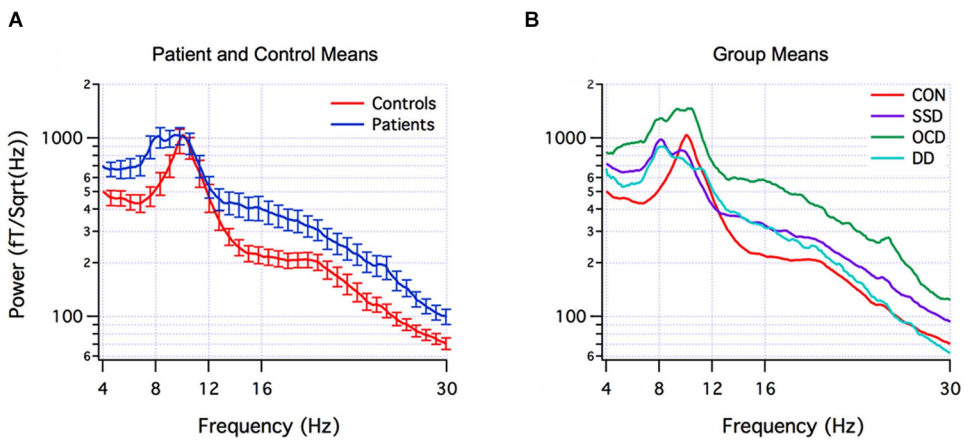

FIGURE 3 | EEG spectral signatures of healthy and psychiatric populations. (Panel A) Mean (± SEM) EEG power spectra of healthy control subjects (red) and psychiatric patients (blue). **(Panel B)** Mean subgroup spectra for controls (CON) (red, $n = 18$), schizophrenia spectrum disorder (SSD) (purple, $n = 14$), obsessive-compulsive disorder (OCD) (green, $n = 10$), depression disorder (DD) (light blue, $n = 5$). From Schulman et al. (2011).

The actual neuromolecular processes underpinning aberrant oscillations are likely to be both complex and diverse across pathologies. Nevertheless, a theoretical model termed *thalamocortical dysrhythmia* (TCD) has been put forward to explain the pronounced spectral alterations observed in number of brain disorders (Llinás et al., 2005; Schulman et al., 2011) which are depicted in **Figure 3** for psychiatric populations. In addition, several reviews have provided in-depth treatments of the diverse cellular mechanisms that appear to subserve (ab)normal brain oscillations (Steriade et al., 1990; Llinás et al., 2005; Wang, 2010). In this respect, however, a fundamental limitation is that disorders conventionally categorized via cognitive/behavioral dimensions are not necessarily neurobiologically homogenous, i.e., multiple neural subtypes may exist within each disorder called "endophenotypes". This can be explained by the presence of multiple comorbidities and the possibility for *similar* behavioral patterns to be generated by *dissimilar* neural substrates (Tognoli and Kelso, 2014). Mounting evidence for this is provided by reports of heterogenous EEG profiles within ADHD (Clarke et al., 2001), depression (Pizzagalli et al., 2002), and schizophrenia (John et al., 2007) patient groups, to name a few. A compounding problem is that many studies in the field consist of small sample sizes ($n < 50$) which, upon averaging, may limit their sensitivity for uncovering distinctive subtypes of EEG signatures. Thus, a mixture of heterogeneity and selective sampling could be a feasible explanation for both the similar and contradicting EEG signatures reported between and within disorders, respectively. A complementary but more statistically-powerful method involves developing and utilizing a *normative database*, which enables patient groups, and importantly *single individuals* to be compared to a much larger sampling distribution of the healthy population (typically $n > 500$) (Thatcher and Lubar, 2009). This approach, originally termed "neurometrics", was first systematically developed by John et al. (1977), by sampling topographical EEG across the full human lifespan and classifying a variety of brain disorders based on their spectral signatures (John et al., 1988). Over time, and upon establishment of several databases (Thatcher and Lubar, 2009), the general approach of examining or classifying patients based on multivariate EEG patterns was re-christened as quantitative EEG (qEEG), to differentiate it from qualitative EEG interpretation. A key objective of qEEG has been to improve sensitivity (i.e., low false-negative) and specificity (i.e., low false-positive) rates in order to aid clinical diagnosis and treatment (Coburn et al., 2006). Recent efforts have concentrated on identifying EEG biomarkers that are recurrently expressed by particular (sub)types of brain disorders (Coburn et al., 2006). Thus for example, in a blinded sample of 159 children and adolescents, an elevated theta/beta power ratio was able to identify ADHD with a remarkable 87% sensitivity and 94% specificity (Snyder et al., 2008); however, this ADHD sample was relatively homogenous, with only 1% of children demonstrating a familiar subtype of increased beta power. It is important to note that biomarker differences can also appear between different age-groups of the same disorder, e.g., ADHD (Poil et al., 2014). Hence the key message is that brain disorders seem to fall on a multi-dimensional continuum, with scarce evidence to support a one-to-one mapping between specific EEG abnormalities and cognitive-behavioral traits (i.e., one cannot be unequivocally inferred from the other). This does not negate the existence of a relationship *per se*, but rather that it is complex and has the interesting property of *degeneracy* (Edelman and Gally, 2001).

THE BRAIN AS A DYNAMICAL SYSTEM

In light of the complex linkage between brain activity and behavior, scientists have tried to expand the scope of their analyses by introducing more *dynamical* measures of neuronal oscillations, such as burst (Montez et al., 2009), fractal (Jagadisha et al., 2003), and entropy metrics (Takahashi et al., 2010). The dynamical designation relates to considering the *temporal* evolution of a brain signal, as this can be overlooked upon computing the traditional Fourier transform (e.g., power vs. frequency). In other words, introducing time into analyses takes into account the fact that brain oscillations are non-stationary, i.e., their oscillatory parameters are not constant across time. Interestingly, such time-varying behavior can be accommodated within the framework of *dynamical systems theory*, opening the door to a whole new world of exotic phenomena: bifurcations, attractors, dynamic repertoires, and phase transitions. Although we cannot give these full treatment (for an excellent review see Stam, 2005, a few visual analogies may serve as an introduction. In essence, a system's operation can be represented in *state-space*, which is best visualized as a multidimensional energy landscape.

As depicted in **Figure 4A**, this can be simplified to 2-dimensions and envisaged as a ball with random energy (i.e., noise) traversing hills and valleys. Here, the ball (dynamic state) will experience greater *stability* (i.e., larger dwell-time) within valleys of low potential, known as *basins of attraction*, and less so at the hills, known as repellors. In **Figure 4B**, a deeper *attractor* (right) offers more stability than a shallower one (left), as it will keep the ball within its basin at relatively greater energy perturbations. However, is there explicit evidence of attractor-like signatures in the brain? Quite wonderfully, it seems that oscillations with distinct frequency "peaks" exhibit attractor properties, such as delta and alpha rhythms (Pradhan et al., 1995; Freyer et al., 2011; MacIver and Bland, 2014). As illustrated in **Figure 5**, when common brain rhythms are plotted in their respective phase-space, slower (alpha/delta) rhythms present stronger attractor-related "orbits" than faster ones (beta) (Pradhan et al., 1995). Equally so, the "waxing-and-waning" of alpha oscillations has been observed to follow a *bimodal* distribution, the latter implying that distinct dynamical processes arising from a single cortical region are alternately expressed (Freyer et al., 2009). Put differently, alternating (de)synchronization patterns can be understood to display non-random statistical properties, exemplified by different temporal distributions (i.e., dwell-times) of low vs. high synchronization states. Such state transitions, known as *bifurcations*, may be driven by both internal (Freyer et al., 2011) as well as external (Avella Gonzalez et al., 2012) network activity. Secondly, phasic or tonic alternations *between* EEG frequencies may also be seen as reflecting dynamic transitions between attractors. One of the clearest examples can be found in the sleep-wake cycle which reveals distinct yet recurring

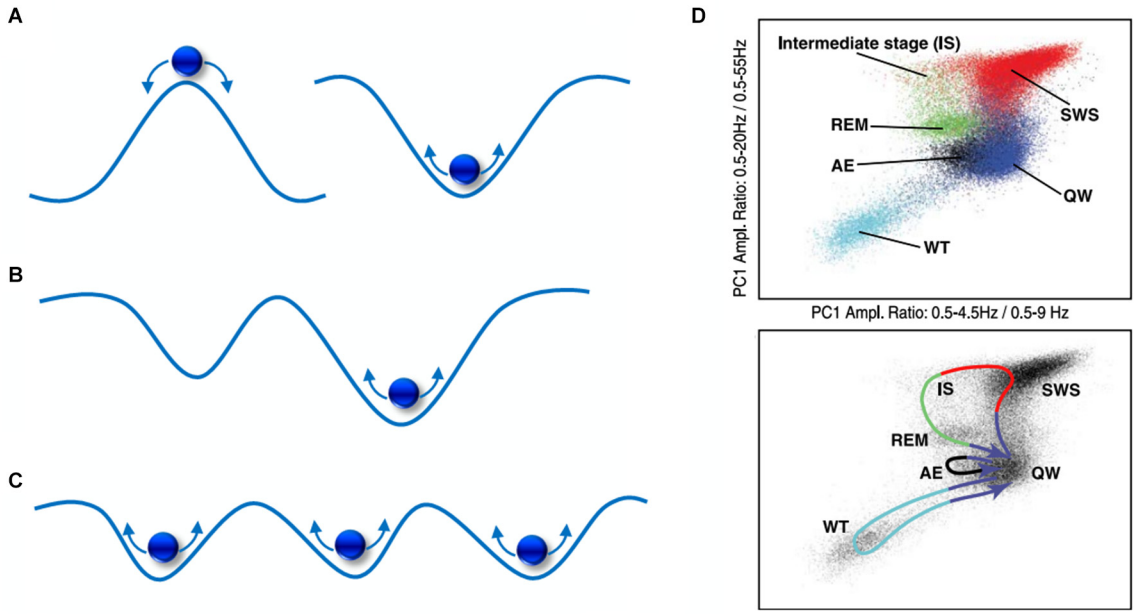

FIGURE 4 | A visual portrayal of state-space landscapes. (A) A hill and valley representation of a repellor (left) and an attractor (right); **(B)** the shallow attractor (left) has a shorter dwell-time than the deeper attractor (right); **(C)** a multi-attractor landscape exhibiting multistability; **(D)** EEG state transitions during sleep-wake activity in the rat, comprising of whisker twitching (WT), active exploration (AE), quiet wake (QW), rapid-eye movement (REM), slow-wave sleep (SWS), intermediate stage (IS). From Gervasoni et al. (2004).

FIGURE 5 | Phase-space dynamical plots of EEG rhythms during sleep. Attractor-like (limit cycle) shapes are more pronounced for alpha **(A)** and delta rhythms **(C)**, compared to the beta rhythm **(B)**. From Pradhan et al. (1995).

states as well as *trajectories* corresponding to each neurobehavioral transition as shown in **Figure 4D** (Gervasoni et al., 2004).

This conveniently brings us the concept of multistability, illustrated in **Figure 4C**. Here, a ball with a continuous source of energy may revisit multiple states without settling into any of them permanently (e.g., sleep-wake states, sensory percepts, memories, network configurations). Thus, it has been proposed that brain function may also exhibit multistability (Deco and Jirsa, 2012; Tognoli and Kelso, 2014), a property of systems that is neither stable nor totally unstable, but which temporally alternates between multiple, mutually exclusive states referred to as the system's *dynamic repertoire* (Ghosh et al., 2008). Evidence for recurring, spatiotemporally discrete brain patterns has emerged from both EEG (Van de Ville et al., 2010; Baker et al., 2014; Mehrkanoon et al., 2014) and fMRI (Hellyer et al., 2014; Tagliazucchi et al., 2014) during tasks and resting-states. The tentative implication is that such patterns reflect dynamic circuit motifs which coordinate specific computational operations, including gating and integration of inputs (Womelsdorf et al., 2014) as well as higher-order modular processing subserved by large-scale brain networks (Baker et al., 2014; Hellyer et al., 2014). The direct impact of neural multistability on cognition is beautifully exemplified by the phenomenon of bistable perception (Braun and Mattia, 2010), where perceptual alternations occur in spite of constant sensory stimulation (e.g., Necker Cube, Vase-Faces illusion). Here, a host of EEG parameters are reported to predict perceptual transitions, including alpha and gamma oscillations (Kornmeier and Bach, 2012).

Last but not least, dynamical systems theory points to a related, equally captivating topic: criticality. Derived from laws of

thermodynamics, critical systems are said to operate at the *edge of chaos*, that is to say, at an optimal "sweet-spot" between order and disorder, which paradoxically affords flexibility *and* stability (!) (Pastukhov et al., 2013; Hellyer et al., 2014). Practically speaking, the brain exhibits both stability when generating consistent behavior, and variability when learning new patterns. By navigating critical boundaries, complex systems fundamentally avoid being dominated by one of two extreme poles. The first, belonging to the *supercritical* regime reflects highly disordered dynamics typified by very brief dwell-times and unpredictable state transitions, i.e., random noise. The second pole belongs to the *subcritical* regime and is characterized by elements so excessively coupled that they converge on a globally stable state, i.e., absolute order. Respective examples of the former and latter are the behavior of a gas and a simple pendulum. Interestingly, from the oscillatory point of view, computing the power spectral density of a gas gives a uniformly flat spectrum, whereas a pendulum produces a single, well-defined frequency peak. Hence, in the frequency domain, we can respectively glimpse features of a stochastic system without any attractors and that of a harmonic oscillator containing a single attractor (called a limit-cycle). Accordingly, EEG activities appear to be a mixture of high-dimensional noise-driven processes as well as low-dimensional phenomena such as rhythmic limit-cycles (e.g., alpha oscillations) (Stam, 2005; Freyer et al., 2011). But this is insufficient to prove the brain actually operates near criticality. Now, if we were to remove the most prominent oscillatory peaks from the EEG power spectrum, we could then observe its background scaling. This is recognized to have a hyperbolic shape (1/f) known as "pink noise", curiously poised between "white noise" (flat) and "brown noise" ($1/f^2$) spectra, both of which are stochastically generated. And so arose a stunning insight: such 1/f scaling might actually reflect scale-free (i.e., fractal) processes characteristic of self-organized criticality (SOC), an active mechanism that maintains complex systems in a critical state (Bak et al., 1987). Since then, an ever-growing body of work has emerged on neuronal avalanches and temporal auto-correlations suggesting that the brain may indeed operate near criticality (reviewed by Hesse and Gross, 2014), which would endow it with maximal dynamic range, information transmission and capacity (Shew and Plenz, 2013). Importantly, *in vitro* as well as modeling studies suggest that tuning the excitation/inhibition balance (e.g., via neuromodulators) is able to alter such putative measures of criticality (Monto et al., 2007; Poil et al., 2012), can be predictive of behavior (Smit et al., 2013), and has been shown to be abnormal in several brain disorders (e.g., Montez et al., 2009).

Hence, tying all the pieces together, we speculate that abnormal synchronization patterns emerge from plastic changes in brain-state attractor landscape(s), which mutually *shape* and *are shaped by* system criticality, manifesting as subcritical or supercritical regimes that characterize disease (Montez et al., 2009; Poil et al., 2012); and secondly, that restoring the pathological oscillatory signatures toward normative values found in the healthy population (e.g., power, phase-locking, peak frequency, 1/f) would restore in good measure the near-critical regime required for optimal information processing (Thatcher et al., 2009; Shew and Plenz, 2013).

NEUROFEEDBACK: UNLOCKING DIRECT CONTROL OF BRAIN OSCILLATIONS

In principle, all that is required to implement neurofeedback (NFB) is an EEG amplifier connected to a computer that provides *real-time* information about a person's brain activity, otherwise known as brain-computer interface (BCI). In so-called "open-loop" applications, specific oscillatory patterns can be recognized by the computer and used to issue a command, helping participants interact with the environment independent of the body's conventional mode of output, which is motor. This is the basis of BCI applications that enable quadriplegics to steer a wheelchair (Millan et al., 2009) or "locked-in" patients to communicate (Birbaumer et al., 2006). On the other hand, in a closed-loop or "NFB" design, a sensory representation of the brain activity is fed-back to users continuously in real-time (as a video game for example), with the aim of controlling the activity *in and of itself*. Put more simply, a NFB interface acts as a virtual "mirror" for neuronal oscillations occurring within the brain, empowering a person to explicitly modify them.

The rationale for NFB can be best understood by taking a historical viewpoint "upon the shoulders of giants". In this case, NFB's foundations may be nicely summarized by a pair of pivotal discoveries. The first one took place a half-century ago, in the mid-1960s, when Kamiya originally demonstrated that volitional control of human brain oscillations can be achieved with sensory feedback from a BCI (for a historical account, see Kamiya, 2011). In this case real-time information of alpha rhythm activity was provided to users via auditory feedback, who reported mental states of relaxation and "letting go" during higher synchronization levels. This phenomenon, since described as "operant conditioning", was later shown to be possible in animals (Wyrwicka and Sterman, 1968; Fetz, 1969). In essence, it demonstrated for the first time the feasibility of achieving *real-time control* of brain activity via sensory feedback channels. Shortly after arrived a second seminal discovery: in cats, NFB was observed to induce long-term changes in spontaneous oscillations outside of the training period i.e., during sleep (Sterman et al., 1970). During what may be described as a serendipitous breakthrough, training such (spindle) oscillations was discovered to have a neuroprotective effect against epileptic seizures in cats (Sterman et al., 1969). Hence, this finding revealed for the first time NFB's ability to induce brain *plasticity*, giving rise to a direct clinical benefit. The union of these two historic discoveries: the feasible control of human EEG rhythms with NFB—on the one hand, and long-term induction of brain plasticity by direct EEG entrainment—on the other, has paved the way for a ground-breaking approach towards modifying brain function in health (Gruzelier, 2013) and disease (Birbaumer et al., 2009; Niv, 2013). Below, we revisit and elaborate on these two major themes of *control* and *plasticity* from engineering and neurobiological angles.

CONTROL I: AN ENGINEERING PERSPECTIVE ON NEUROFEEDBACK CONTROL

Here, Arthur C. Clarke's Third Law may prove an interesting launch pad: "Any sufficiently advanced technology is indistinguishable from magic." At first glance, NFB could be seen as anything but "magical", given that people universally control their

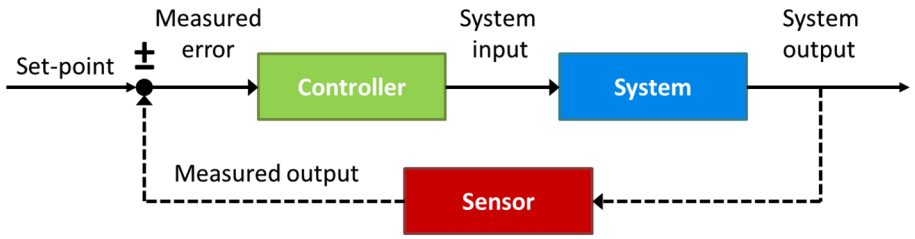

FIGURE 6 | A prototypical closed-loop control circuit. The circuit consists of a Controller (green) which regulates the control parameter until the output of the System (blue), measured by the Sensor (red), matches the internal reference value, or set-point (±).

brain oscillations while thinking or acting. Besides, this may be considered as NFB's major advantage: the fact that it safely harnesses intrinsic brain processes. However, if this is merely the case, is there any reason why introducing a computer should bring anything new to the equation? Why not simply use cognitive-behavioral methods to expose and thereby modify the required brain oscillations and circuits?

To answer this question it will be useful to appeal to insights from *control theory*, an interdisciplinary branch of engineering that deals with the behavior of dynamical systems with inputs, and how their behavior is modified by feedback. The cornerstone of control theory is the *feedback* loop. As depicted in **Figure 6**, a basic control circuit contains a *Controller* which adjusts the system's behavior according to the real-time comparison between the output *Sensor* and the input reference value or *set-point* (±), with the goal of making this difference, or *Measured error*, zero. An illustrative example of a basic control system is the house thermostat, whereby the central heating (controller) is turned on if the current temperature (measured by the output sensor) is observed to be below the desired temperature (set-point), and keeps heating until the difference (error signal) between them is zero.

Recent research on motor control and neuroprosthetics provide convincing data that control theoretic principles can be successfully applied to model brain and behavior. At the most basic level, augmenting error-feedback proportionally improves the speed of both visuomotor (Patton et al., 2013) and BCI (Grychtol et al., 2010) adaptive learning. Remarkably, predictions from advanced models based on optimal control can match experimental data at both the behavioral (Todorov, 2004; Nagengast et al., 2009) and the neural level (Héliot et al., 2010). There is moreover a striking similarity between control system elements (controller, sensor, and set-point) and those of NFB (brain, electrodes, and reward threshold), respectively. Bearing this correspondence in mind, we can try to revisit our former question. We posit that there are (at least) two main advantages for using a closed-loop BCI to control brain activity over simple cognition or behavior. The first is based on the fact that if control is defined in its technical sense of maintaining some variable near a specified value despite disturbances, then a control system does not essentially control what it *does*. Rather, it may only successfully control the parameters that are *observable* to it i.e., what it *senses*. Hence, a thermostat performs best only when it is able to measure (observe) the temperature directly, regardless of complex heat fluctuations occurring inside or outside the house. Conversely, a thermostat without sensory access to the actual parameter of temperature, and irrespective of how complicated its internal model(s) of the environment may be, would quickly accumulate errors and eventually bring about a very large temperature drift. Given evidence that the brain respects control theoretic principles (Todorov, 2004; Marken, 2009; Grychtol et al., 2010), it is reasonable to hypothesize that the *direct sensing* accomplished by a BCI enables control of specific brain oscillations that might otherwise fall outside the scope of conscious awareness. Therefore, the first advantage of NFB may be to quite literally enlarge the cerebral *sensorium*, and thereby enable implicit control of covert brain activity that may have no direct behavioral correlate(s), e.g., activity associated with auditory hallucinations (McCarthy-Jones, 2012).

A second prospective benefit of NFB may be gleaned by considering a car's cruise-control system, which aims to keep a car at a constant speed despite external perturbations (e.g., winds, road gradients). The system is analogous to the thermostat's, once we exchange temperature with speed, with an important difference: the cruise control also has higher *temporal* sampling. Interestingly, feedback-control can be readily applied to the purposeful behavior of both computer (cruise control system) and human (driver), even though the physical make-up of the two systems is quite different—electrical wires, sensors, and motors in the former, but nerves, eyes, and muscles in the latter. Both the cruise control system and human driver can control only what they are able to sense or perceive to be the speed of the vehicle, respectively, albeit the human controller is far less effective at keeping the speed constant. Hence, by analogy, what can be gained by forming a human-computer hybrid for control of brain activity? Based on control-theory, we hypothesize that such a hybrid (i.e., BCI) may enable human controllers to "outsource" their own sensory-feedback processing and augment it with that of the computer, capitalizing on both its superior sensing *accuracy* and/or *temporal resolution*. A testable hypothesis that stems from this interpretation is that NFB-assisted control could prove more effective compared to an unassisted human operator. There is evidence consistent with this account indicating that NFB-regulation induces more pronounced attention (Beatty et al., 1974) and motor-cortical activation (Bai et al., 2014) than unregulated mental practice. This view is strengthened further by reports that fMRI-NFB, which

has a temporal resolution on the order of seconds but a high spatial resolution, significantly boosts whole-brain signal to noise compared to covert behavior alone (Papageorgiou et al., 2013). Conversely, the lack of spatiotemporal specificity is expected to have a negative impact on NFB control, as excessively slow or spatially-distributed feedback signals may lead to an unwelcome "mixing" of irrelevant activities (Bazanova and Aftanas, 2010). Here, the specificity of NFB control could be tested on both the spatial and temporal dimensions of feedback signals, which might include brain regions predefined via inverse-source localization (Congedo et al., 2004) or rhythms that need to be controlled for a particular temporal duration/dynamic (Congedo et al., 2004; Hoedlmoser et al., 2008). In this regard, future NFB studies could also take inspiration from recent BCI approaches which have exploited machine-learning methods (Lotte et al., 2007) for identifying the individual-specific EEG patterns for training, and that may be based on *a priori* behavioral performance (Xiong et al., 2014).

The present framework implies that theoretically any observable measure of brain activity can be extracted and tested for volitional control. But what exactly constitutes successful *control*, and how best to quantify it? Generally, a strict definition of control can be formulated in the engineering sense of enhancing the *signal-to-noise* ratio of a parameter relative to a control condition (e.g., resting-state, sham, or sensory stimulation without control), which could be administered sequentially or interspersed randomly in the experiment. Hypothesis testing may then be used to test whether, during NFB in comparison with control trial(s), there is a significant difference in the mean together with a reduction (or no change) in the variability of the controlled signal. With respect to existing methods in the literature, this approach is technically equivalent to an analysis of variance (ANOVA) or a Student's *t*-test, which similarly account for a variable's mean and variance. If multiple confounding variables are involved, it might then be appropriate to use a multivariate analysis of covariance (MANCOVA). To date, some of the oscillatory parameters reported to be volitionally controlled include amplitude (Kamiya, 2011), frequency (Angelakis et al., 2007), phase-locking (Brunner et al., 2006) and complexity (Wang et al., 2011b). It remains to be seen in future studies to what extent new measures of brain dynamics can be harnessed, such as integration or segregation of multiple brain networks, etc.

CONTROL II: NEUROBEHAVIORAL CONDITIONING

There is the outstanding issue of the theoretical relationship between closed-loop and "behaviorist" operant conditioning models used to describe NFB learning? "Open-loop" models assume causation runs in a one-way path from environmental input to behavioral output; the system's output does not "loop back" and affect its input (Marken, 2009). Hence, the flow of causality is linear in the open but circular in the closed loop. According to behaviorist Stimulus-Response (S-R) theory, environmental stimuli (S) cause behavioral responses (R) via the organism, which is treated as a "black box" in between. Put simply, behaviorist perspectives see inputs causing outputs, whereas feedback implies that outputs cause inputs. The open-loop behaviorist model can technically account for classical conditioning paradigms where stimuli "cause" reflexive behavior (e.g., bell rings, dog salivates), but less convincingly explain operant behavior, which is when behavioral output (the controlled variable) is used to "cause" sensory variables (e.g., pigeon pecks, gets more food). Of course, since the closed-loop is circular, then it could appear that input causes output (more food leads to more pecks). Hence the behaviorist interpretation. However, let us consider how was the relationship established *a priori*? Inherent in any definition of causality is the notion that the effect cannot temporally precede the cause. If this is the case, during the establishment of operant conditioning, the stimulus (S) is presented *after* the correctly generated behavior (R), therefore it cannot be defined as its cause. Recent work points to an intrinsic (neural) source of behavioral variability that may underlie an animal's attempts to "find" the appropriate behavior (Heisenberg et al., 2001). As a result, we propose that NFB learning, whether it be continuous or intermittent, may be better conceptually formulated by control-theoretic closed-loop models (Todorov, 2004; Marken, 2009; Grychtol et al., 2010). In practice, this can be condensed to the following sequence of events: initially the fluctuating feedback signal reflects stochastic (i.e., unconditioned) neural variability (Legenstein et al., 2010), consequently on random occasions this neural variability will infrequently generate activity that will meet the threshold for reward (i.e., which represents zero feedback-error); upon presentation of the sensory cue/reward, the brain may then "memorize" the distinct *neural/behavioral* state as an internal set-point, by releasing a reward-modulated signal for synaptic plasticity, e.g., dopamine (Legenstein et al., 2008). Crucially, the latter is the starting point for subsequent loops during which the human controller (with implicit/explicit neurocognitive strategies) attempts to reproduce, in a feed-forward way, the neural/behavioral state of the previously established set-point (Basso and Olivetti Belardinelli, 2006). Naturally, multiple loops (i.e., conditioning trials) will result in further refinement of the set-point, and translate to a more efficient open-loop strategy. Accordingly, recent data suggest that open-loops operate in the brain (Basso and Olivetti Belardinelli, 2006), coupled with the fact that feed-forward internal representations of input-output transformations seem to occur during motor control, so as to simulate predictions when feedback is not rapid enough (Wolpert et al., 1995). Compatible with our model, latest findings indicate that the initial stage of BCI learning is associated with activations in prefrontal, premotor, as well as parietal cortex (Wander et al., 2013), and that plasticity of cortico-striatal circuits is necessary (Koralek et al., 2012). A pertinent observation is that when NFB is given to patients with frontal lobe lesions, self-regulation of cortical activity is only successful with feedback but abolished during behavioral transfer (no-feedback) (Lutzenberger et al., 1980).

Lastly, we want to point to a likely connection between NFB and more complex neuroprosthetic learning. Although control-theoretic principles are useful for forming a conceptual understanding, the underlying "neural network" reality of learning to move a neuroprosthesis is more complex, since the number of control dimensions and signals is much higher (Perge et al., 2014). Nevertheless, this type of learning is still understood to occur through a combination of intrinsic neural variability,

sensory-feedback, error-minimization, and a global reward-signal (Jarosiewicz et al., 2008; Legenstein et al., 2008, 2010).

CONTROL III: MUST NEUROFEEDBACK SIGNALS BE CONSCIOUS? A GLOBAL WORKSPACE HYPOTHESIS

Biofeedback is marked by a strikingly large range of physiological phenomena that can come under voluntary control, which apart from brain oscillations, includes autonomic functions (Cowan et al., 1990), single motor units (Fetz, 1969) and non-sensory cortical neurons (Cerf et al., 2010). In actual practice, the sensory feedback signals used in NFB are always reportable as conscious. Feedback signals are rarely if ever presented below sensory threshold, or in the presence of distractions or masking noise. Instructions generally draw the subject's attention to the feedback signal before training. Thus intuitively we seem to assume that effective sensory feedback must involve clearly conscious stimuli. In contrast, the physiological events to be trained by NFB, like alpha activity, are generally not conscious. Neurofeedback therefore trains voluntary control over an unconscious physiological process, using conscious feedback signals. In human cognition, it is striking how few operations are conducted in a fully conscious fashion, and how much is allocated to highly practiced unconscious automatisms. Language is a well-studied example, in which only one or two "chunks" (like words or syllables), may be conscious at any moment in time, while fast and complex syntactic, semantic, word retrieval and interpersonal processes remain largely unconscious. Human beings do not consciously decompose sentences into subjects, verbs and objects; rather, in childhood we learn to perform such grammatical operations implicitly and automatically. While conscious cues may trigger syntactic operations, syntax generally operates as a large set of independent modules. Many highly practiced automatisms in the brain seem to operate in such a fashion. One major advantage of this task allocation is that automatic modules do not load central limited capacity.

Over the last 20 years, a growing experimental literature has compared physically identical stimuli that differ only in that one stimulus is conscious and reportable, and the other is not. Conscious sensory input has been shown to trigger more widespread, more coherent, and more stimulus-specific brain activity than closely matched unconscious input (Doesburg et al., 2009b; Panagiotaropoulos et al., 2012; Dehaene, 2014). Binocular rivalry is the classical example, but other techniques have been studied, including visual backward masking, selective attention, change blindness and the attentional blink. It has long been observed that cortical event-related potentials show brain-wide waveforms triggered by conscious stimuli. Baars (1988) and Baars et al. (2013) present a large body of evidence showing that conscious stimuli are widely distributed in the brain. This approach has been called Global Workspace Theory (GWT), and it has been widely tested empirically. Global "broadcasting" in the brain makes sense if we think of the brain as a massively distributed "society" of active and highly specialized neural circuits which retain local processing initiative. Such "agent societies" have been widely studied in computer science and have many biological analogs. A simple example is a college classroom in which all students are equipped with feedback clickers, allowing them to raise questions and pace the presentation rate of powerpoint slides. The speaker's voice is distributed globally to all listeners, who make local decisions whether or not to push a feedback clicker asking the speaker to repeat or explain some point more fully. This non-hierarchical style of functioning works well in many applications.

One can think of NFB as a retrieval problem, a task of finding which particular physiological event is to be linked to the feedback signal. We may draw an analogy with trying to locate a child lost in a large city. It makes sense initially to search for the lost child around home or school, in a local and systematic fashion. But if the child cannot be found, it may help to broadcast a message to all the inhabitants of the city (e.g., via TV), to which only those who recognize it as personally relevant would respond. The message is global, but only the appropriate local units respond to it. Baars (1988) has suggested therefore that NFB may work on a very wide range of neural activities because the signal triggered by conscious stimuli is also distributed very widely in the nervous system. If local alpha sources can generate alpha oscillations, for example, their routine operations may not require conscious involvement or voluntary control. In the special case in which alpha activity evokes conscious feedback, alpha sources may come under voluntary control of the feedback signal (Kamiya, 2011). This is only possible if the feedback signal is widely distributed, as conscious stimuli appear to be. An easily testable prediction follows from these points, namely that a visual feedback signal that is not conscious due to backward masking or binocular rivalry would not work to establish feedback control, even if it were physically identical to the conscious input.

Recently it was shown with intracranial recording in epileptics that NFB permits patients to control single-neuron firing in the temporal lobe (Cerf et al., 2010). Similar findings have been reported in animals (Fetz, 1969). This finding suggests another testable prediction: in epileptic patients who are medically required to wear an implanted cortical electrode grid before brain surgery, a single electrode could be randomly selected among a typical 64-lead grid. If epileptic patients can learn to arbitrarily select any one of 64 electrodes on cue, via conscious feedback, one could measure the patient's accuracy against the *a priori* random probability of controlling 1 out of 64 electrodes at a specific time. This would yield a quantitative index of transmission accuracy from the response-contingent conscious feedback signal to the selected recording electrode. These data could also be analyzed using signal detection theory (i.e., receiver-operating characteristic), mutual information (a measure of neural transmission volume), Tononi's phi (Tononi, 2004), and the like.

PLASTICITY I: HEBBIAN MECHANISMS OF PLASTICITY

The last decade has witnessed a surge of interest in the topic of brain plasticity and the genuine promise it holds for fostering brain health and reversing pathology (Ganguly and Poo, 2013). Although many different techniques can be used to manipulate neural plasticity, either through sensory, pharmacological, optogenetic or electromagnetic interventions, these approaches may fall short when it comes to answering how the intact brain is able to regulate its plasticity intrinsically, i.e., independently of any external stimulus or substance. Studies have indeed reported

correlational evidence for intrinsic plasticity, (Tsukamoto-Yasui et al., 2007), yet animal experiments of this kind are prohibitive in humans. An elegant way this question can be causally approached in humans is via NFB, given that it permits identical sensory stimuli and equivalent frequencies of reward to be used across all users, effectively clamping the external milieu. Hence, participants' entrained neuronal (M/EEG) differences may be considered as resulting minimally from external factors and can instead be regarded as being driven by the modulation of intrinsic, stimulus-independent brain states (Poulet and Petersen, 2008; Zagha and McCormick, 2014). This makes NFB a unique tool for establishing a causal link between endogenous brain oscillations and their cognitive-behavioral functions.

Akin to general learning processes such as skill or language acquisition, NFB usually requires repeated applications of individual "training" sessions of about 20–60 min each, occurring on separate days and spread out over weeks or months depending on the person's response. Accumulating data suggest that maintaining the cortex in a persistent oscillatory pattern via NFB effectively "conditions" the neuronal circuits to produce the same pattern with a higher probability in the future (Sterman et al., 1970; Lubar and Swartwood, 1995; Cho et al., 2008; Ros et al., 2010). At present, the molecular substrates underpinning this *long-term* training effect still remain to be elucidated. However, they may be theoretically explained by evidence that the magnitude of an EEG oscillation increases with the number of neurons/synapses giving rise to it (Musall et al., 2012), combined with the proverbial Hebbian principle that "synapses that fire together wire together, and synapses that fire apart wire apart" (Knoblauch et al., 2012). Consequently, during amplified or "synchronized" oscillations, the population(s) of neurons which are coherently involved in generating an oscillatory pattern would, after some time, further strengthen the connections between themselves, thus making it easier for this population pattern to emerge once again in the future. Conversely, maintaining a group of neurons in a prolonged desynchronized state would weaken the correlated firing of their synapses and attenuate the connections that give rise to synchronization. These outcomes have recently been mathematically modeled *in silico* with neural network models of spike-timing dependent (STDP) Hebbian plasticity (Pfister and Tass, 2010; Zaehle et al., 2010; Knoblauch et al., 2012) and respectively validated *in vivo* by *synchronizing* transcranial alternating current stimulation (tACS; Zaehle et al., 2010) and *desynchronizing* electrostimulation of hippocampal circuits (Tass et al., 2009). In accordance with this model, high-frequency (>90 Hz) DBS can successfully supress low-frequency oscillations (∼9 Hz) in Parkinson's disease, leading to an improvement of symptoms, while low-frequency (<50 Hz) DBS can exacerbate them (McConnell et al., 2012). Importantly, symptom reduction is further improved when stimulation is performed in a closed-loop, and matched to the frequency of the abnormal oscillations (Rosin et al., 2011).

Likewise, coordinated sensory (acoustic) stimulation seems a promising approach for treatment of tinnitus, revealing long-term reductions in slow-frequency rhythms (Adamchic et al., 2014). Hence, as illustrated in **Figure 7**, mechanisms of neural desynchronization can be harnessed to reverse over-pronounced

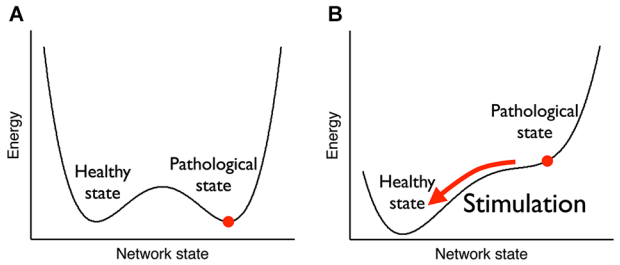

FIGURE 7 | Attractor landscape pre-post therapeutic stimulation. **(A)** Before stimulation, both the pathological state (strong weights, high neuronal synchronization) and the healthy state (weak weights, low neuronal synchronization) are stable, i.e., they are local minima of an abstract energy function. **(B)** During stimulation, the pathological state becomes unstable and the network is driven towards the healthy state. After stimulation has stopped, the network stays in the healthy state. From Pfister and Tass (2010).

(pathological) oscillations which have formed due to excessive synaptic connectivity, by tuning the network into a less-synchronized basin of attraction (Pfister and Tass, 2010). In light of these empirical and modeling results, it is reasonable to expect that similar Hebbian plasticity mechanisms are likely to be at work during endogenous entrainment (synchronization) or extinction (desynchronization) of EEG rhythms with NFB training (Legenstein et al., 2008). Here we select one representative example of the former and latter from the already abundant literature, revealing short-term (<1 day) and long-term (>1 day) changes in rhythmogenesis. To begin with, Sterman et al. (1970) were the first to show that brain oscillations operantly conditioned in awake cats augmented the same type activity during subsequent sleep (<1 day), and even 1 month after termination of training (>1 day). Recently, Cho et al. (2008) have reported a positive correlation ($r = 0.7$) between alpha oscillation amplitude at the end of a NFB session and the following session's resting-state (>1 day). As shown in **Figure 8**, the same positive relationship ($r = 0.6$) is observed between oscillatory power during NFB and the immediate post-session resting-state (<1 day), but this time for alpha-*desynchronizing* (supressing) NFB, controlled by a sham-feedback group (Ros et al., 2013).

This change in resting-state desynchronization was observed to induce a temporally-direct increase of cortical excitability and disinhibition probed via transcranial magnetic stimulation (TMS; Ros et al., 2010), suggesting a causal link between NFB entrainment and changes in intrinsic brain state (Poulet and Petersen, 2008). Moreover, this finding highlights the ability of NFB to impact the excitation/inhibition balance of cortical circuits, thereby potentially tuning system criticality (Poil et al., 2012). An interesting neurobehavioral consequence of alpha desynchronizing NFB is that it enhances functional connectivity within a large-scale resting-state network implicated in intrinsic alertness ("salience network"), correlating with decreased reaction time and frequency of mind-wandering (Ros et al., 2013). Consistent with a circular causality between mind and brain (Freeman, 1999), NFB is thus able to simultaneously impact brain dynamics, mental phenomena and behavior, justifying its promise

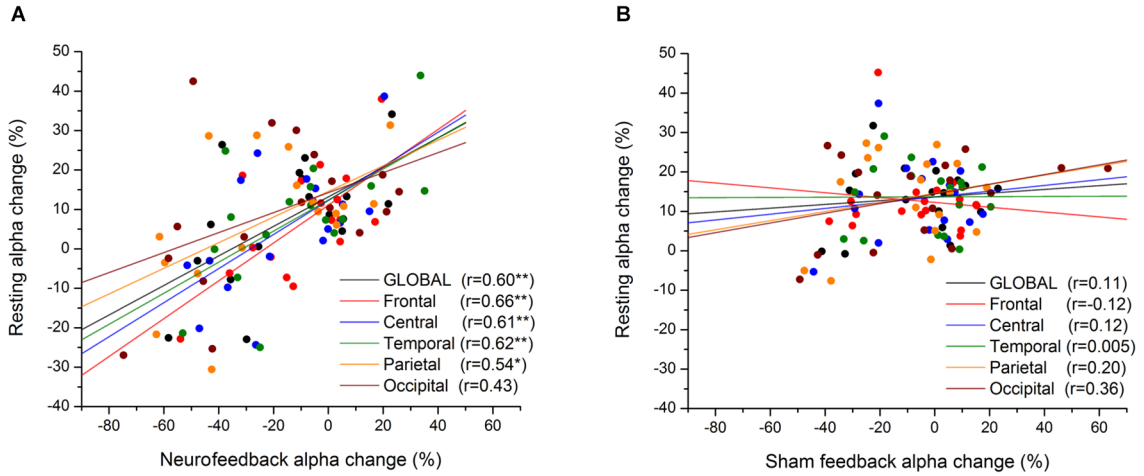

FIGURE 8 | Short-term Hebbian plasticity following neurofeedback (NFB). Scatter-plot of mean alpha amplitude change across electrodes during feedback vs. resting state (post-feedback), for NFB **(A)** and SHAM **(B)** groups. The anatomical location of each subgroup of electrodes is represented by a different color (see legend). $*p < 0.05$, $**p < 0.01$. From Ros et al. (2013).

as a next-generation treatment for neurological and psychiatric disorders. For this reason, we refer to a NFB randomized controlled trial that neatly demonstrates the linkage between clinical improvement and modulations of intrinsic EEG activity in children with ADHD (Gevensleben et al., 2009). The effects are detailed in **Figure 9A** below, disclosing a positive relationship between changes in resting-state EEG synchronization and changes in overall ADHD symptoms (FBB-HKS score), i.e., the children showing greatest attenuations of their theta amplitude (consistent with the NFB protocol), exhibited the largest improvements in clinical scores. Interestingly, as shown in **Figure 9B**, these improvements were furthermore predicted by pre-training (baseline) levels of synchronization, where children presenting the most pronounced theta amplitudes at intake had largest benefits from the NFB training. This outcome is entirely consistent with findings implicating theta excess as a candidate biomarker of ADHD (Chabot et al., 2005; Snyder et al., 2008).

PLASTICITY II: HOMEOSTATIC PLASTICITY

Despite the appealing correlations presented in the earlier section, they seem to tell only one side of the story. It so happens that *intra*-individual variation in brain plasticity induction appears to be equally, if not more, pronounced than *inter*-individual differences. A review of recent studies with non-invasive brain stimulation reports evidence of what is referred to as homeostatic plasticity or "metaplasticity" (Abraham, 2008; Ridding and Ziemann, 2010). Essentially, even though group effects are proven to be reliable, they generally mask a large amount

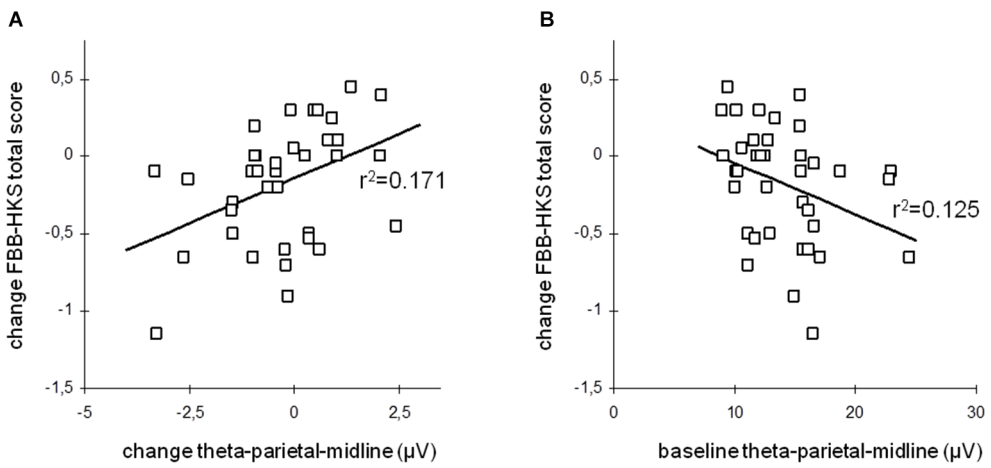

FIGURE 9 | Long-term Hebbian plasticity following neurofeedback (NFB). Theta oscillation amplitude vs. ADHD clinical score change. **(A)** Change of total ADHD score vs. post-NFB change of theta activity. **(B)** Change of total ADHD score vs. pre-NFB theta activity (baseline). From Gevensleben et al. (2009).

of intra-individual variability from test-to-retest, i.e., variable excitability changes on different days (Fratello et al., 2006). Here, the history of prior learning (plasticity induction) in the brain inversely determines the degree of subsequent plastic changes, by following the so-called Bienenstock-Cooper-Monroe (BCM) rule (Cooper and Bear, 2012). In simpler terms, prior increases in synaptic strength (e.g., LTP-like) are more likely to be accompanied by decreases in synaptic strength (e.g., LTD-like) later on if the same induction paradigm is repeated (Müller-Dahlhaus et al., 2008), and vice versa. The brain, it seems, continuously oscillates between well-defined extremes of high and low synaptic strength (Tononi and Cirelli, 2006). This appears to be the consequence of physiological and computational ceiling pressures which occur naturally in synapses, the molecular mechanism of which is still under investigation (Abraham, 2008). Homeostatic plasticity may aid in our understanding why NFB also produces variable intra- and inter-individual effects. Hence, oftentimes changes in EEG synchronization occur in very opposite direction as would be expected according to Hebbian plasticity.

As depicted in **Figure 10**, we have previously reported on a paradoxical "rebound" of EEG synchronization immediately following alpha-desynchronizing NFB in patients with PTSD, which related to increases in subjective well-being (Kluetsch et al., 2014). Here, alpha synchronization during NFB *negatively* correlated with post-NF resting state changes. The important aspect to note here is that PTSD patients have abnormally reduced alpha-power at baseline (i.e., in the resting state) (Jokić-Begić and Begić, 2003). Hence, this may in effect be quite a logical outcome, since who could expect the Hebbian form of plasticity to perpetuate *ad infinitum*, leading to pathologically excessive or reduced oscillations and compromising their essential function? Evidently, as phenomena of epileptic hypersynchrony and flat-line coma suggest, there is good reason why the brain keeps its oscillations in check.

A related phenomenon is the spectral over-synchronization frequently seen following mental fatigue (Huang et al., 2008) or sleep deprivation (Gorgoni et al., 2014), understood to be the product of increases in local experience-dependent plasticity (Hung et al., 2013). Subsequently, following sleep, the EEG is miraculously restored to a less synchronized state the day after (Plante et al., 2013). Fascinatingly, this latter process seems to be compromised in psychiatric disorder (Plante et al., 2013). Tying all this evidence together appears to lead to a beautifully parsimonious conclusion: it is neither high nor low synchronization that may be critical, but rather a golden balance in-between. In addition to abnormalities reported in clinical populations (Coburn et al., 2006), some investigations directly consistent with this view observed that intermediate levels of synchronization best predict conscious perception (Linkenkaer-Hansen et al., 2004), whilst both high and low spectral power are associated with attentional impairment (Pezze et al., 2014). Interestingly, the latter appears to be due to oppositely extreme shifts in the excitatory/inhibitory balance of the prefrontal cortex (Pezze et al., 2014). As discussed in the previous chapter, pathological oscillations can manifest themselves as either low or high synchronization extremes when compared to normative populations. This can equally apply to long-range phase synchronization (e.g., increased phase-locking of alpha rhythm in cognitive impairment, López et al., 2014) as to locally-generated oscillation amplitude (e.g., over-pronounced beta power in Parkinson's, Little and Brown, 2014).

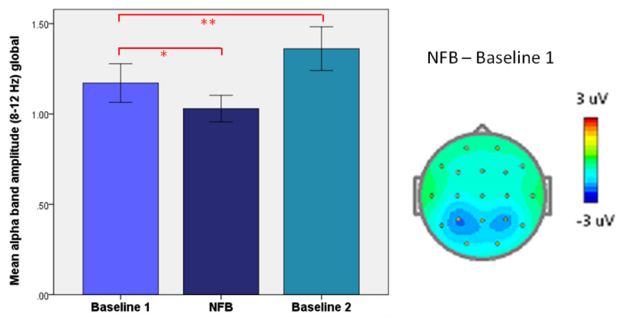

FIGURE 10 | Homeostatic "rebound" following desynchronizing neurofeedback (NFB). **Left**: mean (±SEM) global alpha amplitude in PTSD patients: before (Baseline 1), during (Neurofeedback), and right after neurofeedback (Baseline 2). **Right**: Topographic plot of mean alpha amplitude change during neurofeedback (NFB), relative to resting-state (Baseline 1). *$p < 0.05$, ** $P < 0.005$. From Kluetsch et al. (2014).

In our view, many brain pathologies could thus be succinctly characterized as disorders of homeostatic plasticity, in light of the above evidence as well as the fundamental links between brain oscillations and synaptic potentiation (Tsukamoto-Yasui et al., 2007; Vyazovskiy et al., 2008; Tsanov and Manahan-Vaughan, 2009). This could be especially the case for non-degenerative brain disorders (e.g., ADHD, epilepsy, PTSD etc.), where functional abnormalities are likely not associated with progressive cell loss. In other words, non-degenerative brain disorders may have a *self-tuning impairment*, having lost their dynamic repertoire by being "trapped" in an abnormal resting-state oscillatory pattern (Ghosh et al., 2008). If this is correct, then one might expect measures of neural variability to be lower in brain disorders during task-free conditions. Several reports appear to support this hypothesis, as fluctuations of EEG synchronization are indeed diminished in brain disorders, including Alzheimer's (Stam et al., 2005), psychosis (Müller et al., 1986), OCD (Drake et al., 1996), tinnitus (Schlee et al., 2014) and ADHD (Woltering et al., 2012). During task conditions, however, the relationship can be more complicated seeing that a decrease in variability would indicate more stable "locking" into a particular brain state, which may or may not facilitate task performance (Stam et al., 2002; Deco and Hugues, 2012). An excellent example of this is how stronger theta, but weaker alpha synchronization variability is associated with better performance during a working memory task (Stam et al., 2002). Yet, given evidence of a common functional architecture between resting and task conditions (Smith et al., 2009; Krienen et al., 2014), it is reasonable to posit that the more variable dynamic range of tonic (i.e., resting-state) EEG may underpin that of the phasic (i.e., task-related) EEG, characterized by so called event-related oscillations (EROs), which have been strongly implicated in cognition (Klimesch et al., 2001; Neuper and Pfurtscheller, 2001). Hence, in light of the aforementioned physiological ceiling effects, it is plausible

that resting-state hyper-and hypo-synchrony may dimensionally-restrict the dynamic range of phasic event-related synchronization (ERS) and event-related desynchronization (ERD) patterns (Yordanova and Kolev, 1998; Wascher et al., 2014), respectively. To be exact, we speculate that the *relative* amount of ERS (ERD), represented by percent signal change from baseline (spontaneous) activity, could be reduced in disorders presenting hyper (hypo) synchronization. Neurofeedback designs could thus be made to target either tonic or phasic EEG, given this inextricable linkage between them.

Lastly, we would like to outline two types of homeostatic plasticity, by defining *elastic* homeostatic adaptation as adaptation that does not cause any persistent changes in the system, and *plastic* homeostatic adaptation as adaptation where there is a persistent change in some part of the system (Williams, 2006). The elastic form may be related to short-term changes (<1 day) in EEG synchronization, such as the wake-sleep cycle, or even ERO dynamics themselves (Neuper and Pfurtscheller, 2001). A good example of an elastic homeostatic adaptation after NFB might be the rebound observed by Kluetsch et al. (2014). However, especially relevant to therapeutic applications of NFB may be plastic homeostatic adaptation (>1 day), whereby the homeostatic set-point of the system may be tuned *lastingly*. Here again we revisit control theory, by envisioning a plastic re-tuning of resting-state oscillations towards a new mean (set-point); precisely what is intended by, and classically observed after, NFB therapy (Lubar et al., 1995; Gevensleben et al., 2009). However, the main reason why this mechanism should be considered homeostatic, rather than simply plastic, is in order to also accommodate observations of long-term rebound phenomena. An interesting example supporting this model is a recent NFB study demonstrating a *long-term* (>1 day) alpha rebound in children with ADHD (Escolano et al., 2014), despite evidence of alpha desynchronization within training sessions. This account is further strengthened by reports that bidirectional (up/down) NFB training normalizes targeted ADHD band-powers toward group mean values (Liechti et al., 2012). Hence, as a consequence of homeostatic plasticity, a key prediction of the proposed framework is that both unidirectional and rebound NFB outcomes may be permissive toward normalizing pathological brain oscillation measures (e.g., power, phase-locking, peak frequency, 1/f), as well as the dynamical landscape that subserves them. From this perspective, NFB training could be seen to "tune" the brain's intrinsic mechanisms of homeostasis, which are used to self-organize towards an optimal (i.e., near-critical) set-point following a period of adaptive plasticity (Hsu and Beggs, 2006), but which have become maladaptive in pathology.

PLASTICITY III: STRUCTURAL PLASTICITY

Thus far, we have concentrated on aspects of functional brain activity, yet it is now firmly established that there is an inseparable connection between brain structure and brain function (e.g., Pizoli et al., 2011). Although the brain has often been compared to the functioning of a computer, it differs from the former in a crucial respect: in a traditional computer the physical architecture (i.e., hardware) running the program is not modified by the computations (i.e., software). Instead, in the brain the physical connection strengths making up the neural networks are shaped by their intrinsic activity (i.e., it is a form of "wetware"). On the one hand, the structural pathways in the brain undergrid the flow of neural activity, much like roads shape the flow of traffic (Haimovici et al., 2013). Unsurprisingly then, white-matter integrity has been associated with parameters such as the alpha peak frequency (Valdés-Hernández et al., 2010), while gray-matter is found to positively correlate with EEG power during brain maturation (Whitford et al., 2007). Consistent with this, NFB control of brain oscillations can be predicted by the morphology of underlying cortical generators (Enriquez-Geppert et al., 2013) or associated white-matter pathways (Halder et al., 2013). On the other hand, traffic (brain) dynamics is an emergent process which is governed by the behavior of the drivers (neural activities), e.g., traffic jams may result from a temporal upsurge of activity. Subsequently in the brain, akin to strategic road construction, pathways become reinforced or weakened in response to neural activities through a process known as activity-dependent plasticity (Butz et al., 2009; Ganguly and Poo, 2013). Such "remodeling" involves receptor trafficking, myelination plus spine formation (Butz et al., 2009) and may occur at different timescales, from less than 1 h (Munz et al., 2014) to days (Butz et al., 2009). This symbiotic interplay between structure and function, which defines self-organizing systems, is at the heart of NFB's therapeutic potential: by targeting dynamic activity alone one can unlock and induce changes in the brain's structural architecture, which would in turn support a more persistent functional reorganization. After 50 years since NFB's inception, a recent study has finally provided empirical support for this effect, reporting gray and white-matter increases following a total of 20 h of training in healthy subjects (Ghaziri et al., 2013). If NFB is truly able to "hard-wire" the brain, then one should expect a certain stability of effects *post* intervention. This is indeed observed to be the case: behavioral improvements are robustly conserved at long term follow-up in ADHD (6 months, Gevensleben et al., 2010; Steiner et al., 2014), autism (12 months, Kouijzer et al., 2009), alcoholism (18 months, Watson et al., 1978), learning-disability (2 years, Becerra et al., 2006), and epilepsy (10 years, Strehl et al., 2014). Crucially, in the only study of its kind to date, positive behavioral changes were associated with a sustained, maturational improvement of the resting-state EEG (Becerra et al., 2006).

Let us return to the traffic analogy for a final reflection: the topology (i.e., spatial organization) of road networks is not random but contains a small proportion of long-range highways and a greater proportion of more clustered, local roads. Remarkably, both road networks and brain networks have been observed to exhibit this principle of organization, obeying what has been termed a "small-world" structure. In light of physical constraints and wiring costs, there appears to be an optimal balance between distributed and local connectivity that affords efficient network performance (for a review see Bullmore and Sporns, 2009). However, perhaps the most striking revelation is that a small-world topology apparently facilitates systems to achieve criticality (Russo et al., 2014) and self-generate oscillations (Wang et al., 2011a). We thus seem to have come full circle: the development of a healthy brain requires that it homeostatically organizes both functionally (Boersma et al., 2011) and structurally (Butz et al.,

2014) towards a small-world architecture. If this is true, functional abnormalities due to pathological oscillations would firstly be suggestive of an anomalous topological structure (consistent with Stam, 2014), but, moreover, that normalizing them via NFB would re-establish a small-world network organization. At present, the latter is an intriguing hypothesis that remains to be tested.

This ultimately leads us to the topic of unspecific changes and some evident caveats, given that NFB has been known to induce unpredictable effects on local as well as distributed EEG signatures. For example, long-term training to raise theta (4–8 Hz) over alpha (8–12 Hz) power at parietal sites was associated with a post-training reduction of faster beta (14–18 Hz) activity in the prefrontal cortex (Egner et al., 2004). Initially, this outcome could be explained by an overall leftward shift in central frequency due to entrainment of lower-frequency rhythms. However, it should be borne in mind that intact brain reorganization is assumed to be regulated via complex homeostatic interactions (Butz et al., 2009). As we have argued above, plastic changes cannot necessarily be expected to follow a linear path when the underlying topology is strongly non-linear (e.g., small-world). Moreover this conundrum inevitably holds true for all interventions, extrinsic or intrinsic, which deal with the brain and its panoply of networks (Mangia et al., 2014). Nevertheless, we believe this is all the more reason to explore the brain's innate capacity for self-organization: the sooner its mechanisms are elucidated, the better will be our prospects to exploit them.

CLOSING REMARKS: WHY NEUROFEEDBACK?

Apart from some interesting insights on how the brain's resident orchestra may tune its rhythms, we would be remiss not to discuss whether NFB might possess any real therapeutic advantage(s) over currently available techniques? Most of them, including pharmacotherapy and non-invasive brain stimulation (rTMS, tDCS), are also known to modulate brain oscillations, albeit indirectly. So one should technically ask, why NFB? We contend that NFB's chief strength may not only rest in its direct control of brain oscillations, but in its *safety* and *long-term stability*. When applied judiciously, reported adverse effects of NFB are very rare (Hammond, 2010), and most appear limited to mild headaches which resolve in the aftermath of training. In comparison to the well-known side effects of medications and the exceptional but grave complications that may ensue from electromagnetic stimulation (Rosa et al., 2006), NFB could be regarded as the more favorable option safety-wise. Furthermore, being artificial, transcranial stimulation techniques produce electromagnetic driving forces that are not intrinsic to the brain, and thus still need to be validated for their long-term safety (Davis, 2014). Therefore, the fact that NFB may produce changes under physiologically-normal conditions may be its greatest asset. Interestingly, this very property may be responsible for another, arguably even more fundamental benefit: long-term stability. A distinguishing feature of NFB is that it is purely endogenous, whereby self-organization is invoked by the system itself, i.e., from the "inside out" rather than from the "outside in". This could ultimately minimize treatment tolerance/withdrawal and prove to be a critical distinction, given collective evidence that the brain obeys principles of homeostasis, combined with reports of NFB's exceptionally persistent effects (e.g., Strehl et al., 2014). In light of the amazing plasticity displayed by the human brain, the prospect that such an approach could offer is important and urgent enough to motivate future investigations so as to further validate the extent of its impact on normal and pathological brain function. The fruits of such an inquiry could lead to a remarkably safe, non-invasive and above all natural approach for directing neuroplastic change.

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What future research should bring to help resolving the debate about the efficacy of EEG-neurofeedback in children with ADHD

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In recent years a rising amount of randomized controlled trials, reviews, and meta-analyses relating to the efficacy of electroencephalographic-neurofeedback (EEG-NF) in children with attention-deficit/hyperactivity disorder (ADHD) have been published. Although clinical reports and open treatment studies suggest EEG-NF to be effective, double blind placebo-controlled studies as well as a rigorous meta-analysis failed to find support for the efficacy of EEG-NF. Since absence of evidence does not equate with evidence of absence, we will outline how future research might overcome the present methodological limitations. To provide conclusive evidence for the presence or absence of the efficacy of EEG-NF in the treatment of ADHD, there is a need to set up a well-designed study that ensures optimal implementation and embedding of the training, and possibly incorporates different forms of neurofeedback.

Keywords: EEG-neurofeedback (EEG-NF), attention-deficit/hyperactivity disorder (ADHD), efficacy, methodology, non-pharmacological interventions

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, affecting about 5% of all children worldwide. ADHD is characterized by a pattern of inattention and/or hyperactivity and impulsivity (Polanczyk et al., 2007).

While medication is the most effective treatment in ADHD (Faraone and Buitelaar, 2010), it also entails a number of concerns. Firstly, side effects have been reported and for some serious and life-threatening side effects, the risk is not clear and will likely remain so due to the rarity of these events (Graham et al., 2011). Children with ADHD and their parents also have significant reservations about possible negative long-term effects of medication (Berger et al., 2008). Secondly, there is insufficient evidence of long-term efficacy of medication for ADHD (van de Loo-Neus et al., 2011). Thirdly, the symptoms of ADHD have been found to reappear after discontinuing drug treatment (Jensen et al., 2007; Murray et al., 2008). These misgivings about ADHD medications have contributed to the interest in developing non-pharmacological approaches to treatment, such as electroencephalographic-neurofeedback (EEG-NF). EEG-NF is based on the rationales that (1) the neural basis of ADHD is characterized by deviant EEG patterns that play a role in the pathophysiology of the disorder; and (2) voluntary modulation of specific brain activity patterns can be learned by operant learning strategies. The first rationale originates from the finding that the majority of resting state electroencephalography (EEG) in children with ADHD is characterized by increased slow-wave activity (primarily in theta range) and decreased fast-wave activity (primarily in beta range). These slow and fast waves are often coupled, resulting in elevated theta/alpha and theta/beta ratios (see Barry et al., 2003 for a review). Although a deviant theta/beta ratio has been found in ADHD rather consistently (Arns et al., 2013), the exact role of such a deviant pattern in the pathophysiology of ADHD is not clear yet (van Dongen-Boomsma, 2014). In addition, although voluntary modulation of specific brain activity patterns might be possible, clear-cut proof is still lacking. If these rationales are correct, they will provide for a rational neuroscience-based treatment of ADHD that brings about normalization of the underlying neural abnormality and thereby clinical improvement.

EEG-NF; THE CURRENT STATE OF AFFAIRS

In recent years, a number of randomized controlled trials, reviews, and meta-analyses relating to EEG-NF in children with ADHD have been published. Although particularly non-blinded studies conclude that EEG-NF is probably effective, robust evidence

based on methodologically sound studies is still lacking. The majority of studies did not include a placebo group and/or blinded measures. Studies that did include a placebo group or a blinded design have not found superior effects of EEG-NF compared to placebo-NF (Perreau-Linck et al., 2010; Arnold et al., 2012; van Dongen-Boomsma et al., 2013[1]). In addition, a systematic review and meta-analysis of randomized controlled trials (RCTs) of non-pharmacological interventions in children with ADHD including EEG-NF studies, reported non-significant results for the blind rating of symptoms (ES 0.29, $p = 0.07$; CI = −0.02, 0.61) (Sonuga-Barke et al., 2013). One of our previous studies (Vollebregt et al., 2013) did not find any effects at a neurocognitive level following EEG-NF treatment of ADHD participants. This paper also included a systematic review of the extant literature which indicated that our findings were in line previous studies.

However, absence of evidence does not equate with evidence of absence. If EEG-NF truly has no effect, then the possibility of regulating brain activity via EEG-NF to improve ADHD symptoms can be refuted. Alternatively, a true effect of EEG-NF may be hidden by methodological flaws which would imply that the optimal way to apply or study this therapy is not yet known.

Improvements in a number of different areas will be needed to overcome discrepancies in the EEG-NF literature. Firstly, improvements will be needed in study-design. Secondly, the implementation and embedding of the training may have to be improved. Thirdly, the assessment of other forms of neurofeedback, alongside EEG will also help to clarify outstanding questions. These three levels of recommendations will be discussed below.

STUDY-DESIGN

While placebo-controlled RCTs are the gold standard in pharmacological research, there is no consensus regarding the optimal design for EEG-NF experiments.

PLACEBO-CONTROLLED RCT'S

A major advantage of the inclusion of a placebo condition is that all aspects of both treatments are identical except for the underlying hypothesized working element. This enables allocation of positive findings to the working element only. Another advantage is that the amount of expectancy is equal between groups in contrast to all other control condition options, in which an equal amount of expectancy is difficult or even impossible to assess and correct for. The inclusion of a placebo condition also allows blindness of the child and parents, making blind assessments by proximal individuals possible. A common misconception of placebo-controlled RCTs which also exists in EEG-NF research (e.g., Heinrich et al., 2007; Gevensleben et al., 2012) is that it would be unethical to deprive participants of an effective treatment by allocating them to the placebo condition instead of the treatment condition. However, in cases where the efficacy of a treatment is not known and the purpose of the study is to determine if the treatment may be effective, then allocation of participants to a placebo group does not involve depriving a participant of treatment, as long as medication which a participant may be taking for his or her condition is continued during the course of the experiment.

A randomized placebo-controlled trial also has drawbacks, namely the fact that it is time- and energy- intensive, expensive, and may not be the strongest design for all interventions or settings (West and Spring, 2014).

Applying a randomized placebo-controlled trial design to EEG-NF experiments might create a selection bias. In certain cases, placebo-controlled RCT's may thereby limit the external validity of the findings (West et al., 2008). Only people that are willing to accept that they may be allocated to the placebo group will participate in the study. However, this problem may partly be alleviated by ensuring that participants that are taking medication continue their regime unaltered throughout the duration of the study. In addition, including a placebo condition may make it more difficult to recruit participants due to a potential participant's reluctance to receive the placebo treatment. This can be (partially) overcome by conducting a multi-site center study and allowing ADHD medication to be used through the study period. Furthermore, lowering the expectancy by the possibility of allocation to the placebo group may make it more difficult for the treatment to have a positive effect of the treatment (like neuroregulation) (Gevensleben et al., 2009). In accordance, most participants of EEG-NF placebo-controlled RCTs conducted until now seem to experience the treatment as a placebo condition (Logemann et al., 2010; Lansbergen et al., 2011; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013). One might speculate that this absence of efficacy is caused by reduced motivation of the participants or—on the other hand—from flaws in the protocol. The feasibility of the training should therefore be rated by evaluating EEG indices during the sessions of both groups (i.e., learning curves), in addition to measuring the guessing rate (i.e., how well parent and child were able to guess to what group they were allocated), as well as analyzing the differences between pre and post quantitative EEG measurements. Until now, of the randomized placebo-controlled trials, Vollebregt et al. was the only study that evaluated EEG indices during the sessions and did not show any learning effect.

Generally, a placebo condition is only justified if the condition meets the following criteria. Firstly, the placebo condition must be inert with no possibility that this treatment trains a measurable physiological effect. This should be assessed by analyzing EEG indices during the sessions in the placebo condition. Secondly, all participants (i.e., the child, his/her parents, teacher(s)) as well as all examiners (i.e., the raters, but also the EEG-NF therapist) should be blinded. Due to technical restrictions in placebo-controlled studies it has not been possible to blind the therapist while implementing manual thresholding. However, the promising proposal by Kerson (2013) has overcome these restrictions by creating a design in which real-time noise is superimposed on the placebo data creating the illusion of real time EEG recordings.

[1]The study by van Dongen-Boomsma et al. (2013) describes behavioral data acquired from a project registered in the Clinical trial register under "Project ADHD and EEG-Neurofeedback THERapy"; www.clinicaltrials.gov; NCT00723684. Lansbergen et al. (2011) describe the pilot data of this project. Vollebregt et al. (2013) describe the neurocognitive data of this project and in addition provide a systematic review.

ALTERNATIVES TO PLACEBO-CONTROLLED RCT'S

In relation to psychotherapy research, problems with the use of placebo-conditions have been emphasized (Borkovec and Sibrave, 2005). Clinical trials which attempt to eliminate unspecific treatment components by the use of placebo-conditions, might give an inaccurate estimate of the clinical value of the treatment if nonspecific variables (e.g., expectations) interact with active treatment components. Jeopardizing treatment fidelity in such a way might also happen in EEG-NF. All problems discussed in relation to psychotherapy can certainly not readily be generalized to the research of EEG-NF in which the target of training is non-psychological in nature, in contrast to the psychological target psychotherapy has. Nevertheless, internal validity should not be readily assumed in either design. The external validity of alternatives to placebo-controlled RCT is often stronger than of placebo-controlled RCTs, but they also face a serious limitation in terms of ensuring internal validity (West et al., 2008). A number of promising alternatives to placebo-controlled RCTs, which attempt to overcome these difficulties, do exist. Disadvantages of performing a placebo-controlled RCT in certain situations and possible solutions to deal with them were elaborately discussed by West and Spring (2014). Their points and arguments on alternatives to placebo-controlled RCT's will be used further to discuss the use of such alternatives to study EEG-NF. When studying EEG-NF, the placebo condition can for instance be replaced with "additive comparison" or "treatment dismantling" in which aspects that are hypothesized to contribute to the efficacy of the treatment are added or left out of the treatment respectively. Alternatives to random assignment could be time-series, counterbalanced, cross-over and group randomized designs. These alternatives avoid unfair allocation and thereby circumvent a selection bias. "Partial blinding" is a method which allows for manual thresholding while minimizing the number of people that have to be unblinded. Another option is an "equipoise design" in which two treatments are equally well valued at the onset of the study which makes blinding less relevant.

A concrete example of an alternative approach to a placebo-controlled RCT for EEG-NF is "interrupted time series analysis" in which the treatment is introduced at different time points, but endpoints are equal (West et al., 2008). If the rater is unaware of the duration of treatment, the measurement can still be blind and expectancies of parents and children are controlled relatively well, i.e., they all receive the treatment that they expect to be effective. This design allows blind measures and comparable expectations in each group despite the lack of a placebo group. However, the design does assume that the amount of time spent on the training predicts the amount of improvement.

THE OPTIMAL DESIGN

Regardless of the manner in which internal validity is maximized, the study design can also be improved in other areas. For instance, the sample size should be in congruence with the power analysis, thereby enhancing the power and allowing more analyses (such as subtype analyses). In addition, the study-design should seek to determine whether or not EEG-NF is efficacious as a monotherapy or alternatively is valuable as an add-on therapy received in conjunction with medication. Although few studies to date have compared medication to neurofeedback (Duric et al., 2012; Meisel et al., 2013; Ogrim and Hestad, 2013), these studies struggled with major limitations and inconsistent findings. A more thorough comparison between medication and EEG-NF can be achieved by including additional subgroups that assess participants without medication together with participants on medication. A strong design should furthermore obtain objective measures of ADHD symptoms, e.g., by using school observations by an independent observer, actometers, or neurocognitive tests. Finally, a strong design should have an optimal implementation and embedding of the treatment, discussed further below.

In summary, an improved design can be achieved by addressing the above mentioned points either through a placebo controlled RCT or an alternative design. Importantly, a design can only be optimal if reliable and valid outcome measures are selected and good quality control is maintained throughout data collection. Internal validity should be maximized while bias should be minimized (West and Spring, 2014).

IMPLEMENTATION AND EMBEDDING OF THE TRAINING

EEG DEVIATION

Most EEG-NF protocols focus on ADHD-related deviation in frequency bands during rest; up-regulation of theta power and down-regulation of beta power (Monastra et al., 2005). While the majority of children with ADHD exhibit diminished beta-power, a subgroup of children with ADHD have been found to have excessive beta-power (Arns, 2012). Thus, the idea of repairing a deviate EEG pattern would not apply on these children without a personalized protocol.

REWARD FEEDBACK

The percentage positive feedback that should be given has been under debate. Some researchers argue that for instance 80% positive feedback would to be too high for optimal learning (Arns et al., 2014). The percentage should not be too high not allowing sufficient learning, neither should the percentage be too low preventing a feeling of control. Consensus on what this percentage should be has not been reached and should be investigated.

LEARNING PARADIGMS

To further improve the training, the development of a paradigm with instructions that are clearly goal-directed and in which the participant is encouraged to actively attempt to reach a certain "brain-state" might be more effective than strictly following an operant learning principle in which learning occurs through performance rather than through following a preceding intention. Creating awareness of the desired behavior might not only be more effective during training itself, but might also facilitate transfer into daily life since the participant is actively aware how to achieve a goal. Achievement of explicit goals might in addition enhance motivation. Since no placebo-controlled studies until now have been able to show specific treatment effects, a possible explanation besides design-related explanations discussed above, could be that a paradigm lacking clear instructions might not lead to a learned behavior being able to be incorporated in a participant's daily life.

TRANSFER

Without transfer of the (during treatment) learned skills into daily life, the usefulness of EEG-NF can seriously be questioned. To facilitate potential transfer effects into daily life, the following recommendations can be made. Explicit feedback on the deviation of oscillations might enable awareness of how to minimize this deviation, thereby creating a possibility to consciously prompt this minimization in any situation in daily life as well. This could be further strengthened by implementing transfer trials; a block within the training in which no immediate feedback is given. The participant is required to act as if immediate feedback is given at that moment, even though feedback is only given after the block has ended. In this way a daily life situation, in which no immediate feedback is provided either, is simulated more realistically. The implementation of transfer trials has already been applied (e.g., Strehl et al., 2006; Drechsler et al., 2007; Heinrich et al., 2007; Leins et al., 2007; Gevensleben et al., 2009, 2014), but has not been studied in a sufficiently well designed trial. Finally, transfer effects can be optimized by combining the pure EEG-NF sessions with sessions including behavioral therapeutic aspects to teach the participant to recognize daily life situations in which to apply the new skills learned from the EEG-NF (Heinrich et al., 2007; Gevensleben et al., 2009). Despite different aspects of EEG-NF that have been under debate as discussed above, a clear consensus of how the optimal implementation of EEG-NF should look like has not been reached.

DIFFERENT FORMS OF NEUROFEEDBACK

Of course, the conventional EEG-NF is not the only alternative treatment for ADHD that could be studied. Different methods than the most popular most practiced resting state oscillatory EEG-NF could be scrutinized. Examples are online tomographic NF (tNF) computed from multichannel scalp EEG (Liechti et al., 2012), real-time functional magnetic resonance imaging neurofeedback (fMRI-NF) (Sulzer et al., 2013) or magnetoencephalographic neurofeedback (MEG-NF) (Foldes et al., 2011). The advantage of tNF is that more specific brain regions can be targeted due to the use of more electrodes. At least the same advantage can be reached when using MEG, without all the preparatory hustle that usually comes along with EEG. fMRI is of course spatially even more precise but deals with a temporal delay of measurement. Both MEG and fMRI based neurofeedback are far more expensive than EEG; however difference in costs may be less when only a few sessions are needed. Studies have shown that all these methods are feasible, each having its own advantages and disadvantages. All these methods seem to outperform conventional EEG-NF since they allow more direct feedback, based on more specific brain structures.

When sticking to the EEG-NF protocol or more specifically to a personalized EEG-NF protocol, it can be questioned how deviations should be determined. Children in the active group of our study received a personalized protocol, but EEG data recorded during the sessions showed that not all desired training directions were met (Vollebregt et al., 2013). Significant improvement on group level can only solidly be interpreted if all training conditions hypothesized to improve ADHD (either on behavioral or neurocognitive level) are actually improved in the desired direction. Determining deviations during rest might differ from deviations during task performance. Generalization to daily life might be greater when the neurofeedback is based on EEG deviations during task performance. The most often replicated EEG-deviation in ADHD has been shown at rest (Arns et al., 2013), but does not show an unambiguous relationship with behavioral and cognitive performance (van Dongen-Boomsma, 2014). Still, the existence of a straightforward relationship between these two is the basis of the conventional EEG-NF therapy. Since dysfunction due to the core ADHD-symptoms is primarly experienced during cognitive or motor activity, a focus on electrophysiological indices during activity may have a better rationale than during rest. In addition, generalization to daily life (hence, transfer) might be greater when the neurofeedback is based on EEG deviations during task performance. These arguments plead for real-time deviation determined during interactive task performance. A clear example of such an application of neurofeedback (in healthy individuals) is by real-time training alpha oscillations during task performance in an MEG scanner (e.g., Jensen et al., 2011).

In the early days, alpha enhancement neurofeedback (6–13 Hz) protocols failed to find a specific effect on hyperkinetic behavior (Nall, 1973). After this starting point, the alpha frequency band has not been the focus of neurofeedback. Nevertheless, alpha activity is associated with active inhibition of brain areas, which is hypothesized to result in allocation of attention (Klimesch et al., 2007). Aberrant modulation of alpha activity during task performance has been associated with attention problems on clinical level (i.e., adults with ADHD) (ter Huurne et al., 2013). Hence, a relationship has actually been shown between behavioral measures (to what extent the cue induced allocation of attention) and alpha oscillations (the lateralized difference in alpha power expected due to allocation of attention following the inhibition notion) in ADHD. In addition, the height of the alpha frequency peak has been shown to be lower in a subgroup of children with ADHD (Vollebregt et al., in press) and predictive to treatment outcome of several treatments (Ulrich et al., 1984; Arns et al., 2008, 2009, 2012; Arns, 2012). Different characteristics of the alpha frequency band therefore seem to be relevant to ADHD. It is worthwhile to further investigate neurofeedback possibilities training this frequency band. These results could be related to the neurophysiological substrate of the disorder. To study this active inhibition notion, active task involvement is necessary implying interactive task performance. By improving the therapy with suggestions mentioned above, other forms of neurofeedback might also have potential as treatment for ADHD.

CONCLUSION

The debate whether EEG-NF is an effective treatment for ADHD can be closed by setting up an optimal study with a study-design that tackles the drawbacks of a randomized placebo-controlled trial design that are consequential to studying EEG-NF while keeping blind measurements and avoiding other ways of desecrating the internal validity. In addition, EEG-NF should be implemented in an optimal learning setting both on the technical level of the EEG-NF and with respect to embedding of

the learning strategies into daily life. Finally, alternative forms of neurofeedback to conventional EEG-NF, may offer other, maybe even better, promising alternatives.

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EEG-based local brain activity feedback training—tomographic neurofeedback

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Along with the development of distributed EEG source modeling methods, basic approaches to local brain activity (LBA-) neurofeedback (NF) have been suggested. Meanwhile several attempts using LORETA and sLORETA have been published. This article specifically reports on "EEG-based LBA-feedback training" developed by Bauer et al. (2011). Local brain activity-feedback has the advantage over other sLORETA-based approaches in the way that feedback is exclusively controlled by EEG-generating sources within a selected cortical region of training (ROT): feedback is suspended if there is no source. In this way the influence of sources in the vicinity of the ROT is excluded. First applications have yielded promising results: aiming to enhance activity in left hemispheric linguistic areas, five experimental subjects increased significantly the feedback rate whereas five controls receiving sham feedback did not, both after 13 training runs (U-test, $p < 0.01$). Preliminary results of another study that aims to document effects of LBA-feedback training of the Anterior Cingulate Cortex (ACC) and Dorso-Lateral Prefrontal Cortex (DLPFC) by fMRI revealed more local ACC-activity after successful training (Radke et al., 2014).

Keywords: neurofeedback (NF), sLORETA, tomographic neurofeedback (tNF), EEG-based local brain activity (LBA-) feedback training, rtfMRI neurofeedback

INTRODUCTION

Due to the volume conduction genesis of scalp-EEG signals, single- or few-channel EEG-recordings barely convey sufficient information to trace their spatial origin inside the brain. Classical neurofeedback (NF), which typically uses such EEG-recording is, therefore, also spatially unspecific. As a consequence, the "how and where" of changes due to classical NF training in the trainees' brain is quite uncontrolled and may also vary from person to person, which might reduce the efficacy of NF training.

PROPOSED SOLUTIONS

Concerning improvement of the spatial specificity of NF training, several options have been proposed and partly evaluated during the last two decades. All utilize links between the feedback signal and information from spatially restricted brain areas.

Aiming for high spatial resolution, real time functional magnetic resonance tomography (rtfMRT) was explored by Yoo and Jolesz (2002) and implemented as NF procedures by Posse et al. (2003), Weiskopf et al. (2003) and deCharms et al. (2004). In the ensuing years, the basic usability of rtfMRT-NF was demonstrated in several applications—see Sitaram et al. (2011) and Weiskopf (2012). Near infrared spectroscopy (NIRS), another blood oxygen level dependent (BOLD) technique capable of capturing information on focal cortical activity, has also repeatedly been proposed for brain-computer-interface (BCI) applications and recently utilized in NF procedures (Mihara et al., 2012; Kober et al., 2014). Compared with rtfMRT-NF, NIRS-NF is cost-effective and offers higher portability and usability although it lacks sensitivity to subcortical sources.

In the same period, electromagnetic tomographic techniques have been suggested. LORETA neurofeedback (LNFB)—also referred to as tomographic NF (tNF)—was the first application of this kind, developed by M. Congedo and published in 2004 (Congedo et al., 2004). It is based on LORETA, an inverse solution technique developed by Pascual-Marqui et al. (1994) for localizing sources of multi-channel time or frequency domain EEG/MEG signals within the cortical gray matter volume using a three shell spherical head model. With this procedure the feedback signal is directly linked to the current density (CD) of voxels selected from the solution space as region of training (ROT). Electroencephalogram frequency domain LNFB, as proposed by Congedo et al. (2004), was used, with varying degrees of success in studies by Cannon et al. who investigated its behavioral and cognitive effects and impact on EEG characteristics (Cannon et al., 2006, 2007, 2008, 2009, 2014). Interestingly, the more advanced method "sLORETA", also developed by Pascual-Marqui (2002) was applied only recently in a tNF-study of 13 children with ADHD by Liechti et al. (2012) (partly also in Maurizio et al., 2014). Aiming to evaluate the therapeutic efficacy of tNF, this study used theta-beta frequency as well as slow cortical potential (SCP) signal components and a single voxel within the anterior cingulate cortex (ACC) as "ROT". Although no learning in the ACC was observed, this study is quite informative about tNF and more general aspects of NF.

It needs to be emphasized, however, that in all these EEG-based tNF-studies, the spatial specificity of the feedback is still a matter of debate. The (s)LORETA algorithm localizes generating sources by approximating a smooth 3D intra-cortical CD distribution which corresponds to a given EEG/MEG topography. That leads to overlapping current densities from neighboring voxels i.e., to spatial blurring. Consequently, stronger current densities in voxels adjacent to the ROT affect those within the ROT.

An attempt to reduce these consequences has been addressed and discussed by Congedo (2006). In that paper two filters in combination with sLORETA are described and tested on simulated data; one, a spatial filter, reduces the influence of spatial blurring in the ROI, the other filter acts on the input signal, enhancing the signal-to-noise ratio (SNR). However, to our knowledge, no reports on NF-applications of this particular approach have appeared in the literature to date, and Cannon et al. have used the LORETA-based procedure published in 2004 (Congedo et al., 2004) up to 2014. An *a posteriori* elimination of spatial blurring effects by partial correlation analyses on selected ROIs as suggested by Cannon et al. (2009) is inapplicable for controlling the NF learning process directly and also needs to be questioned critically: e.g., correlations in this context are inherently taken as causally determined, which is not assured with LORETA derived CD data sets.

Beamformer spatial filters have evolved with MEG- and BCI-research. A beamformer consists of weights for each electrode with which the scalp signal distribution is spatially filtered to achieve an estimate of the source power at a specific location in the cortex. By constructing beamformers for each location, less blurry 3D estimates of the source power throughout the cerebral cortex can be compiled and generator localization is achievable by identifying local maxima (Van Veen et al., 1997; Green and McDonald, 2009; Grosse-Wentrup et al., 2009).

New approaches for solving the EEG/MEG inverse problem continue to appear in this field e.g., with the aim of identifying and modeling multiple sources of different spatial extent. Haufe et al. (2011), for example, propose a decomposition of the CD into a small number of spatial basis fields; a real-time version, however, is not yet available.

Apart from the spatial blurring issue, it should be borne in mind that only restricted information on the ongoing 3-dimensional neural activity pattern within the cortex is accessible via Scalp potential topographies (SPTs). With respect to this real activity pattern, estimates yield dispersed and overlapping sources in the solution space and it is reasonable to exploit only the local maxima of the estimated activity. Local Brain Activity (LBA-) feedback training was developed with these limitations in mind: EEG topographies are analyzed online by sLORETA and, crucially, feedback is strictly related to generating sources that have their center i.e., local CD maximum, located within the preselected ROT (Bauer et al., 2011).

THE EEG-BASED LBA-FEEDBACK TRAINING: THE PRINCIPLE

Neurofeedback aims to initiate and maintain instrumental learning. This requires correct and consistent reward during the ongoing training—LBA-feedback enforces that. Scalp potential topographies are generated in most cases by several sources and possible weaker sources within the ROT should not be missed for feedback. Taking these facts into account "simultaneous multiple sources (SMS-) LORETA" was developed as the core procedure of LBA-feedback. It identifies all generator loci i.e., all local maxima, in sLORETA-derived CD solutions automatically and rapidly utilizing individual electrode coordinates projected on a 3-shell realistic head model (Pllana and Bauer, 2008, 2011).

The time-domain SMS-LORETA procedure consists of

1. an iteration loop: recorded potential topography > *sLORETA transformation > storage of the maximum current density's spatial location > calculation of a forward solution (i.e., surface potential topography) that corresponds to a standardized source at this location > cumulative subtraction of this forward solution from the recorded potential topography > as new input to sLORETA until the initially recorded potential topography is flat*; and
2. a "spatial" cluster analysis of all stored maximum CD locations; and
3. the identification of all cluster centers which then are taken as loci of generating sources with the maximum CD within each cluster as their corresponding strength—for details see Pllana and Bauer (2008, 2011).

Screening applications of quasi continuous LBA-feedback revealed quite infrequent feedback with sometimes long waiting epochs and turned out to be insufficient to initiate learning. These observations have led to the current implementation of LBA-feedback training which is executed in a stepwise task-/stimulus-linked manner. This strategy also has the advantage that it allows SNR-enhancement by application of single-trial evoked potential (EP) estimation. Trainees are presented with short duration stimuli or tasks (1–8 s) via computer display. To a greater or lesser extent these involve the ROT-structures. Trainees are asked to respond to these stimuli/tasks accordingly, and mentally retain these responses during the presentation period. EOG- and pre-stimulus-baseline corrected SPTs are extracted from the ongoing multi-channel EEG at selectable latencies and SMS-LORETA analyzed. If this analysis identifies a source within the predefined ROT its strength determines the brightness of a green feedback signal presented as a narrow frame around the stimulus/task presentation area. If no source is detected within the ROT the narrow frame remains or turns gray. This feedback is updated after each stimulus/task according to the current SMS-LORETA result. As a crucial additional instruction, trainees are asked to try to keep this frame green as long and as bright as possible.

FIRST APPLICATIONS

In order to explore the feasibility of LBA-feedback, a screening study was performed that investigated if subjects are able to learn to enhance the activity within left hemispheric linguistic areas (BA 6,21,22,40,44,45) by means of the task-linked procedure (Bauer et al., 2011). Ten healthy right-handed subjects participated in daily training sessions on seven consecutive working days beginning on Mondays. Five subjects received consistent feedback

(experimental group; EG) the other five sham feedback (control group; CG). A session had 2 runs of 120 item presentations each. Items were sketches of simple actions, each presented on a computer screen for 3 s with varying inter-stimulus intervals of 6 +/− 2 s. The subjects' task was to covertly name the verb that corresponded to the presented item and, simultaneously, turn the gray frame around the item presentation area as intensively green as possible as the feedback signal. While each item was presented, 59-channel DC-EEG signal epochs (equidistant montage, 125 samples/s, corrected for eye movement artifacts, referenced to a 500 ms pre-stimulus baseline) were recorded and immediately analyzed by SMS-LORETA at three latency windows. Members of the EG received feedback via green frames whenever generating sources were detected within the ROT. The intensity of the green was proportional to the sum of the strengths of the identified sources. Green feedback for members of the CG was randomly presented with varying intensity in 20% of the items, which corresponded to the average initial feedback rate of the EG. The second run of the last session was a so-called "transfer run" i.e., no feedback was shown, but subjects were informed about this and instructed to behave as they did during the more recent runs. The aim of this study was to check whether trainees who receive correct feedback are able to increase the feedback rate across runs where in controls this rate does not change. Taking the relative feedback rate per run as a measure of the NF learning process, we observed an increase in the EG across the runs but no change or even a decrease in the CG. The feedback rate increase i.e., the feedback rate difference between the transfer and the initial run, was significantly higher in the EG than in the CG (Mann-Whitney U test; $p < 0.01$).

First very preliminary results of a recent screening study performed by B. Derntl's group (RWTH Aachen, Germany) demonstrate the effect of LBA-feedback training on the behavioral and neurophysiological level (Radke et al., 2014). Ten right-handed subjects were asked to enhance the activity in their ACC (ROT: BA24/32) and another 10 subjects to enhance the activity in their Dorso-Lateral Prefrontal Cortex (DLPFC) (ROT:BA46). The NF-training consisted of 10 sessions with two consecutive runs per day, each consisting of 70 stimuli of a Stroop-test variant, the "Age-Stroop". The "Age-Stroop" items were portraits of people of a range of ages, annotated congruently or incongruently (50/50%) as "YOUNGER/MIDDLE/OLDER" and were presented for 3 s in inter-stimulus intervals of 4 +/− 1 s. Trainees had to judge the person's age as younger, middle or older by button press. While each item was presented, 58-channel DC-EEG epochs (equidistant montage, 125 s/s, corrected for eye movement artifacts and a 500 ms pre-stimulus baseline) were recorded and immediately analyzed by SMS-LORETA at three latency windows. In order to improve localization accuracy, individual head models (IHMs) were used. Whenever a generating source occurred in the ROT the gray feedback-frame turned green as a feedback signal, whereas its intensity corresponded to the strength of the detected source. This feedback was updated after each item according to the current outcome. The subjects were instructed to keep this frame green for as long and as intensely as possible. First results from the ACC-group ($N = 10$) showed a significant increase of the mean feedback-frequency during training ($p < 0.05$). Functional magnetic resonance tomography checks with this group before and after the training using an event-related design and separate sequences of Age-Stroop items and Emotional-Stroop items [portraits of fearful, happy and sad faces, annotated congruently or incongruently (50/50%) as "FEARFUL/HAPPY/SAD"; portrayed emotions had to be judged] yielded the following preliminary observations: (1) reaction times to Emotional-Stroop items were longer after the feedback training; and (2) a voxel-cluster in the mid-orbital gyrus extending to the ACC showed more activity with the Age-Stroop after than before the training—see **Figure 1**.

DISCUSSION

Although results only exist for these two preliminary studies to date, it seems clear that EEG-based feedback training of LBA is feasible. As the first study demonstrates this for a rather large ROT, the latter confirms it for a quite small area and moreover on a neurophysiological level using fMRI.

Most NF control studies focus on questions such as "does it work" or "how well does it work", but only a few are concerned with the changes in the trainees' brain specifically caused by NF. Therefore, also the specificity and efficacy of a particular NF protocol are predominantly determined by its therapeutic outcome described on the behavioral and introspective level, not by specific changes in particular brain structures—the "where and how it works" was rarely addressed. How inadequate such efficacy measures can be became apparent in the Liechti et al. (2012) study: unsuccessful tNF training (feedback of single voxel current densities) of ACC activity in children with ADHD was, nevertheless, accompanied by significant clinical improvement. Not control over ACC activity was efficient, but the training process on its own appeared to be an effective behavioral and cognitive treatment at least for ADHD patients. More generally, in case a consistent localizable and NF-mediated change in brain activity can be observed, we can assume that the clinical or behavioral NF outcome may be due to this change. Validation using fMRI is possible directly with SCP-NF as aimed at by Hinterberger et al. (2003). With frequency domain NF, fMRI checks allow only indirect proofs (e.g., Kinreich et al., 2012). In principle, however, such validations are essential in order to evaluate the extent to which NF acts directly on the neurophysiological level.

Compared with fMRI, sLORETA has its limits: (1) not all activity hot spots within the cerebral cortex at a particular time can be detected; (2) the spatial resolution is predominantly a matter of implementation and varies between 5–8 mm and; (3) the accuracy of localization depends on the source configuration, the precision of the head model used and the adequate capturing of the SPTs.

Concerning point (1) there is no room for improvement. As already been mentioned, full information on the 3-dimensional intra-cortical activity pattern is not accessible via 2-dimensional SPTs. Similarly, point (2)—resolution—can hardly be improved because sLORETA yields smooth solutions with attainment and optimization of source localization.

Accuracy (point 3), however, is improvable since the head model can be made more realistic and a sufficient number of

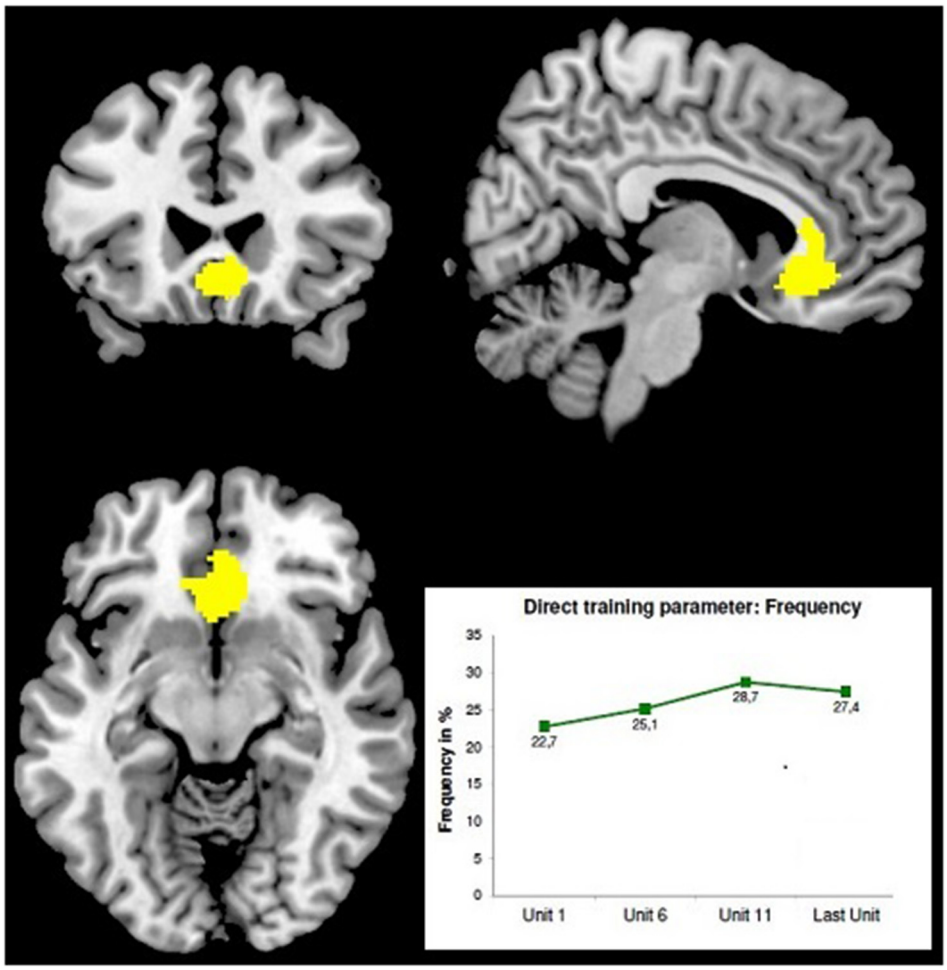

FIGURE 1 | Stronger BOLD-effect with the Age-Stroop after LBA-feedback training of the ACC [maximum at 6 24 −10; *z* = 7.77; FMRI-image thresholded at *T* = 4.86; MRT: 3T, TE = 28, TR = 2 s, 34 slices, 3.3 mm^3 voxel size] adapted from Radke et al. (2014). The minor displacement of the BOLD-maximum from the ROT may result from slightly inaccurate individual ROT-localization—IHMs were already used, but no localizer EPs. Bottom right: averaged learning curve of 10 subjects.

electrodes can be applied. Therefore the LBA-feedback procedure uses already IHMs and session-specific Cartesian coordinates of 58 electrodes.

Individual head models in current use are constructed by reshaping all parts of the standard BEM-based 3-shell head model including the Brodmann area (BA) map according to a trainee's individual electrode coordinates. Afterwards, the solution space within the newly shaped cerebral volume is readjusted and the appropriate lead field matrix recalculated. In this way, individual voxel-electrode distances are taken into account.

Utilizing localizer procedures to exactly locate ROTs can additionally improve the spatial accuracy of LBA-feedback training. For many cortical structures i.e., possible targets for LBA-feedback training, characteristic EP components are known which are generated in these structures, e.g., aSSR for A1 or ERN and FRN for the ACC. Pre-training EP acquisition and subsequent sLORETA source localization of the appropriate EP-components can indicate the center location for individual ROT definition. More generally, acquisition of several localizer EPs together, e.g., from V1, A1, ACC and DLPFC, may even enable realignment of BA maps within IHMs.

Since SPTs are the only source of information in this analysis it is extremely important to capture them accurately. Applying electrodes on the scalp means sampling in space, where the same regularities must be observed as in the time domain, but for spatial frequencies i.e., potential changes over distances. Studies have shown that about 60 electrodes equally distributed over the scalp are sufficient to avoid spatial aliasing (Srinivasan et al., 1998; Luu et al., 2001; Freeman et al., 2003). The drawback of spatial under-sampling is twofold: (a) higher spatial frequencies remain undetected; and (b) unidentifiable spatial aliasing frequencies will be generated, which cannot be filtered out.

Altogether, the application of IHMs, session-specific electrode coordinates and appropriate localizer methods makes EEG-based

LBA- and rtfMRI-feedback comparable, as far as spatial accuracy is concerned.

With NF applications, in general, deactivation of cortical structures is also of interest. However, EEG-based LBA-feedback as described above needs to be explored and evaluated in this respect—because initiating and pursuing NF-learning of targeted deactivation via inverse solutions based on time domain EEG signals is presumably more complex than learning of targeted activation. Since classical NF is dominated by using EEG frequency components/bands, frequency-domain LBA-feedback preferably is intended to become implemented. This way also targeted deactivation at least for some structures is achievable, for example, by enhancing local alpha activity.

CONCLUSION

With the development and publication of the EEG-based LBA-feedback procedure, real EEG-based local/targeted brain activity feedback training is available for the first time. Utilizing knowledge on the functional role of cortical structures and neuronal networks gathered by social, cognitive and affective neuroscience, this procedure is particularly suited to enable NF with enhanced physiological specificity. EEG-based LBA-feedback enables various *targeted* NF applications: in Neurology and neurological rehabilitation, as psychiatric/psychological treatments and as training to expand cognitive and behavioral abilities of healthy humans. In order to fine-tune all constituents of tNF, however, further intensive research is necessary.

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EEG spectral analysis of attention in ADHD: implications for neurofeedback training?

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Objective: In children with attention-deficit/hyperactivity disorder (ADHD), an increased theta/beta ratio in the resting EEG typically serves as a rationale to conduct theta/beta neurofeedback (NF) training. However, this finding is increasingly challenged. As NF may rather target an active than a passive state, we studied the EEG in a condition that requires attention.

Methods: In children with ADHD of the DSM-IV combined type (ADHD-C; *N* = 15) and of the predominantly inattentive type (ADHD-I; *N* = 9) and in typically developing children (*N* = 19), EEG spectral analysis was conducted for segments during the attention network test (ANT) without processing of stimuli and overt behavior. Frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes were included in the statistical analysis. To investigate if EEG spectral parameters are related to performance measures, correlation coefficients were calculated.

Results: Particularly in the ADHD-C group, higher theta and alpha activity was found with the most prominent effect in the upper-theta/lower-alpha (5.5–10.5 Hz) range. In the ADHD-I group, a significantly higher theta/beta ratio was observed at single electrodes (F3, Fz) and a tendency for a higher theta/beta ratio when considering all electrodes (large effect size). Higher 5.5–10.5 Hz activity was associated with higher reaction time variability with the effect most prominent in the ADHD-C group. A higher theta/beta ratio was associated with higher reaction times, particularly in the ADHD-I group.

Conclusions: (1) In an attention demanding period, children with ADHD are characterized by an underactivated state in the EEG with subtype-specific differences. (2) The functional relevance of related EEG parameters is indicated by associations with performance (reaction time) measures. (3) Findings provide a rationale for applying NF protocols targeting theta (and alpha) activity and the theta/beta ratio in subgroups of children with ADHD.

Keywords: neurofeedback, ADHD, EEG, spectral analysis, attention, brain-behavior-relationship, subtypes

INTRODUCTION

Theta/beta training belongs to the neurofeedback (NF) protocols which are frequently applied in children with ADHD; for review see Arns et al. (2014) and Gevensleben et al. (2014). In theta/beta training, the aim is to decrease theta activity and to increase activity in the beta band of the EEG or to decrease the theta/beta ratio with feedback being calculated typically from electrode Cz. In randomized controlled trials, it has been found to be superior in reducing the children's inattentive, hyperactive and impulsive behavior (medium effect sizes) compared to computerized attention training (Gevensleben et al., 2009a) and EMG biofeedback (Bakhshayesh et al., 2011).

Specificity of training effects is further supported by findings at the neurophysiological level (Gevensleben et al., 2009b). Higher baseline theta activity in the resting EEG (recorded in an eyes open condition) over centro-parietal regions was associated with a larger reduction of the severity of ADHD symptoms after theta/beta training and larger decreases of theta activity from pre- to post-training were accompanied by larger clinical improvements. These findings also indicate that it should be possible to derive EEG-based indication criteria for which children theta/beta training may be more appropriate.

As a rationale for applying theta/beta training in ADHD, authors typically referred to findings from resting EEG studies comparing children with ADHD to typically developing controls (see e.g., Heinrich et al., 2007).

RESTING EEG STUDIES IN ADHD

A series of resting EEG studies in ADHD (eyes open and eyes closed condition) have been conducted since the 1980s and

reviewed e.g., in Barry et al. (2003). Consistently, elevated levels of theta activity and reduced relative levels of beta and alpha activity (corresponding to increased theta/beta and theta/alpha ratios) were found compared to typically developing children. Slow activity was described to have a fronto-central distribution although group differences were most prominent over posterior regions (Banaschewski and Brandeis, 2007). Deviances appeared to be more prominent in the DSM-IV combined type of ADHD compared to the predominantly inattentive subtype.[1]

The theta/beta ratio measured at Cz was reported to discriminate reliably between children with ADHD and controls (classification rate: *ca.* 90%; Monastra et al., 1999; Snyder et al., 2008). On the other hand, Barry et al. (2003) stated EEG heterogeneity in ADHD and suggested to define EEG-based subtypes of ADHD.

Applying theta/beta training was thought to "normalize" the cortical slowing. However, recent studies question if the major part of children with ADHD are actually characterized by an increased theta/beta ratio in the resting EEG. Arns et al. (2013) conducted a meta-analysis studying theta/beta ratio in an eyes-open condition at electrode Cz. Including nine studies with about 1200 children and adolescents with ADHD and about 500 children without ADHD, they found a medium effect size of 0.62 (age range from 6 to 18 years). However, the authors argued that this number is misleading as *post hoc* analysis revealed a decreasing difference in theta/beta ratio across years due to an increasing theta/beta ratio for the non-ADHD (control) participants.

This point of view is further supported by two studies, which were published after this meta-analysis and did not find differences between children with ADHD and typically developing children in any frequency band considered (Liechti et al., 2013; Buyck and Wiersema, 2014). However, subdividing the ADHD group revealed increased theta/beta ratios in children and adults of the predominantly inattentive subtype in Buyck and Wiersema (2014) who analyzed EEG activity at midline electrodes.

EEG STUDIES IN ADHD DURING TASK PERFORMANCE

Interpreting NF as a neurobehavioral approach, training rather targets an active than a passive state (Gevensleben et al., submitted). For example, training may also comprise trials combined with tasks (e.g., reading, listening). In this respect, it appears to be more relevant to consider the EEG during task processing though it has to be kept in mind that the resting EEG does not only reflect a trait but also a state marker (Hagemann et al., 2005).

Up to now, EEG profiles in ADHD during cognitive tasks have less often been studied. Monastra et al. (1999) did not only study the theta/beta ratio in a resting condition at single electrode Cz but also while children were reading, listening and drawing. For all conditions, the ADHD group was characterized by increased theta/beta ratios. In El-Sayed et al. (2002), increased slow activity (mainly over frontal electrodes) was found especially during an attention (continuous performance) task but also during eyes-open resting condition.

Loo and Smalley (2008) investigated familiality of spectral EEG measures in ADHD during resting and cognitive activation (sustained attention task) conditions. Effects were clearly stronger for the activation compared to the resting conditions and did not show topographic specificity. Sibling correlations of 0.6–0.7 were obtained for the theta, alpha and beta band. Theta and alpha power were associated with task performance (reaction time variabililty, omission errors). So, not only theta and beta activity but also alpha activity should be considered when studying EEG activity during an activation condition in the context of ADHD. However, in our opinion, two points were not realized in an optimal way in the study of Loo and Smalley (2008). First, associations between EEG and performance measures were not controlled for potential developmental effects and, second, we would prefer to analyze EEG segments reflecting an attentive state without processing of task-related information (stimuli) as event-related EEG components interfere with the spontaneous activity.

Lazzaro et al. (2001) reported increased pre-stimulus theta activity in children with ADHD during an oddball task. Theta activity correlated inter alia with the latency of the event-related potential component P3 indexing attention.

INFORMATION ABOUT THE DATASET/OBJECTIVES OF THE STUDY

In the present case-control study, we conducted EEG spectral analysis in children with ADHD during an attentive state. For this analysis, we used a previously published dataset (Kratz et al., 2011). In Kratz et al. (2011), attentional processing was studied in children with ADHD during the attention network test (ANT). At the neural level (event-related potentials), deviant cue processing (reduced cue-P3) was the most prominent effect. The contingent negative variation (CNV)[2] reflecting inter alia cognitive preparation processes was not found to be smaller—probably due to the younger age of this sample compared to other studies (e.g., Albrecht et al., 2013). Differences between ADHD subtypes (combined type vs. predominantly inattentive type) could be observed.

Using this dataset for the present analysis allowed to consider segments during the ANT reflecting a state of activation/(tonic) alertness and free of stimulus processing. We expected that children with ADHD show increased theta activity and/or an increase theta/beta ratio across the scalp surface during an attentive state serving as a rationale to apply related protocols in NF training.

We were also interested in comparing DSM-IV subtypes of ADHD. In order to learn more about the functional significance of the spectral EEG parameters, we studied associations (correlations) between these spectral EEG parameters and performance measures (particularly reaction time measures).

MATERIALS AND METHODS

PARTICIPANTS

Fifteen children with ADHD of the combined type (ADHD-C; according to DSM-IV criteria), nine children with ADHD of the predominantly inattentive subtype (ADHD-I) and 19 typically

[1]In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000), three subtypes of ADHD (combined type, predominantly inattentive type, predominantly hyperactive-impulsive type) are distinguished reflecting the heterogeneity of the disorder. In clinical practice, the combined type appears to be most common. Besides the combined type, research focuses also on the predominantly inattentive type.

[2]A reduced CNV is typically considered as a rationale to apply training of slow cortical potentials (SCPs) in children with ADHD (Heinrich et al., 2007).

developing children were included in the study. Children had to be aged 8–11 years and to have a full-scale IQ of at least 80. All children had normal or corrected-to-normal vision. Adequate task performance in the ANT and sufficient EEG data quality was also necessary to be included in this study (for details see below). The three groups (ADHD-C, ADHD-I, controls) were comparable regarding age and sex (Demographic and clinical variables of the sample are summarized in **Table 1**). IQ was significantly lower in the ADHD-I group but IQ had no significant influence on the group-specific results as tested by comparing the ADHD-I group to a subgroup of typically developing children with comparable IQ; see also Kratz et al. (2011).

Patients were either recruited from a child and adolescent psychiatric practice in Bamberg (Germany) and took part in a medication trial (Kratz et al., 2012) or were recruited via the outpatient department of the Department of Child and Adolescent Mental Health at the University Hospital of Erlangen and participated in a NF trial (Gevensleben et al., 2009a). Baseline measurements (conducted before starting treatment) were considered for the present analysis. Diagnostics comprised a clinical interview conducted by a child and adolescent psychiatrist or a clinical psychologist. ADHD diagnoses were confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD (Döpfner and Lehmkuhl, 2000). Patients had no comorbid diagnoses other than oppositional defiant disorder, emotional disorder and dyslexia. All children with ADHD included in this study were drug-naive. Typically developing children were recruited from the personal environment of employees of the clinic. For none of the children of the control group, parents reported a psychiatric or neurological disorder.

For all children, the German ADHD rating scale (FBB-HKS: Döpfner and Lehmkuhl, 2000) was assessed (filled out by parents). The FBB-HKS is a 20-item questionnaire related to the DSM-IV and ICD-10 criteria for ADHD (nine inattention items, seven hyperactivity items, four impulsivity items). Severity of each item is rated on a scale from 0 to 3. The questionnaire provides a total score (mean value of all 20 items) as well as subscores for inattention and hyperactivity/impulsivity. For the typically developing children included in the study, FBB-HKS scores (total score and subscales) were not more than one standard deviation above normative means. Control and ADHD groups differed on all FBB-HKS scales ($F_{(2,40)} > 46.9$; $p < 0.001$). For the two ADHD groups (ADHD-C vs. ADHD-I), the FBB-HKS total score ($t_{(22)} = 1.38$, n.s.) and the score for the inattention subscale ($t_{(22)} = -0.20$, n.s.) were comparable. However, the score for the hyperactivity/impulsivity subscale was higher in the ADHD-C group ($t_{(21)} = 2.45$; $p < 0.05$).

The study, which was approved by the Ethics Committee of the Medical Faculty of the University of Erlangen–Nuremberg, was conducted in accordance with the Declaration of Helsinki. Children gave their assent and parents provided written informed consent.

PROCEDURE AND TASK

In the testing session, children sat on a comfortable chair in front of a computer monitor (viewing distance: 72 cm). During EEG preparation, the children could watch age-appropriate films. The ANT, which consisted of four blocks of 48 trials each, lasted about 15 min (including short breaks between the task blocks). During the test brain electrical activity was recorded. The children received standardized instructions before performing a practice block of 24 trials. After each task block, a summary of the task performance was shown on the screen.

Children were instructed to "feed" a hungry fish that would appear above or below a fixation cross. If the fish pointed to the right (resp. left) side, the children had to press the right (resp. left) mouse button in order to feed the fish. This target fish was the center fish in a row of five fish with the flanking fish either looking in the same direction (congruent condition) or in the opposite direction (incongruent condition).

One of three cue conditions (equal probability) preceded the presentation of the fish: in the NeutralCue condition, an asterisk

Table 1 | Sample characteristics and performance data of the attention network test.

	Children with ADHD		Controls (*N* = 19)	Statistics
	ADHD-C (*N* = 15)	ADHD-I (*N* = 9)		
Age (months)	117.8 ± 12.0	112.6 ± 12.6	122.0 ± 11.9	$F_{(2,40)} = 1.9$, n.s.
IQ	114.3 ± 11.3	102.7 ± 11.6	114.7 ± 11.1	$F_{(2,40)} = 4.4$, p = 0.02
Sex (m/f)	10/5	8/1	15/4	$\chi^2 = 1.65$, n.s.
German ADHD rating scale (FBB-HKS)				
Total score	1.56 ± 0.37	1.34 ± 0.38	0.34 ± 0.22	$F_{(2,40)} = 67.9$, $p < 0.001$
Inattention	1.77 ± 0.44	1.81 ± 0.47	0.50 ± 0.33	$F_{(2,40)} = 52.4$, $p < 0.001$
Hyperactivity/impulsivity	1.42 ± 0.48	0.96 ± 0.38	0.21 ± 0.20	$F_{(2,40)} = 46.9$, $p < 0.001$
Associated disorders				
Oppositional defiant disorder	2	0	–	
Emotional disorder	1	1	–	
Dyslexia	1	2	–	
Attention network test				
Hits (correct responses)	171.5 ± 19.4	181.0 ± 5.8	175.1 ± 17.2	$F_{(2,40)} = 0.9$, n.s.
Reaction times—median (ms)	535.0 ± 99.7	643.3 ± 122.9	508.3 ± 70.3	$F_{(2,40)} = 6.5$, $p = 0.004$
Reaction time variability (ms)	142.6 ± 39.2	160.5 ± 48.5	112.0 ± 29.0	$F_{(2,40)} = 6.0$, $p = 0.005$

at the center of the screen indicated that the target fish was about to appear soon. In the SpatialCue condition, an asterisk was presented at the location of the target fish, indicating not only that the target was about to appear soon but also its location on the screen. In the NoCue condition, the fish were presented without a cue stimulus.

A schematic illustration of the ANT as applied in the present study, including technical details is presented in **Figure 1**. The test was realized in Presentation (Neurobehavioral Systems, Albany, CA, USA).

EEG RECORDING AND PREPROCESSING

A Brainamp recording system (Brainamp standard amplifier, Brain Products, Munich, Germany) was used. Brain electrical activity was recorded from 23 sintered Ag/AgCl electrodes (10/20 system; Fpz, Oz, mastoids). Positions for reference and ground electrode were FCz and CPz, respectively. Vertical and horizontal electrooculogram was recorded from electrodes placed above and below the right eye and at the outer canthi. A sampling rate of 500 Hz was used. Filter bandwidth at recording was 0.016–120 Hz. Impedances were kept below 20 kΩ.

For preprocessing and data analysis, the VisionAnalyzer software (Brain Products, Gilching, Germany) was used. After applying a 50 Hz notch filter and bandpass filtering (0.05–30 Hz, 24 dB/oct Butterworth filters), eye movement artifacts were corrected using independent component analysis (ICA, Jung et al., 2000). Signals were re-referenced to linked-mastoids. If amplitudes exceeded ±100 μV at any electrode, a segment of −300 to +700 ms around this artifact was excluded from further analyses.

EEG spectral analysis was conducted for NoCue segments of 1.5 s length, i.e., for segments before the onset of flanker stimuli which were not preceded by a cue stimulus. These were the segments with the longest "pure" EEG period without processing of cue or target stimuli and correspond to an attentive state.

For each child, at least 20 artefact-free segments (followed by a correct response to the target stimulus) had to be available. The number of segments without artefacts were slightly but not significantly smaller in the ADHD groups (control: 47.2 ± 9.6; ADHD-C: 44.3 ± 9.8; ADHD-I: 38.1 ± 14.6; $F_{(2,40)} = 2.13$, $p = 0.13$).

DATA ANALYSIS

The number of hits, median of reaction times and reaction time variability were determined. ANT-specific performance measures (alerting score, orienting score and conflict score; Fan et al., 2002) had not been significantly different for ADHD groups and control group in Kratz et al. (2011). So, for simplicity, they will be omitted in this manuscript. Reaction time measures were based on trials

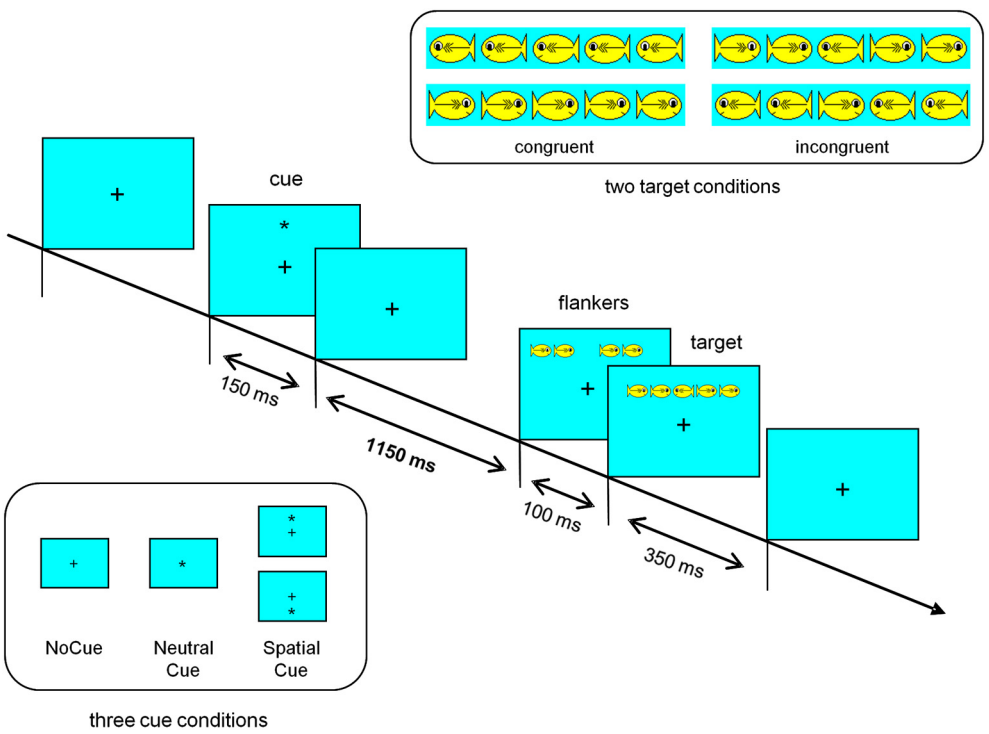

FIGURE 1 | Schematic illustration of the attention network test (ANT) as applied in our study. A fixation cross located on the center of the computer screen was shown during the complete test. The row of hungry fish appeared above or below the fixation cross (about 1°). The target fish, i.e., the center fish, was visible for 350 ms. Presentation of the flanking fish started 100 ms before the center fish appeared. Cue stimuli were visible for 150 ms, starting 1400 ms before the target stimulus (fish). A cue stimuli was always followed by a target stimulus. In comparison to the original child version of the ANT (Rueda et al., 2004), a longer interval between cue and target stimulus was used (1400 ms instead of 600 ms) to elicit a contingent negative variation. Each fish subtended 1.6° of visual angle and the contours of adjacent fish were separated by 0.21°. The intertrial interval varied randomly between 3.5 and 5.0 s.

with correct responses. Only trials with reaction times between 200 and 1500 ms after target stimulus onset were included in the analysis.

For each NoCue trial, a voltage density spectrum was computed after applying a Hanning window and these spectra were averaged then. From the averaged spectra, voltage values for theta (4–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–20 Hz) band as well as the theta/beta ratio were calculated at different electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). In **Figure 2**, the grand average spectra for control, ADHD-C and ADHD-I groups are depicted. Based on visual inspection, the largest differences between the groups seem to occur within an upper-theta/lower-alpha (5.5–10.5 Hz) band. Therefore, we decided to consider this band in addition to the traditional EEG bands.

STATISTICAL ANALYSIS

Performance data (hits, reaction time measures) were analyzed using a one-way ANOVA with between-subject factor GROUP (control, ADHD-C, ADHD-I). *t*-tests were applied for *post hoc* analysis (pairwise comparisons of two groups) using Bonferroni-Holm correction to control for multiple comparisons.

For the different EEG frequency bands, repeated-measure ANOVAs were computed with between-subject factor GROUP and repeated-measurement (electrode) factors Y (frontal [F3, Fz, F4], central [C3, Cz, C4], parietal [P3, Pz, P4]) and X (left [F3, C3, P3], midline [Fz, Cz, Pz], right [F4, C4, P4]) to test potential topography/laterality effects. *Post hoc* analysis also comprised correction for multiple comparisons (Bonferroni-Holm). Corrected *p*-values are reported.

Associations between EEG spectral parameters and performance measures were studied focusing on those EEG measures for which largest group-specific effects were obtained in the before-mentioned analysis. We controlled for age-related effects. However, as the portion of 8 year-old children was higher in the ADHD groups, controlling/correcting for age-related changes by considering the complete sample would lead to an overestimation of age-related changes at the cost of group-related effects. Instead, we decided to correct for age-related changes in the complete sample based on the regression coefficient of the control group. Pearson's correlation coefficients were calculated for potentially age-corrected measures. If significant correlations were found for the complete sample,

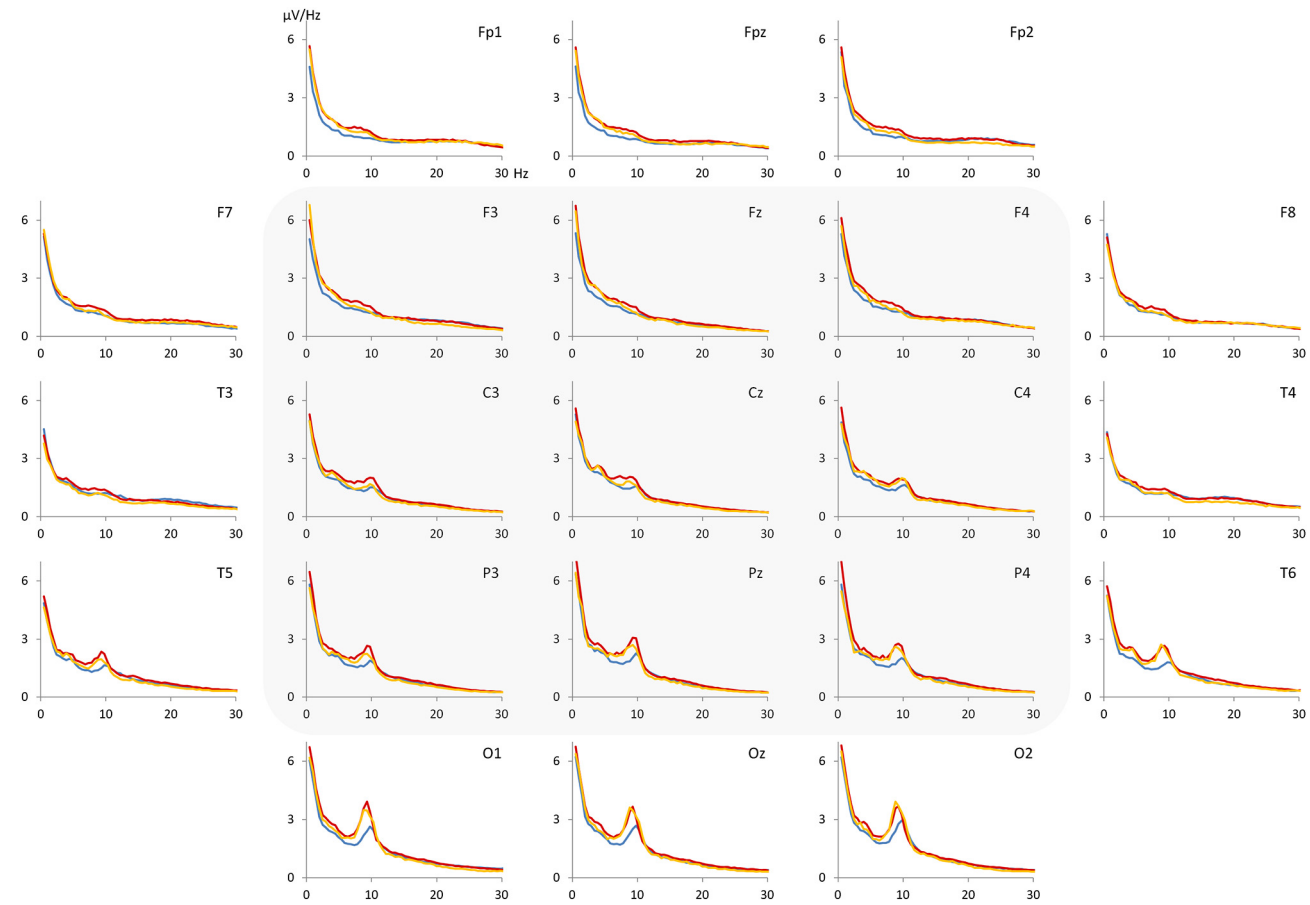

FIGURE 2 | Grand average spectra (voltage density) for control group (blue), ADHD-C group (red) and ADHD-I group (orange). The most pronounced differences between the groups appear to be in the range of 5.5–10.5 Hz. Electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 were considered for statistical analysis.

Table 2 | EEG measures and statistical results.

	Children with ADHD		Controls (*N* = 19)	Statistics (repeated-measure ANOVAs)
	ADHS-C (*N* = 15)	ADHS-I (*N* = 9)		
Theta (3.5–7.5 Hz)	8.73 ± 1.72	8.22 ± 1.65	7.37 ± 1.14	G: $F_{(2,40)}$ = 3.7, p = 0.034; part. η^2 = 0.16 X: $F_{(2,80)}$ = 67.3, p < 0.001; part. η^2 = 0.63 Y: $F_{(2,80)}$ = 20.4, p < 0.001; part. η^2 = 0.34 X*Y: $F_{(4,160)}$ = 4.9, p = 0.002; part. η^2 = 0.11
Alpha (7.5–12.5 Hz)	8.92 ± 1.93	7.85 ± 1.40	7.16 ± 1.83	G: $F_{(2,40)}$ = 4.0, p = 0.026; part. η^2 = 0.17 X: $F_{(2,80)}$ = 6.1, p = 0.004; part. η^2 = 0.13 Y: $F_{(2,80)}$ = 80.4, p < 0.001; part. η^2 = 0.67 X*Y: $F_{(4,160)}$ = 15.2, p < 0.001; part. η^2 = 0.28
Upper-theta/lower alpha (5.5–10.5 Hz)	9.96 ± 2.34	9.01 ± 1.32	7.78 ± 1.42	G: $F_{(2,40)}$ = 6.3, p = 0.004; part. η^2 = 0.24 X: $F_{(2,80)}$ = 26.1, p < 0.001; part. η^2 = 0.40 Y: $F_{(2,80)}$ = 61.6, p < 0.001; part. η^2 = 0.61 X*Y: $F_{(4,160)}$ = 11.1, p < 0.001; part. η^2 = 0.22
Beta (12.5–20 Hz)	6.46 ± 1.18	5.55 ± 1.37	5.98 ± 1.40	G: $F_{(2,40)}$ = 1.4, n.s.; part. η^2 = 0.07 X: $F_{(2,80)}$ = 74.1, p < 0.001; part. η^2 = 0.65 Y: $F_{(2,80)}$ = 21.6, p < 0.001; part. η^2 = 0.35 X*Y: $F_{(4,160)}$ = 16.5, p < 0.001; part. η^2 = 0.29
Theta/beta ratio	1.40 ± 0.29	1.55 ± 0.39	1.30 ± 0.27	G: $F_{(2,40)}$ = 2.1, n.s.; part. η^2 = 0.09 X: $F_{(2,80)}$ = 184.8, p < 0.001; part. η^2 = 0.82 Y: $F_{(2,80)}$ = 23.3, p < 0.001; part. η^2 = 0.37 X*Y: $F_{(4,160)}$ = 11.0, p < 0.001; part. η^2 = 0.22

For control and ADHD groups, the group's mean (for the average regarding the different EEG frequency bands over frontal, central and parietal electrodes considered in the ANOVAs) ± SD is presented. Unit (except theta/beta ratio): μV. For the repeated-measure ANOVAs, the results obtained for the between-subject factor Group (G), the within-subjects factors X (left, midline, right) and Y (frontal, central, parietal) and their interaction are provided.

we also tested ADHD groups separately to exclude spurious correlations.

IBM SPSS Statistics (Version 20.0) was used for statistical analysis.

RESULTS

PERFORMANCE MEASURES

Results of performance measures are summarized in **Table 1**. Reaction time variability was significantly higher in the two ADHD groups compared to the control group (control vs. ADHD-I: $t_{(26)} = -3.32$; p (corr.) = 0.009; control vs. ADHD-C: $t_{(32)} = -2.61$; p (corr.) = 0.03). For the median of reaction times, a GROUP effect was obtained due to higher reaction times in the ADHD-I group in comparison to the control group (control vs. ADHS-I: $t_{(26)} = -3.71$; p (corr.) = 0.003) as well as the ADHD-C group (ADHD-C vs. ADHD-I: $t_{(22)} = -2.36$; p (corr.) = 0.05).

SPECTRAL EEG PARAMETERS

Results of the ANOVAs for the different frequency bands are summarized in **Table 2**. For all frequency bands considered, the repeated-measure ANOVAs revealed (highly) significant effects for the within-subject factors X, Y and their interaction X*Y related to the topography of the EEG activity in the different frequency bands. Theta, alpha and 5.5–10.5 Hz activity were highest at electrode Pz (parietal, midline); see also **Figure 3**. The highest beta activity was measured at left and right frontal electrodes (F3 and F4). The theta/beta ratio had its maximum at electrode Cz. No significant interaction effect containing the factor Group was obtained, i.e., topography did not differ significantly between the groups.

For theta activity, alpha activity and particularly upper-theta/lower-alpha (5.5–10.5 Hz) activity, significant group main effects indicated higher activity in the ADHD groups. *Post hoc* analysis revealed that 5.5–10.5 Hz activity was higher particularly in the ADHD-C group (control vs. ADHD-C: $t_{(32)} = -3.35$; p (corr.) = 0.006) and to a smaller extent in the ADHD-I extent in the ADHD-I group (control vs. ADHD-I: $t_{(26)} = -2.17$; p (corr.) = 0.08, p (uncorr.) = 0.04).

No significant main effect for the theta/beta ratio was found. However, a medium effect size (part. $\eta^2 = 0.09$) may indicate some effect which did not turn out to be significant due to the limited sample size. So, we decided to look at the theta/beta ratio in more detail in an exploratory way. At least a tendency for a higher theta/beta ratio (averaged over the nine electrodes) in the ADHD-I group (control vs. ADHD-I: $t_{(26)} = -2.0$; $p = 0.057$; Cohen's $d = 0.8$) was obtained whereas no effects were observed for the ADHD-C group (control vs. ADHD-C: $t_{(32)} = -1.02$; n.s.). When group at single electrodes, significant effects were found for electrodes F3 and Fz (control vs. ADHD-I: $t_{(26)} \leq -2.28$; $p \leq 0.03$).

ASSOCIATIONS BETWEEN SPECTRAL EEG PARAMETERS AND PERFORMANCE MEASURES

As only GROUP main effects were found in the ANOVAs, we considered the average of all electrodes for the correlational analysis. A significant correlation was found between the activity in the 5.5–10.5 Hz band (averaged over frontal, central and parietal electrodes) and reaction time variability

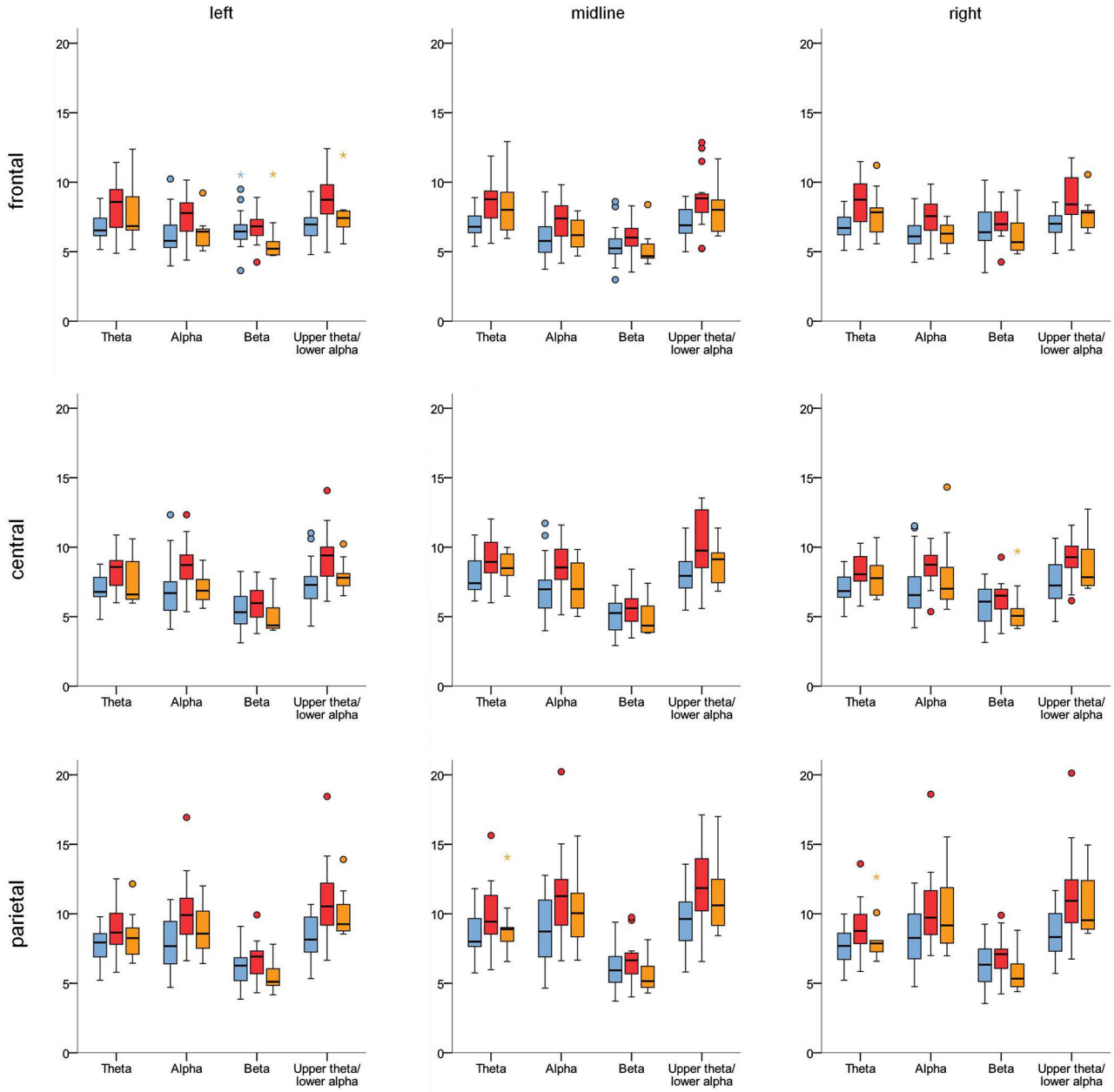

FIGURE 3 | Boxplots illustrating the topography of EEG activity in the different frequency bands for control group (blue), ADHD-C group (red) and ADHD-I group (orange). Unit: μV.

(r = 0.34, p = 0.025): Higher activity in the 5.5–10.5 Hz band was associated with higher reaction time variability (see **Figure 4A**). For the ADHD-C group, the correlation coefficient was 0.48.

A significant correlation was also obtained between the theta/beta ratio (averaged over frontal, central and parietal leads) and the median of reaction times (r = 0.42, p = 0.005); see **Figure 4B**. The higher the theta/beta ratio was, the longer reaction times were. This effect was most prominent in the ADHD-I group (r = 0.54).

Hence, significant associations were found for those frequency bands and performance (reaction time) measures with deviations in the ADHD groups. It has to be noted that these correlations did not reach statistical significance in the respective ADHD group due to the small group sizes.

DISCUSSION

In the present study, we conducted EEG spectral analysis during an attention demanding period in children with ADHD (compared to typically developing controls). Deviant EEG patterns

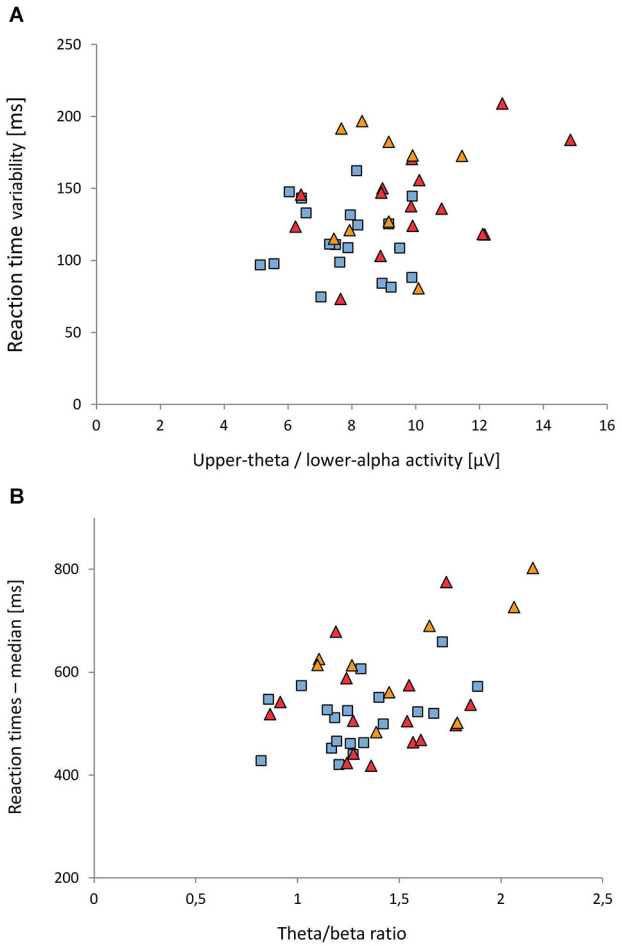

FIGURE 4 | Associations between EEG and reaction time measures. **(A)** Upper-theta/lower-alpha (5.5–10.5 Hz) activity vs. reaction time variability. **(B)** Theta/beta ratio vs. median of reaction times. Reaction time measures were adjusted for developmental effects (for details see text). Control group: blue rectangles; ADHD-C group: red triangles; ADHD-I: orange triangles.

were obtained with subtype-specific differences between the DSM-IV combined type and the predominantly inattentive subtype.

SPECTRAL EEG MEASURES DURING AN ATTENTIVE STATE IN ADHD (SUBTYPES)

In contrast to recent resting-EEG studies (e.g., Ogrim et al., 2012; Liechti et al., 2013), significant differences related to the theta band and the alpha band were obtained between children with ADHD and typically developing children: activity in these frequency band was significantly larger in children with ADHD. In the ADHD-C group, effects were most prominent when considering the 5.5–10.5 Hz (upper-theta/lower-alpha) band. Global statistical analysis did not reveal a significant group effect for the theta/beta ratio, i.e., the major part of the children with ADHD was not characterized by an increased theta/beta ratio. On the other hand, a large effect size for the comparison of control and ADHD-I group may indicate an increased theta/beta ratio in children of the predominantly inattentive subtype comparable to the findings of Buyck and Wiersema (2014) obtained in the resting EEG. However, this finding is limited by the rather small size of our ADHD-I group.

As inattention scores of the German ADHD rating scale were comparable for ADHD-C group and ADHD-I group we argue that the differential pattern does not reflect different severity of inattention symptoms but rather suggest that there are different neural mechanisms accounting for attentional dysfunctions in ADHD subtypes. In Heinrich et al. (submitted), we had already reported different distributions of cue-P3 single trial amplitudes for the two ADHD groups further strengthening this point of view.

ASSOCIATIONS BETWEEN SPECTRAL EEG PARAMETERS AND REACTION TIME MEASURES

Interestingly, significant (positive) correlations between those spectral EEG parameters and reaction time measures (5.5–10.5 Hz activity and reaction time variability; theta/beta ratio and median of reaction times) were found for which differences between the ADHD groups and the control group had been obtained. These associations suggest a functional relevance of the EEG parameters, particularly in the context of ADHD: a suboptimal neural state at stimulus presentation results in impaired performance. As we controlled for age effects and also considered the ADHD groups separately, it seems rather unlikely that the correlations obtained for our data reflect spurious correlations.

Loo and Smalley (2008) had also reported a positive correlation between reaction time variability and activity in the theta and alpha band during an attention (continuous performance) test. Increased reaction time variability is a robust finding in children with ADHD with medium to large effect sizes being reported (meta-analysis for example in Kofler et al., 2013: Hedges' $g = 0.76$). Increased activity in the upper-theta/lower-alpha band, which may be interpreted as an underactivated neural state, could reflect a neural mechanism underlying increased reaction time variability in ADHD besides top-down control and motor preparation processes (Karalunas et al., 2014). It seems unlikely that slower reaction times in the ADHD-I group of our sample are mainly due to very slow reaction times in a few trials but they rather reflect a generally slower processing/response style. Findings indicate that this slowing may be related to a higher theta/beta ratio. The differential associations regarding ADHD-C and ADHD-I groups further support the notion of distinct neural mechanisms underlying attentional dysfunctions in ADHD subtypes.

POTENTIAL IMPLICATIONS FOR NEUROFEEDBACK TRAINING IN ADHD

NF may be interpreted as an approach to gain self-control over a certain aspect of neural activity associated with a specific cognitive or emotional state (Gevensleben et al., submitted). In this respect, findings of the present study may have the following implications for NF training in ADHD.

In children with ADHD of the combined type, an upper-theta/lower-alpha (5.5–10.5 Hz) protocol associated with an

attentive state may be more effective than theta/beta training. It will have to be studied if indication criteria for the use of a specific protocol based on (inter alia) EEG characteristics at pre-training can be developed. As theta activity in the resting EEG at pre-training was found to be a predictor for the effects of theta/beta training (Gevensleben et al., 2009b), this seems to be a realistic task.

Up to now, only a single EEG channel is typically used to calculate feedback information in EEG NF training. For theta/beta training in ADHD, most often electrode Cz is considered. In our data, increased upper-theta/lower-alpha activity in the ADHD-C group and a higher theta/beta ratio in the ADHD-I group were not topographically specific, i.e., they were not restricted to/particularly pronounced at a certain electrode. Looking at single electrodes, effects at electrode Cz appeared rather smaller than larger compared to frontal, electrodes (F3, Fz).

It has to be taken into consideration that frontal midline theta (associated with working memory and cognitive control processes; Jensen and Tesche, 2002; Enriquez-Geppert et al., 2014) could interfere with the more generalized theta pattern addressed for example in theta/beta training if feedback information is calculated from Cz only. So, in our opinion, a more robust/more specific feedback signal may be obtained if not a single channel but a combination of several electrodes is used. If NF training does not target a topographically specific EEG pattern, the average of a grid of distributed electrodes may be preferable.

NF training trials may also be combined with attention tasks to facilitate training effects at the performance level: depending on the protocol applied, faster or less variable reaction times may be achieved. Regarding other tasks (e.g., reading, listening), it will have to be tested whether refined frequency bands and feedback parameters, respectively, may also be more characteristic for children with ADHD.

LIMITATIONS OF OUR STUDY

Findings are limited by the generally small sample size. However, we'd see sample size more critical if findings had not turned out to be significant. Large effect sizes were obtained and effects were not just due to outliers suggesting clear differences in the distribution of control and ADHD groups. In any case, larger samples will have to be studied to see if results are confirmed and to what extend EEG-based subtypes can be found.

We could not compare resting and active EEG conditions directly. Thus, it cannot be excluded that corresponding effect sizes could have also been found in the resting EEG of our sample. However, in our opinion, our findings complement/are compatible with results of recent studies that either report no significant global differences in recent resting EEG studies (e.g., Liechti et al., 2013; Buyck and Wiersema, 2014) and/or more pronounced effects in active compared to resting conditions (e.g., Loo and Smalley, 2008).

CONCLUSIONS

During an attentive state, children with ADHD are characterized by an underactivated state in the EEG with subtype-specific differences. Whereas the most prominent effect was obtained for the upper-theta/lower alpha (5.5–10.5 Hz) range in children of the combined type, hints for an increased theta/beta ratio were found in children of the predominantly inattentive subtype. The functional relevance of these EEG parameters was indicated by associations with reaction time measures, which were pronounced most in the ADHD groups. Findings may provide a rationale for applying NF training protocols targeting theta activity and theta/beta ratio in subgroups of children with ADHD to achieve an attentive state. In this respect, it will be interesting if indication criteria for a specific protocol in an individual child can be developed which can be applied in clinical practice.

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Neurofeedback of slow cortical potentials: neural mechanisms and feasibility of a placebo-controlled design in healthy adults

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To elucidate basic mechanisms underlying neurofeedback we investigated neural mechanisms of training of slow cortical potentials (SCPs) by considering EEG- and fMRI. Additionally, we analyzed the feasibility of a double-blind, placebo-controlled design in NF research based on regulation performance during treatment sessions and self-assessment of the participants. Twenty healthy adults participated in 16 sessions of SCPs training: 9 participants received regular SCP training, 11 participants received sham feedback. At three time points (pre, intermediate, post) fMRI and EEG/ERP-measurements were conducted during a continuous performance test (CPT). Performance-data during the sessions (regulation performance) in the treatment group and the placebo group were analyzed. Analysis of EEG-activity revealed in the SCP group a strong enhancement of the CNV (electrode Cz) at the intermediate assessment, followed by a decrease back to baseline at the post-treatment assessment. In contrast, in the placebo group a continuous but smaller increase of the CNV could be obtained from pre to post assessment. The increase of the CNV in the SCP group at intermediate testing was superior to the enhancement in the placebo group. The changes of the CNV were accompanied by a continuous improvement in the test performance of the CPT from pre to intermediate to post assessment comparable in both groups. The change of the CNV in the SCP group is interpreted as an indicator of neural plasticity and efficiency while an increase of the CNV in the placebo group might reflect learning and improved timing due to the frequent task repetition. In the fMRI analysis evidence was obtained for neuronal plasticity. After regular SCP neurofeedback activation in the posterior parietal cortex decreased from the pre- to the intermediate measurement and increased again in the post measurement, inversely following the U-shaped increase and decrease of the tCNV EEG amplitude in the SCP-trained group. Furthermore, we found a localized increase of activity in the anterior cingulate cortex (ACC). Analyses of the estimation of treatment assignment by the participants indicate feasibility of blinding. Participants could not assess treatment assignment confidently. Participants of the SCP-group improved regulation capability during treatment sessions (in contrast to the participants of the placebo-group), although regulation capability appeared to be instable, presumably due to diminished confidence in the training (SCP- or sham-training). Our results indicate that SCP training in healthy adults might lead to functional changes in neuronal circuits serving cognitive preparation even after a limited number of sessions.

Keywords: neurofeedback, EEG-biofeedback, SCP training, fMRI, CNV, anterior cingulate cortex

INTRODUCTION

Local cortical oscillations shape sensory, motor, and cognitive processes (Rothenberger, 2009). Such changes in neuroelectric activity are assumed to indicate the excitability of neuronal networks and have gained increasing interest in the investigation of mental functioning (e.g., executive functions, especially

attention research, (Banaschewski and Brandeis, 2007; Calderone et al., 2014) as well as mental and emotional malfunctioning (Dennis, 2010; Henderson, 2010). In the search for neurophysiological conditions of (child- and adolescent) mental disorders different neuro-psychiatric disorders came into focus (Banaschewski and Brandeis, 2007). In first line, attention deficit/hyperactivity disorder (ADHD), epilepsy, and tic-/tourette disorder appeared to be associated with dysfunctions in the regulation of cortical excitation (Heinrich et al., 2007). Especially in children with ADHD, investigation of brain activity pattern do not only enrich the knowledge of neurophysiological concomitants of the disorder (for a review see Albrecht et al., under review) but built the theoretical background for neurofeedback as an innovative treatment tool, emerging from neurophysiological theory to clinical application (Pine, 2009). Recent randomized controlled trials document efficacy and clinical significance of neurofeedback in children with ADHD (Arns et al., 2014). Within a pool of different neurofeedback protocols applied in children with ADHD, SCP-training currently might be considered the best validated approach in this field (Mayer et al., 2013). However, mechanisms of action are neither on the neurobiological nor on the cognitive-behavioral level elucidated sufficiently (Gevensleben et al., 2014). A combination of EEG- and fMRI methodology within the scope of this double-blind, placebo-controlled study should give new insights in neurobiological and psychological mechanisms of SCP neurofeedback.

Slow cortical potentials (SCPs) are shifts in the cortical electrical activity lasting from several hundred milliseconds to several seconds. SCP might be externally triggered or self-induced. Their moderating impact on information processing has been demonstrated in numerous studies (Bauer and Nirnberger, 1981; Birbaumer et al., 1992; Schupp et al., 1994). Negative SCPs are assumed to reflect lowered thresholds for the excitation of underlying neuronal structures, leading to facilitation of processing e.g., during states of behavioral or cognitive preparation. Empirical evidence indicates e. g. accelerated reaction times during task performance (Lutzenberger et al., 1982; Rockstroh et al., 1982). Positive SCPs indicate reduction of cortical excitation of the underlying neural structures (e.g., during behavioral inhibition; Birbaumer et al., 1990), resulting e.g., in an attenuated startle reflex (Schupp et al., 1994).

The generation of a contingent negative variation (CNV), a characteristic negative SCP representing anticipatory attention, motivation, and motor preparation (Walter et al., 1964; Fan et al., 2007) relies on the activity of a thalamo-cortical-striatal circuit encompassing the prefrontal cortex (Rockstroh et al., 1993; Rosahl and Knight, 1995) primary and supplementary motor areas (Ioannides et al., 1994), posterior parietal cortex (Durstewitz, 2004) anterior cingulate cortex (ACC) and thalamic nuclei (Nagai et al., 2004). However, distinguishing early (initial, iCNV) and late (terminal, tCNV) components, different cortical and subcortical structures are assumed to be involved. This is indicated by differential source distributions for iCNV and tCNV in previous EEG studies. While the iCNV seems strongest at bilateral frontal electrodes, the tCNV appears to unfold maximum activity at the vertex (Birbaumer et al., 1990). Further evidence results from a previous trial of our laboratories. Using a continuous performance test (CPT) with a long interstimulus-interval (ISI) of 6 s, we found evidence for distinct cortical and subcortical brain regions associated with early and late components of the CNV (Lütcke et al., 2009). The late CNV mainly appeared to be associated with activations in the frontal cortex, dorsal ACC and thalamus and increased activity in midbrain dopaminergic nuclei (very likely corresponding to the substantia nigra). The initial CNV was localized mainly in motor and premotor cortical areas and the caudate nucleus.

Regulation of SCPs appears to be attenuated in children with ADHD, as indicated by a reduced CNV during CPT tasks (Banaschewski et al., 2003; Banaschewski and Brandeis, 2007). Furthermore, several controlled trials demonstrate that SCP training increases regulation of cortical excitability in terms of an enhanced post-treatment CNV and reduces ADHD symptomatology (Heinrich et al., 2004; Drechsler et al., 2007; Doehnert et al., 2008; Gevensleben et al., 2009, 2010; Mayer et al., 2013). Concerning children with ADHD, a more pronounced CNV seems to predict better outcome of a SCP training (Wangler et al., 2011).

Beyond neurobiological considerations, psychological (cognitive behavioral) operators or mechanisms of neurofeedback are hypothesized, but not empirical validated. Generation of SCP regulation capability (learning of neuro-regulation of SCPs) is assumed to rely on operant learning mechanisms, sharing pathways with skill motor acquisition (Strehl, this issue; Birbaumer et al., 2013). In how far effort, attributions, motivation or personality factors contribute to the outcome of SCP treatment is not sufficiently elucidated, although there is some evidence that there is an impact of such mental pattern (Gevensleben et al., 2014). It will take several trials to investigate the selective influence of distinct cognitive-behavioral (and emotional?) variables on the efficacy of different neurofeedback protocols. In the short run it seems important to get a rough idea of the impact of e. g. attributions (expectations, individual evaluations) on the course of neurofeedback training in order to distinguish valid from invalid strategies in the evaluation of treatment efficacy of NF. There is "pestering" request for double-blind, placebo-controlled trials, although the proof of feasibility in neurofeedback research is still weak, especially in children with ADHD. The NF-procedures (protocols and applications) used in those placebo-NF trials have been criticized for several reasons (inter alia poor treatment fidelity) and may account for the contradictory outcome (Arns et al., 2014; Gevensleben et al., 2014). Among other shortcomings of previous double-blind, placebo-controlled trials, none of the previous trials in children with ADHD could demonstrate validity of the treatment design in terms of "learning of neuro-regulation". Acquisition of regulation capability during the treatment sessions is considered an indispensable prerequisite for a positive outcome of training. However, no previous placebo-trial could demonstrate learning. Contrariwise the latest placebo-trial in children with ADHD asserted that participant did not learn to regulate the targeted EEG parameters during treatment sessions (Vollebregt et al., 2014). Due to the fact that most participants of placebo-neurofeedback-trials consider the training a placebo

treatment (even most of the participants of the "real treatment" group; Lansbergen et al., 2011; van Dongen-Boomsma et al., 2013) the lack of acquisition of regulation capability might result from impaired confidence in the treatment credibility during training.

In order to investigate neurobiological and psychological mechanisms of action of SCP training, we analyzed the impact of SCP training on the tCNV and conducted fMRI-whole brain analysis (parietal cortex ACC) in a CPT with long ISI. Using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) enabled us to investigate neural correlates of late anticipation (related to negative SCPs) at high temporal resolution (EEG) and at high spatial resolution (fMRI).

A second aim was to analyze the relation between the treatment evaluation (believe to get through a SCP- or placebo-training) and the acquisition of neuro-regulation capability during the training sessions.

MATERIALS AND METHODS

SUBJECTS

Twenty healthy adults (age 18–29) participated in a SCP or sham NF-training, as well as in fMRI and EEG assessments. All experimental procedures conformed fully the institutional guidelines. The trial was approved by the local ethics committee of the University Medical Center Göttingen (UMG). Participants were informed about the purposes of the study and gave written informed consent. They were paid 85€ for the completion of the study. All participants were screened for mental/psychiatric disorders with the SKID-I screening questionnaire (Wittchen et al., 1997) supplemented by the assessment of symptoms of an attention deficit and hyperactivity disorder (Wender-Utah-Rating-Scale, short version; WURS-k; Retz-Junginger et al., 2002) and a general psychopathological profile (symptom-checklist, SCL-90-R; Leonard and Derogatis, 1994). General cognitive ability (GCA) was determined by the mean of four subtests of the WAIS-III (Wechsler, 1997; **Table 1**). There were no significant differences between the samples.

PROCEDURE

The study consisted of a SCP training and pre-, intermediate-, and post- training EEG and fMRI measurements. Subjects were, in a double-blind procedure, pseudo-randomly assigned to either real-SCP or sham-SCP training. Both trainings consisted of 16 training units of about 45 min each. Two units, divided by a short break, were conducted in each training session. The 8 training sessions were spread across 3 weeks, with generally two to three sessions per week depending on the schedule of the participants.

EEG- and fMRI-measurement were conducted before the first session (pre-test), after 4 sessions (intermediate-test), and after the final session (post-test). EEG measurements were performed in the EEG laboratory of the Department of Child and Adolescent Psychiatry, University Medical Center, Göttingen (UMG). FMRI measurements were performed at the Biomedizinische NMR Forschungs GmbH, Max Planck Institute for Biophysical Chemistry, Göttingen. The EEG and fMRI measurements at each time point were conducted within a week.

Table 1 | Demographic and clinical characteristics of the sample.

Sample	SCP (n = 9) M (SD)	Placebo (n = 11) M (SD)
Age (years, month)	23.2 (2.91)	22.9 (2.98)
Sex (female/male)	7/2	7/2
GCA (WAIS-III)	10 (2.56)	10.30 (1.44)
WURS-k (ADHD)	21.44 (9.15)	16.45 (4.30)
SCL-90-R (psychopathology)	0.15 (0.14)	0.29 (0.34)

Description of the sample: GCA = mean of the four subtests vocabulary, bloc design, similarities, matrix reasoning of the WAIS-III; WURS-k: questionnaire which assesses symptoms of ADHD in childhood; SCL-90-R: GSI = global severity score (mean of all symptoms).

TREATMENT (TRAINING)

The neurofeedback program SAM ("Self-regulation and Attention Management") was used for both the SCP and the sham training. The SAM-system has been developed by our study group for scientific purposes and has been employed effectively in different previous NF studies (Heinrich et al., 2004; Drechsler et al., 2007; Gevensleben et al., 2009).

SCP training

Within the SAM training units, participants were asked to direct a ball on a computer screen upwards (negative SCP trials) or downwards (positive SCP trials) by generating negative or positive SCPs. All participants were instructed to get into an attentive (negative SCP trials) or relaxed state (positive SCP trials). Negative SCP and positive SCP trials were presented with equal probability in random order. One trial lasted for 8 s (baseline period: 2 s, feedback period: 6 s), inter-trial-interval was set to 5 ± 1 s. During the feedback phase, the mean SCP amplitude (moving time window: 1 s) was calculated at a rate of 10 Hz (10 times per second). Each SCP training unit presented approximately 120 trials and lasted 25–30 min. At least 1/3 transfer trials were conducted, where no feedback was provided. Transfer trials are thought to facilitate generalization (Heinrich et al., 2007).

Feedback was calculated from the Cz electrode, which is standard for SCP training (Heinrich et al., 2007; reference: mastoids, bandwidth: 0.01–30 Hz for SCP training, sampling rate: 250 Hz). Vertical eye movements, recorded from electrodes above and below the left eye, were corrected online using regression-based algorithms (Kotchoubey et al., 1997). Artifact thresholds were set to ± 100 μV in the EEG channel and ± 200 μV in the EOG channel. For segments containing artifacts exceeding this threshold no feedback was calculated. However, in individual cases thresholds were adapted (due to alternating signal quality, primarily at the beginning of the training) to enable contingent (less artifact-contaminated) feedback.

Sham training

In placebo training, the feedback data of participants of a previous study were used, providing an appropriate range of different

feedback curves. These curves were weighted by coefficients to control the development of positive and negative SCPs in the course of the training such that participants should have the impression of the development of poor, average or good regulation skills over the course of the training. Three subjects (one third) of the placebo group were assigned to each of this "skill impression" group. Different approaches were taken to guarantee the blindness of the participants as well as of the trainers towards the training condition. Trainers did not see the online recorded EEG signal, but only the (real or simulated) feedback curve. Participants also saw the (real or simulated) feedback curve. For all participants (SCP and sham) the online recorded EOG signal was shown on the screen during the trials and the artifact detection was based in both training groups on the actual online EEG and EOG signals. This is considered to be an essential component to guarantee blindness of trainer and participant in a placebo-controlled study.

ESTIMATION OF TREATMENT ASSIGNMENT

On a five-point-scale (0 = "I strongly agree"; 1 = "I rather agree; 2 = "I don't know; 3 = I rather disagree; 4 = "I strongly disagree") participants rated their estimation of group assignment ("I'm involved in a regular neurofeedback training") following each training sessions. The assessment controls for blinding and/or differences in the evaluation/estimation of the training. Furthermore the analysis of the guessed treatment assignment allowed investigating a potential relation between the estimation of the training and the development of regulation capability in the SCP group.

NEURO-REGULATION ASSESSMENT AND ANALYSIS

During the training sessions subjects were instructed to generate shifts of cortical excitability (SCPs) towards positivity (reduced excitability) or negativity (enhanced excitability). Regulation indices were calculated as the difference between the EEG-activity during positivity trials vs. negativity trials, reflecting a measure of neuro-regulation capability. Due to the slow development of a SCP, only the last 4 s of the 6-s-feedback-interval of a trial were taken into account (Hinterberger et al., 2005). Analysis of regulation capability encompassed regular feedback as well as transfer trials combined.

The difference in the activity between positivity trials and negativity trials of one session in terms of a *regulation index* is considered as the regulation capability during a session.

The *session regulation index* describes the difference in the activity between positivity trials and negativity trials within one session. The *mean regulation index* represents the average of the in-session regulation indices of all 8 training sessions for each subject.

CONTINUOUS PERFORMANCE TASK (CPT)

In the pre-, intermediate-, and post-training EEG and fMRI measurements, a cued version of a continuous performance task (CPT; van Leeuwen et al., 1998; Heinrich et al., 2004) with an extended stimulus onset asynchrony (SOA) of 6000 msec was applied. This duration closely corresponds to the standard duration of SCP trials during training sessions and conforms to the time resolution of the BOLD fMRI measurements (Lütcke et al., 2009).

For the CPT, subjects were presented with the letters O, X, or H. During EEG measurements black letters against a light gray background were shown in the center of a 17-inch CRT monitor with 800 × 600 points resolution against a light gray background at a viewing angle of 1.58 vertically and 1.08 horizontally. For fMRI measurement a dedicated setup was used (Schaefter and Kirchhoff, Hamburg, Germany) to project the stimuli on a screen within the MRI bore. Here black letters against a white background were presented. Two black vertical bars were continuously present above and below the stimulus location, to direct subjects' attention to the center of the screen.

The letters were presented for 250 ms, with an inter stimulus interval of 5750 ms. The subjects were instructed that the letter O acted as an attentional signal (cue) and that they should press a response button as fast as possible with their right thumb or index finger if the following letter was an X (target) and to refrain from pressing the response button if the following letter was an H (distractor). To encourage fast responses, correct responses (button presses) had to occur within 1000 ms from stimulus onset. After the measurement subjects received visual feedback about the percentage of correct responses, as well as their average reaction time achieved.

A total of 80 stimuli were presented in one measurement (one block, total duration about 8 min.), the probability of an O-X pair (cued target) as well as the O-H pair (cued distractor) was 20% each (16 pairs/measurement). Additionally, there was a 10% chance of an uncued H (non-target) or X being shown. The test consisted of four blocks with a short break between each block.

EEG RECORDING AND PROCESSING

Electrical activity of the brain was recorded with a BrainAmp amplifier (Brain Products, Munich, Germany) and sintered Ag/AgCl electrodes with Abralyt2000 electrolyte from 23 sites according to an extended 10–20 system (recording reference: FCz, ground electrode: CPz). Electrooculogram electrodes were placed above and below the right eye and at the outer canthi. Impedances of the electrodes were kept below 10 kOhm. Data was sampled at a rate of 500 Hz (bandwidth: 0.016–120 Hz).

Data were processed with Vision Analyzer software (Brain Products, Munich, Germany). Brain electrical activity was re-referenced to the average, and filtered offline with 0.05–30 Hz, 24 dB/oct Butterworth filters. Ocular artifacts were corrected by the methods described by Gratton et al. (1983). If the amplitude at any EEG electrode exceeded ±100 μV, a segment 150 ms before and 800 ms following was excluded from further analyzes. The Cue-related averages (−200–6500 ms) included at least 20 sweeps, and the tCNV was assessed as the mean amplitude 5000–6000 ms following cue onset at electrode Cz.

fMRI IMAGING AND DATA ANALYSIS

All MRI measurements were conducted at 3T (Siemens Tim Trio, Erlangen, Germany) using a 12-channel receive-only head coil. Individual structural T1-weighted MRI datasets were acquired using a 3D MP-RAGE sequence (1.3 × 1 × 1.3 mm^3, interpolated

to 1 × 1 × 1 mm^3). fMRI was acquired with a single-shot, gradient-echo EPI sequence (TR = 2000 ms, TE = 36 ms, flip angle = 70°, 244 volumes per run) with a spatial resolution of 2 × 2 × 4 mm^3 (matrix = 96 × 96, 192 mm FoV, 7/8 parial Fourier, bandwidth = 1336 Hz/pixel, echo spacing = 0.81 ms). 22 slices were acquired without gap in an interleaved fashion, positioned in the transvers-to-coronal plane, approximately parallel to the body of the corpus callosum and covering the whole cerebrum. To facilitate registration of fMRI data to the anatomical 3D image, one EPI volume with the same specifications as the functional series but with additional slices (36 slices) was acquired at the end of each fMRI session.

Evaluation of fMRI data was performed using tools from the FMRIB Software library (FSL).[1] Scans were corrected for subject motion both in k-space (Siemens, Erlangen, Germany) as well as by image-based registration (Jenkinson et al., 2002). Nonbrain tissue was removed (Smith, 2002) and all volumes were intensity-normalized by the same factor and temporally high-pass filtered (Gaussian-weighted least-squares straight line fitting, with high-pass filter cutoff at 100 s). Data were smoothed using a Gaussian kernel of 5 mm FWHM. Boxcar models were convolved with a Gamma function to take into account temporal properties of the hemodynamic response (HR). Model fit was estimated by statistical time-series analysis in the framework of the general linear model (GLM) and with local autocorrelation correction (Woolrich et al., 2001).

First level regressors were describing the last 2 s before the presentation of the next letter in the cue (O-X, O-H) and the non-cue (H-O, H-X,) trials. Contrast of interests was set up as cue (32 trials) vs. non-cue trials (24 trials). This contrast emphasizes brain activation associated with anticipation, since subjects prepare for a possible reaction after the cue, but have no need for preparation in the non-cue trials. Contrast images were spatially normalized to the MNI152 template brain by means of their respective anatomical scan. Second-level fixed-effect analysis combined the 4 fMRI measurements within each session on the individual subject level. To summarize results across all subjects, mixed-effects group analysis was performed (Beckmann et al., 2003; Woolrich et al., 2004). Significant activations based on Z statistic (Gaussianized T/F) images were obtained by cluster thresholding determined by an initial threshold of $Z > 2.3$, and a corrected cluster significance threshold of $p = 0.05$ (Worsley et al., 1992). Group contrasts were set to compare brain activation changes from the pre- and intermediate-, the pre- and the post-, as well as the intermediate- and the post- measurements (TIME effect), between the groups of SCP- and placebo-trained subjects (GROUP effect) and the interaction between the two effects.

EEG DATA ANALYSIS

The mean score of the *estimation of the assignment to the treatment* of the 8 training sessions was compared between both groups (*t*-test of independent samples) to control for blinding and/or differences in the evaluation/estimation of the training.

By comparing the difference of the *session regulation index* of session 1 with the *session regulation index* of session 8, intra-group development of regulation capability was analyzed for both groups (by paired *t*-tests). Mean regulation performance across all sessions between both groups was compared by independent *t*-test of the *mean regulation index* between both training groups.

The relation between the mean values of *estimation of the treatment assignment* and the mean regulation capability *(mean regulation index)* of the participants was analyzed by correlation analysis as well as the relation between the SCP in negativity trials in the single training sessions and the tCNV during the EEG-lab sessions (Pearson correlation coefficient).

CPT performance data (reaction time) in the EEG lab session and tCNV activation repeated measure ANOVAs (factor time: pre, int, post) was computed with group (SCP, sham) as between-subject factor.

Data analyses were performed using PASW Statistics (v.18).

RESULTS

ESTIMATION OF TREATMENT ASSIGNMENT

On a five-point-scale participants rated their estimation of group assignment. The average rating across all 20 participants was $M = 2.61$ (SD = 0.75). Considering the range of the scale from 0–4 (0 = "I strongly disagree to the estimation that I am involved in neurofeedback training", 4 = "I strongly agree . . ."), the average estimation of the participants indicates ambivalence about the treatment condition. Ratings of both groups did not differ significantly, neither regarding the mean score across all sessions [SCP group: $M = 2.73$ (SD = 0.57), Placebo group: $M = 2.52$ (SD = 0.89); $t = 0.62$; $p = 0.54$)] nor concerning the rating after the last session, when the estimation of the treatment assignment should have been established by the participants [SCP group: $M_{S8} = 2.67$ (SD = 0.87); placebo group: $M_{S8} = 2.27$ (SD = 1.27); $t = 0.79$. $p = 0.44$]. In the end, across both groups, no change in the estimation of group affiliation across the sessions resulted [MANOVA: factor time: $F = 0.66$. $p = 0.62$; factor group: $F = 0.24$, $p = 0.63$; time × group: $F = 0.87$. $p = 0.49$]. **Figure 1** illustrates the ratings of the SCP- and the placebo group across all sessions. Three subjects of the placebo group and no subject of the SCP group scored below "2" in the mean estimation of treatment assignment.

SCP-REGULATION PERFORMANCE

For two subjects of the placebo group, session regulation data were lost due to hard disk problems. The analysis therefore encompassed SCP group = placebo group = 9 subjects. Due to organizational problems two subjects of the placebo group conducted only seven double-sessions. For these cases we chose a last-observation-carried-forward-approach (LOCF).

Find mean positivity and negativity for each session and session regulation indices in **Table 2**. Comparison of SCP amplitudes during positivity trials vs. negativity trials during the first session revealed no significant difference between both conditions, neither for the SCP group ($M_{pos1} = 7.83$; SD = 7.31; $M_{neg1} = 3.42$; SD = 5.98; $t = 1.16$. $p = 0.28$) nor for the placebo group ($M_{pos1} = 10.16$; SD = 8.78; $M_{neg1} = 13.35$; SD = 17.24; $t = 0.77$. $p = 0.47$). For the 8th session, a significant difference between positivity and negativity trials could be obtained in the SCP group ($M_{pos8} = 6.84$; SD = 7.31; $M_{neg8} = -0.32$; SD = 7.47; $t = 2.73$,

[1] www.fmrib.ox.ac.uk

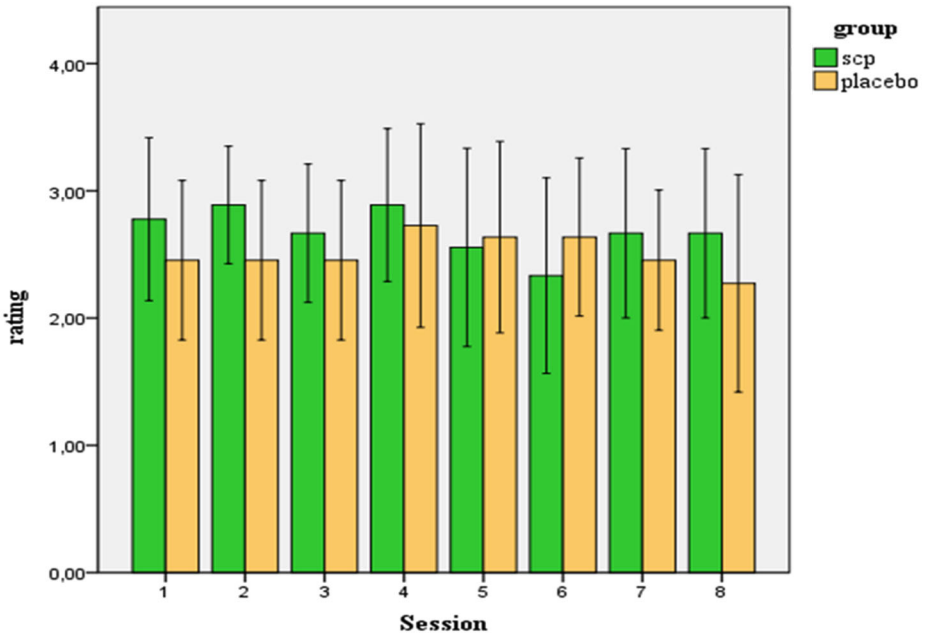

FIGURE 1 | Ratings (confidence intervals 95%) of the participants of how convinced they are to be involved in a true SCP training (in contrast to placebo training).

Table 2 | Regulation performance during SCP training sessions.

Session	Regulation indices (μV) sessions 1–8						
	SCP group (n = 9)			Placebo group (n = 9)			Contrast
	Pos. (SD)	Neg. (SD)	Reg. (SD)	Pos. (SD)	Neg. (SD)	Reg. (SD)	Diff (p)
1	7.83 (7.31)	3.42 (5.98)	4.41 (11.37)	10.16 (8.78)	13.35 (17.24)	−3.19 (12.48)	7.60 (0.20)
2	3.29 (9.95)	0.69 (8.02)	2.60 (5.23)	7.45 (13.78)	6.40 (10.10)	1.05 (5.81)	1.55 (0.48)
3	2.15 (5.73)	1.83 (8.90)	0.32 (7.36)	5.58 (13.16)	8.68 (11.10)	−3.10 (5.95)	3.42 (0.16)
4	1.12 (8.31)	−3.51 (5.01)	4.64 (8.63)	3.06 (10.28)	5.38 (11.02)	−2.32 (5.05)	**6.96** (0.05)
5	4.88 (7.41)	0.76 (8.23)	4.12 (5.61)	10.39 (17.10)	13.58 (17.05)	−3.19 (11.35)	7.32 (0.10)
6	−1.53 (3.03)	−1.08 (6.00)	−0.45 (6.87)	6.97 (11.71)	7.52 (8.29)	−0.54(6.07)	0.09 (0.98)
7	5.40 (5.63)	−1.22 (7.28)	6.62 (8.12)	1.96 (8.28)	4.10 (5.18)	−0.52 (6.82)	7.14 (0.06)
8	6.84 (8.84)	−0.32 (7.47)	7.16 (7.86)	6.35 (7.74)	5.79 (5.92)	1.82 (6.69)	5.34 (0.14)

Comparison of positivity trials, negativity trials, and session regulation indices (positivity trials − negativity trials) between both training groups for each session. Positive values of the regulation-indices indicate differences between negativity and positivity trials in the desired direction.

$p = 0.026$) but not in the placebo group ($M_{pos8} = 8.92$; SD = 12.16; $M_{neg8} = 7.10$; SD = 8.08; $t = 0.82$, $p = 0.44$).

Comparing the mean regulation index (positivity—negativity trials across all sessions) reveals a significantly enhanced regulation capability in the SCP group ($M_{reg} = 3.68$, SD = 5.03) compared to the placebo group ($M_{reg} = -1.25$, SD = 3.85; $t = 2.33$, $p = 0.03$).

Differences in regulation capability primarily result from enhanced activity during negativity trials in the SCP group (illustrated in **Figure 2**). There is no difference in mean activity during positivity trials across all sessions between both training groups (SCP group: $M_{pos} = 3.75$, SD = 3.15; placebo group: $M_{pos} = 7.28$, SD = 10.83), $t = 0.94$, $p = 0.36$), but significant more negativity during negativity trials in the SCP-group (SCP group: $M_{neg} = 0.07$, SD = 4.38; placebo group: $M_{neg} = 8.53$, SD = 9.56; $t = 2.41$, $p = 0.03$). Altogether, regulation capability evolves only in the SCP group and results from enhanced regulation toward negativity in negativity trials.

INTERRELATION OF REGULATION CAPABILITY AND ESTIMATION OF TREATMENT ASSIGNMENT

No significant relation between general regulation capability (*mean regulation index*) and mean estimation of group assignment (across all session) could be obtained in the SCP group ($r = 0.04$, $p = 0.91$). **Table 3** presents Pearson correlation coefficients between the participants' ratings of group assignment

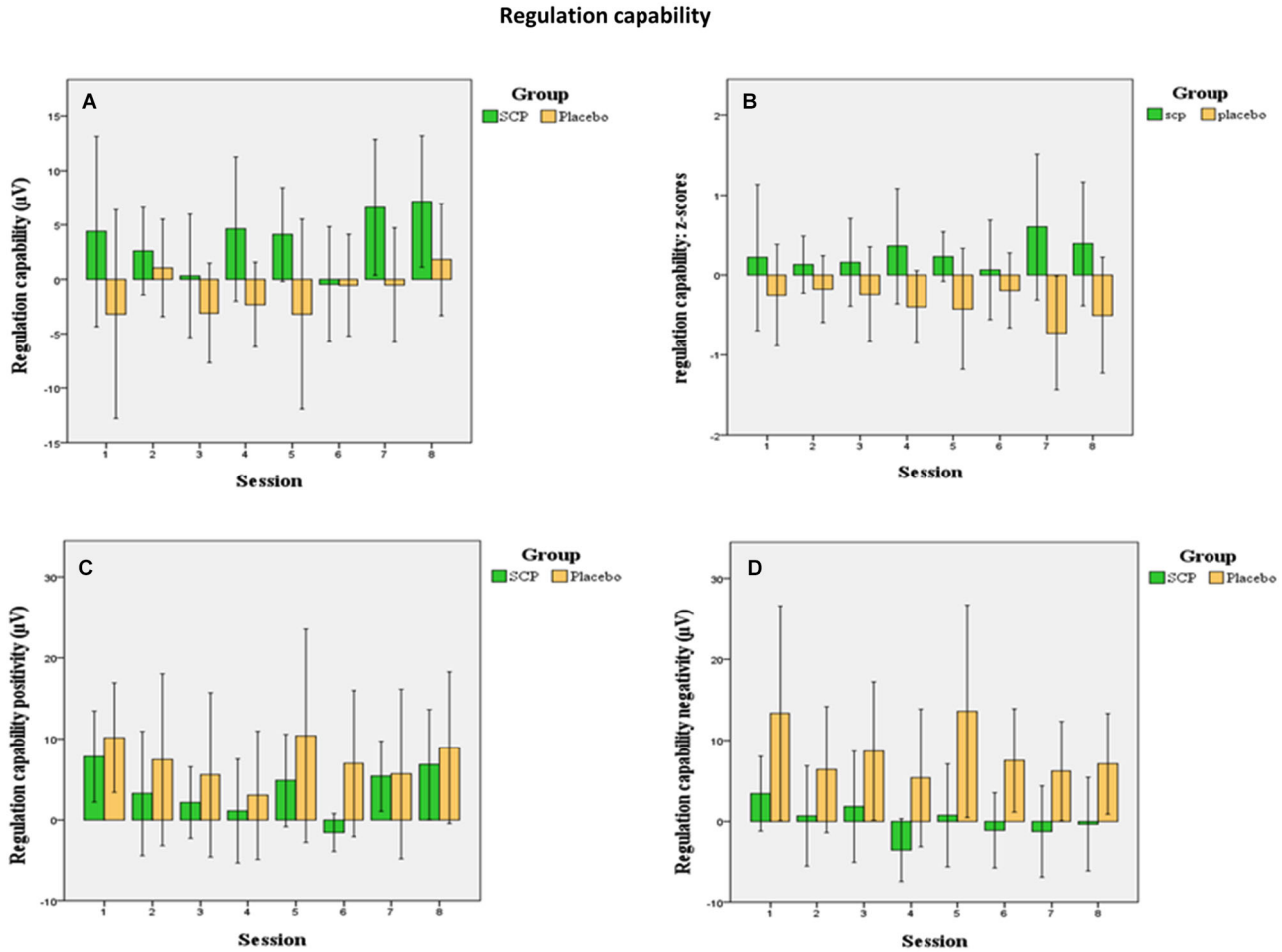

FIGURE 2 | Mean *session regulation indices* across all sessions (A) show an increase in the regulation capability in the SCP group (confidence intervals 95%). In the placebo group no significant development of regulation capability appears. This appears more evident in the illustration of the *z*-transformed (standardized deviation from the mean) *session regulation indices*. **(B)** Changes in regulation capability across all sessions for positivity trials **(C)** indicate no differences between the groups during positivity trials while only the SCP group develops the capability to generate negativity during negativity trials **(D)**.

and the regulation performance for each session separately. No systematic relation between estimation of group assignment and regulation capability could be obtained, excluding two significant correlation coefficients for the sessions 4 and 5 concerning positivity regulation (session 4) and differentiation (session 5).

NEUROPHYSIOLOGICAL TEST SESSION: tCNV AND PERFORMANCE

The event-related potential following cue stimuli showed the expected slow negative tCNV with a maximum at central leads that terminates with the onset of the next stimulus (see **Figure 3**). Exploratory analyses revealed that the maximum was located at electrode Cz where it was further evaluated. As illustrated in **Figure 3**, the tCNV mean amplitude shows distinct changes during the training course (Time: $F_{(2,34)} = 3.4$, $\varepsilon = 0.96$, $p = 0.05$, part $\eta^2 = 0.17$ and Training × Time: $F_{(2,34)} = 3.6$, $\varepsilon = 0.96$, $p = 0.04$, part $\eta^2 = 0.18$): whilst the Placebo group (**Figure 3A**) shows a tendency towards increased tCNV from Pre to Post assessment, the SCP group demonstrates a significant increase from Pre to Intermediate, and a significant decrease from Intermediate to Post, back to the Pre-training level (see **Figures 3B,C**).

Eight of nine subjects of the SCP group (but only the half of the placebo group) exhibited an enhancement of the CNV in the intermediate testing compared to initial measurement (pre-training testing), indicating that the intermediate CNV enhancement in the SCP group does not result from separate outliers.

Moderate to strong relations (correlation coefficients between 0.5 and 0.6) between the regulation performance (SCP during negativity trials) during single training session and the tCNV in the EEG-lab sessions developed, which however did not turn out to be significant due to the small sample size.

Response speed of correct responses showed a steady increase from pre to intermediate to the post assessment (Time: $F_{(2,34)} = 7.5$, $\varepsilon = 0.76$, $p < 0.01$, part $\eta^2 = 0.31$), which was similar

Table 3 | Correlation coefficients between rating of group assignment and regulation performance in the SCP group.

n = 9	Rating session 1–8: correlation (p)							
Regulation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Positivity	−0.38 (0.32)	0.50 (0.17)	−0.41 (0.27)	**0.83 (0.01)**	0.58 (0.10)	0.40 (0.28)	0.04 (0.92)	0.27 (0.49)
Negativity	0.46 (0.21)	0.58 (0.10)	−0.18 (0.64)	0.24 (0.53)	0.02 (0.95)	0.27 (0.48)	−0.27 (0.48)	0.51 (0.16)
Differentiation	−0.48 (0.19)	0.05 (0.89)	−0.10 (0.80)	0.24 (0.53)	**0.74 (0.02)**	−0.06 (0.88)	0.27 (0.48)	−0.19 (0.63)

Pearson correlation coefficients for the SCP group between regulation performance (positivity, negativity, and differentiation = positivity − negativity) and the subjective ratings of the participants guessing the group assignment (SCP vs. placebo condition).

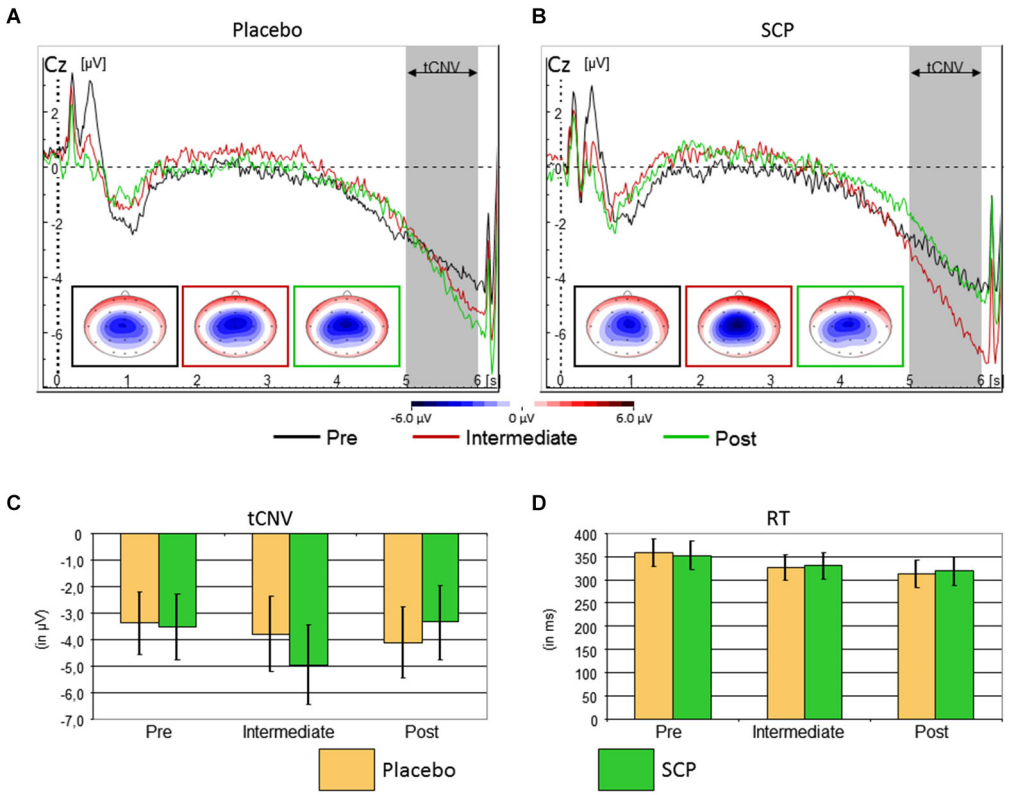

FIGURE 3 | Top: Time course of the brain electrical activity related to cue processing at site Cz from the Placebo **(A)** and SCP **(B)** training groups at pre-training (black), intermediate (red) and post-training (green) assessment. The tCNV is assessed in the time window 5 to 6 s following cue onset and shows a central maximum. **Bottom:** Confidence intervals of tCNV and reaction-time (RT) with $p = 0.05$ for the comparison between Placebo and SCP training groups. The tCNV (with $p = 0.05$) displays a distinct time course throughout assessments: the Placebo training group exhibits as a tendency a steady increase in amplitude from pre-training to post-training assessment, whilst the SCP training group shows an inverted U-like shift with a significant and homogenous maximum at the Intermediate assessment **(C)**. Response speed became faster in later assessments in both training groups **(D)** CPT-performance in the neurophysiological test session was characterized by a generally high accuracy with on average less than 1.5% of omission and commission error rates in both SCP and Placebo training groups.

for SCP and Placebo training (Training: $F_{(1,17)} < 1$, $p > 0.91$, part $\eta^2 < 0.01$, Training × Time: $F_{(2,34)} < 1$, $\varepsilon = 0.76$, $p = 0.76$, part $\eta^2 < 0.01$). There was further a marginal trend for an interaction "Block × Training" ($F_{(2,34)} = 2.2$, $\varepsilon = 0.78$, $p = 0.12$, part $\eta^2 = 0.11$), but *post hoc* tests revealed no clear differences in time-on-task effects across training groups. See **Figure 3B** for further details.

Response speed variability (RT-SD) was lower in the first compared to the later three blocks (Block: $F_{(3,48)} = 2.8$, $\varepsilon = 0.81$, $p = 0.06$, part $\eta^2 = 0.15$), but did not reveal any further effects (all $p > 0.18$).

FUNCTIONAL MRI

fMRI BOLD-activation of the last two seconds of the CPT anticipation phase was compared between SCP-trained and placebo-trained group for the three time points (pre, intermediate, post). All three analyses (pre vs. intermediate, intermediate vs. post, pre vs. post) showed no significant TIME × GROUP interaction

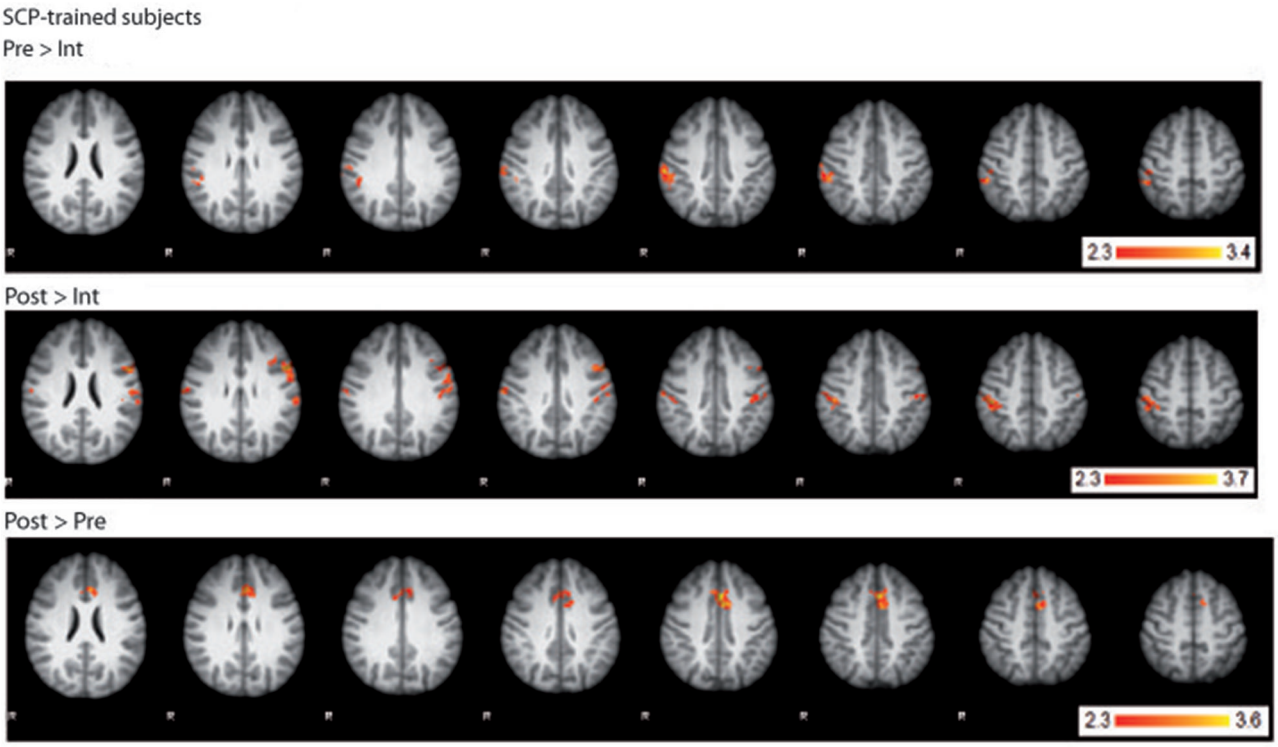

FIGURE 4 | BOLD-activation changes in the SCP-trained group across the training. Top: BOLD-activation higher in the pre- compared to the intermediate measurement. **Middle:** BOLD-activation higher in the post- compared to the intermediate measurement. **Bottom:** BOLD-activation higher in the post- compared to the pre- measurement. *R* = right.

in brain activation. However, computing within-group contrasts, three different BOLD-activation patterns became visible within the group of SCP-trained subjects (**Figure 4**) whereas no significant changes could be seen in the placebo group. In the comparison of the pre- and the intermediate measurement the SCP group showed lower BOLD-activation in the right parietal cortex (postcentral gyrus, peak coordinates: $x = 50$, $y = -28$, $z = 56$) and insular cortex ($x = 32$, $y = 14$, $z = -4$) at the Intermediate measurement. In the intermediate to post comparison, the BOLD-activation in the right and left parietal cortex (postcentral gyrus right: $x = 48$, $y = -28$, $z = 48$, postcentral gyrus left: $x = -58$, $y = -16$, $z = 20$) and insular cortex ($x = 34$, $y = 16$, $z = 2$) was again lower during the intermediate measurement. The pre-to-post comparison revealed a distinct increase in BOLD activation in the ACC (left ACC $x = 0$, $y = 14$, $z = 40$, right ACC $x = 2$, $y = 20$, $z = 36$) in the post measurement, which could also be detected in the overall pre-to-post comparison incorporating both, the SCP- and the placebo-group (main effect TIME).

DISCUSSION

NEURONAL PLASTICITY: tCNV, fMRI, AND PERFORMANCE

At the electrophysiological level we found a result somehow contrary to our primary expectations. The pre- to intermediate assessment in the SCP group revealed—according to our expectations—a strong increase of the tCNV during the CPT in the EEG-lab sessions. This increase in the SCP group significantly exceeded the increase of the tCNV in the placebo group. This enhancement of the parameter targeted by the SCP training (primarily related to negativity trials) was followed by a coequal tCNV decrease in the post-training assessment in the SCP group (back to baseline). Interestingly, this inverted U-like shift of the tCNV in the SCP group was accompanied by a continuing decrease in reaction time during CPT performance from pre- to intermediate assessment and from intermediate to post assessment. The continuing improvement in reaction time was comparable to the decrease of the reaction time in the placebo group. In contrast, in the placebo group the tCNV (as the assumed associated parameter of the performance on the neurophysiological level) showed a continuing increase in accordance with the decreasing reaction time. It appears that in the placebo group the increasing mobilization of neurophysiological resources (enhancement of the tCNV) is accompanied by coinciding improvement in the test performance (decreasing reaction time). Obviously the participants of the sham-group learned to optimize their CPT-performance, mobilizing more neurophysiological resources to continuously improve performance (learning/repetition effects). On the other hand, in the SCP group, the continuing improvement in reaction time is accompanied by an initial increase in the mobilization of neurophysiological resources in case of an enhanced tCNV in the intermediate testing, followed by reduction of neurophysiological effort accompanied by a further enhancement of the performance. Hence, it may be that subjects conducting SCP training require

less neurophysiological resources to achieve a comparable performance in the long run (at post-training assessment).

This interpretation is in accordance with observations concerning e.g., professional musicians or elite athletes engaged in highly over-learned motor skill tasks. Long term practicing motor performance might lead to a more efficient generation of neural activity (reduced or more focused activity accompanying improvements in performance). In professional piano players motor areas were activated to a lesser degree during finger tapping tasks than in non-musicians (Jäncke et al., 2000; Krings et al., 2000). The same was true for Neymar (one of the most esteemed soccer players today), recruiting less resources in the motor-cortical regions controlling foot movement compared to less trained soccer players or athletes of other sporting disciplines, executing a simple foot movement task (Naito and Hirose, 2014).[2] From the perspective of an athlete, this leaves a greater extent of motor cortical resources for accompanying or concurring motor tasks during the competition.

The decrease of the tCNV in the SCP group in the post-training assessment (compared to the intermediate testing) therefore might reflect the lesser effort which is needed after NF training to fulfill the same task with comparable adequacy. For the same task lesser neurons need to be activated (Krings et al., 2000). Hence, the same way that long term motor skill training induces plastic change in central motor systems, SCP training in healthy humans might result in reorganization of the cortical resource management, presumably leaving more resources for additional challenges.

Generally, the tCNV is considered to be associated with the negative SCPs which have to be generated during the SCP-sessions (Heinrich et al., 2004). We found some further support for this notion. The tCNV seemed to appear in relation to the development of the regulation performance during the training as indicated by moderate to strong (although non-significant) correlations between SCPs during negativity trials within the training sessions and the tCNV during EEG-lab sessions.

The development of the tCNV in the time course of this trial reveals results from previous trials studying the effects of SCP training in children with ADHD in a different light. The usual finding of SCP trials with children with ADHD is an enhanced (or less reduced) CNV after SCP training (Heinrich et al., 2004; Doehnert et al., 2008; Wangler et al., 2011). These are findings corresponding to the result of the intermediate assessment of our present trial with healthy adults. However, SCP regulation is impaired in children with ADHD (Banaschewski and Brandeis, 2007) so this might indicate, that even more sessions than usually practiced in research trials are necessary in children with ADHD to (firstly acquire an adequate regulation capability and) finally reach significant optimization on the neurophysiological level (on the other hand one might speculate that this optimization is seriously impaired in children with ADHD and might therefore not result even after a larger number of training sessions).

[2]This provides empirical evidence for the general impression that professional soccer players often do not make much use of their mental resources (at least while executing their complex movement patterns).

The additional whole brain data of the complementary fMRI CPT measurements may provide additional indications for the interpretation of the EEG results. Even if no significant difference in the GROUP × TIME interaction of the BOLD-activation could be detected between the groups of SCP- and placebo-trained subjects, significant changes in brain activation can be seen in the SCP-group across the time course of the training (within group contrasts) but not in the placebo-group. In the posterior parietal cortex activation, peaking at the right postcentral sulcus, decreases from the pre- to the intermediate measurement and, in the posterior parietal cortex of both hemispheres, increases again in the post measurement. This pattern inversely follows the U-shaped increase and decrease of the tCNV EEG amplitude in the SCP-trained group. Since the posterior parietal cortex is a multisensory motor association area, involved in motor planning (Andersen and Buneo, 2002), this change in BOLD-activation could reflect an aspect of the initial acquisition (pre to intermediate) and the following optimization process (intermediate to post) of the more efficient use of the neurophysiological resources. However, this interpretation should be taken with precaution, because these results are not significant in the overall GROUP × TIME interaction. The pre to post measurement increase in ACC BOLD-activation in the SCP-trained group, which is also seen in the overall contrast (main effect TIME), adds another facet, probably being more related to the changes induced by feedback processing during completing a neurofeedback (or placebo-) training. The ACC, being part of the decision making process in the frontal cortex (Rushworth et al., 2012), is also known to be specifically involved in processing of feedback signals to select the response, which is followed by a reward (Amiez et al., 2012; Rushworth et al., 2012). However, this change in ACC-activity was found in both groups and could therefore also reflect learning-/repetition effects of the CPT.

Taken together, for the SCP trained group, these BOLD-activation changes in two different areas of the brain, although being on the level of indications, provide some incidence that a successful training could not only involve multiple brain areas, but also encompass changes in different brain networks at different levels of optimization.

BLINDING, ESTIMATION OF TREATMENT ASSIGNMENT, AND REGULATION CAPABILITY

There is controversy about the feasibility of placebo-controlled trials in NF research. Firstly, previous trials failed to keep up blinding throughout the training and blinding came into question in placebo controlled NF (Holtmann et al., 2014) just as in psychopharmaceutical research, where as well blinding often might fail (Margraf et al., 1991; Morin et al., 1995). However, at least single-/double-blind, placebo controlled trials have been conducted with promising results concerning the application of blinding (and placebo control) in NF (Berner et al., 2006; Schabus et al., 2014). Secondly, placebo-control may affect fidelity of the training, e.g., diminish the credibility of the training or the effort spent by the participant (Gevensleben et al., 2012).

The estimations of our participants concerning the guessing of the treatment assignment display successful blinding. The estimation does not differ between SCP- and sham-training. The mean

rating close to the middle of the rating scale reflects indecisiveness of the participants with little variance in the estimation. No significant correlation between estimation of group assignment and regulation performance could be obtained, making a significant influence of the estimation of the participants (as expected) quite improbable. However, there was not much variance in the estimations, making it hard to obtain an assumed connectivity between estimation and regulation capability. In further trials we would prefer to manipulate the estimation of the treatment directly (e.g., via opposed instructions).

Anecdotally we would like to note, that at least one participant (of the placebo-group) reported after completion of the trial that he was quite sure, that he had practiced placebo-training. He delineated his strategy that he once in a while reversed his regulation strategies but could not observe any systematic change in his displayed feedback following his switch of strategy. Additionally this underlines possible problems inherent in placebo-control in NF-research, participants spending effort in elucidating treatment assignment rather than struggling for enhanced regulation capability.

As expected, regulation capability developed differently in the SCP- compared to the placebo-group. While there was no difference in the generation of positivity during positivity trials between groups, the SCP-group learned to enhance negativity during the negativity trials (in contrast to the placebo-group). However there resulted no linear increase in regulation capability. Regulation performance in the SCP-group appeared to be instable with no significant differences in the regulation indices between SCP- and placebo-group for most of the sessions. However, acquisition of SCP-regulation capability is difficult (Neumann and Birbaumer, 2003) and probably further impaired by affected self-confidence and/or confidence in treatment credibility due to the implementation of a placebo-condition in this trial.

LIMITATIONS AND CONCLUSIONS

The generalization of our results is limited by different factors among which we consider the most important the small sample size, which hardly allows for parametric testing. We consider the results as very relevant but preliminary and like to underline the need for replication with stronger sample sizes. The design of the study is compromised by the many repetitions of the CPT, due to the separated assessment of the EEG and fMRI measurement. This makes the test susceptible for learning processes overwriting or influencing systematic but sensible effects of the training. A combined EEG-fMRI assessment would significantly reduce the test repetitions and allow to directly put the EEG- in relation to the fMRI activity.

Nevertheless we consider these results a further step in understanding mechanisms of change in NF training, indicating neuronal plasticity even after a short number of SCP sessions although learning of SCP regulation does not appear to be optimal, probably due to blinding and uncertainty about the training condition (SCP or placebo).

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Slow cortical potential and theta/beta neurofeedback training in adults: effects on attentional processes and motor system excitability

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Neurofeedback (NF) is being successfully applied, among others, in children with attention deficit/hyperactivity disorder (ADHD) and as a peak performance training in healthy subjects. However, the neuronal mechanisms mediating a successful NF training have not yet been sufficiently uncovered for both theta/beta (T/B), and slow cortical potential (SCP) training, two protocols established in NF in ADHD. In the present, randomized, controlled investigation in adults without a clinical diagnosis ($n = 59$), the specificity of the effects of these two NF protocols on attentional processes and motor system excitability were to be examined, focusing on the underlying neuronal mechanisms. Neurofeedback training consisted of 10 double sessions, and self-regulation skills were analyzed. Pre- and post-training assessments encompassed performance and event-related potential measures during an attention task, and motor system excitability assessed by transcranial magnetic stimulation. Some NF protocol-specific effects have been obtained. However, due to the limited sample size medium effects did not reach the level of significance. Self-regulation abilities during negativity trials of the SCP training were associated with increased contingent negative variation amplitudes, indicating improved resource allocation during cognitive preparation. Theta/beta training was associated with increased response speed and decreased target-P3 amplitudes after successful theta/beta regulation suggested reduced attentional resources necessary for stimulus evaluation. Motor system excitability effects after theta/beta training paralleled the effects of methylphenidate. Overall, our results are limited by the non-sufficiently acquired self-regulation skills, but some specific effects between good and poor learners could be described. Future studies with larger sample sizes and sufficient acquisition of self-regulation skills are needed to further evaluate the protocol-specific effects on attention and motor system excitability reported.

Keywords: neurofeedback, slow cortical potential (SCP) training, theta/beta training, event-related potentials (ERPs), transcranial magnetic stimulation (TMS), contingent negative variation (CNV)

INTRODUCTION

During neurofeedback (NF) training individuals learn to acquire self-regulation skills of particular brain activity patterns by receiving positive feedback on brain activity changes in the desired direction. The rationale of NF is derived from observations that a specific mental state (e.g., attention) is associated with a certain brain state (e.g., more pronounced beta activity). Thus, by training to acquire a specific brain state, NF aims at enhancing the mental state associated with this brain state, and thereby improving behavioral self-regulation in daily life situations (Gevensleben et al., 2012; Moriyama et al., 2012).

A whole variety of NF protocols has been developed in order to target different mental states and associated behavior. Two basic types of NF protocols can be distinguished: frequency band training and training of slow cortical potentials (SCPs).

In a frequency band training, a decrease and/or increase of the amplitudes of specific encephalogram (EEG) frequency bands are rewarded. One established frequency band training is the theta/beta training which aims at enhancing a state of sustained attention by reinforcing reductions in theta (4–8 Hz) and increases in beta (13–20 Hz) amplitudes[1] recorded at the vertex (Cz).

A training of SCPs (SCP training) is based on recordings of SCPs at the vertex, which last from several hundred milliseconds to several seconds and which are related to the level of excitability of the underlying cortical areas (Birbaumer et al., 1990; Heinrich et al., 2007). Surface-negative SCP shifts reflect increased excitation of the underlying cortical areas and typically occur during behavioral and cognitive preparation. Surface-positive SCP shifts

[1]It has to be considered that the exact realization of the theta/beta protocol differs between research groups, e.g., with respect to the frequency range.

are related to decreased excitation and are observed among others during behavioral inhibition. During SCP training, participants learn to change between an activated/attentive state and a deactivated/relaxed state by modulating their SCPs toward more negative and positive amplitudes, respectively.

The NF protocols described above have been applied both in clinical and peak performance domains. Neurofeedback in clinical domains targets reducing clinical symptomatology in patients, with one main application in children with attention deficit/hyperactivity disorder (ADHD). Neurofeedback as a peak performance training is applied in healthy persons with the aim of further enhancing already good performance.

In children with ADHD, for both theta/beta and SCP training positive effects on reducing clinical symptomatology (inattention, hyperactivity/impulsivity) and improving cognitive performance have been reported (for review, see, e.g., Mayer et al., 2012b; Moriyama et al., 2012; Arns et al., 2014), and with especially more recent studies being based on randomized-controlled designs (e.g., Drechsler et al., 2007; Gevensleben et al., 2009; Duric et al., 2012; Meisel et al., 2013; Steiner et al., 2014). In the so far largest NF study in ADHD which included both theta/beta and SCP NF training, the effectiveness of these NF protocols in ADHD has been shown (Gevensleben et al., 2009). A recent meta-analysis indicated the effectiveness of both theta/beta and SCP training protocols in children with ADHD (Arns and Strehl, 2013), even though currently there is a controversial discussion on the effectiveness of NF in ADHD (Lofthouse et al., 2012; Sonuga-Barke et al., 2013; Arns et al., 2014). In recent review articles NF, especially theta/beta and SCP NF, was concluded to be a clinically effective treatment in ADHD (Arns et al., 2014) and the importance of gaining further insights on the underlying mechanisms of action as well as on disentangling specific from non-specific effects was stressed (Gevensleben et al., 2012; Moriyama et al., 2012; Arns et al., 2014).

In the peak performance domain, so far NF studies were mainly conducted in adult participants (for a comprehensive review, see Gruzelier, 2013). Overall, theta/beta and SCP protocols are less well established in the peak performance domain compared to the field of ADHD, but some results have been published. Theta/beta training protocols were observed to enhance arousal (Egner and Gruzelier, 2004), but not musical performance (Egner and Gruzelier, 2003). SCP training was reported to exert positive effects on response speed during "negativity" trials (Birbaumer et al., 1990; Birbaumer, 1999).

So far, more commonly applied protocols in the peak performance domain comprise, among others sensorimotor rhythm (SMR) training as well as alpha/theta training. Sensorimotor rhythm training was reported to enhance semantic working memory (Vernon et al., 2003), sustained attention (Egner and Gruzelier, 2004), microsurgical skills (Ros et al., 2009), reaction times (RTs), and spatial rotation abilities (Doppelmayr and Weber, 2011). However, no positive effects of SMR training were observed for the D2 attention test (Doppelmayr and Weber, 2011), for creativity (Doppelmayr and Weber, 2011), and for musical performance (Egner and Gruzelier, 2003). Alpha/theta training has been observed to enhance, e.g., musical performance (Egner and Gruzelier, 2003; Gruzelier, 2009, Gruzelier et al., 2013a), and cognitive creativity (Gruzelier et al., 2013b), as well as to enhance dance performance in one study (Raymond et al., 2005a) but not in another (Gruzelier et al., 2013b).

Overall, positive effects of different NF protocols have been reported both for their clinical application, e.g., in children with ADHD, as well as for different applications (e.g., attention, performing arts) in the peak performance domain. But despite the evergrowing diversity of NF protocols and their applications, mechanisms mediating a successful NF training are still not completely understood.

In order to study the mechanisms underlying the treatment effects of different NF protocols, especially more recent NF studies have employed neurophysiological measures like event-related potentials (ERPs), and one study has applied transcranial magnetic stimulation (TMS; Ros et al., 2010). The rationale for applying these methods in NF studies is derived from the association of specific brain electrical activity to distinct mental states and behavior (Moriyama et al., 2012).

ERP components, such as the P3 and the contingent negative variation (CNV) are related to cognitive stimulus processing stages (Banaschewski and Brandeis, 2007) and have been used to study covert attention, e.g., in ADHD and NF research. The P3 is thought to reflect attentional resource allocation, stimulus evaluation as well as context updating processes (Banaschewski and Brandeis, 2007; Polich, 2007). In adults, an increase in P3 amplitude has been revealed after a combined beta1 (15–18 Hz) and SMR (12–15 Hz) training (Egner and Gruzelier, 2001), and in a later study after a beta1 but not after an SMR training reflecting increased activation in an attentional alertness network (Egner and Gruzelier, 2004). In children with ADHD, no increase in P3 amplitude was revealed after a combined SCP and theta/beta training (Wangler et al., 2011). The CNV, a negative polarization of an SCP occurring between a warning and a target stimulus, reflects attentional processes related to anticipation and preparation (Birbaumer et al., 1990). Increased CNV amplitudes, have been observed after SCP training in children with ADHD (Heinrich et al., 2004; Wangler et al., 2011) and according to preliminary results also in adults with ADHD (Mayer et al., 2012a,b) indicating improved resource allocation.

Transcranial magnetic stimulation allows investigating excitatory mechanisms of the motor system (Reis et al., 2008), and to distinguish processes of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF; Kujirai et al., 1993). One study has examined the effects of a single session of NF (alpha suppression or low beta enhancement) in healthy adults on corticomotor excitability by means of TMS (Ros et al., 2010). Based on a non-conservative statistical analysis, this study provided hints for decreased SICI after an alpha, but not after a low beta training.

Self-regulation ability is a measure assessing changes in the trained EEG parameters in the course of NF training and is considered to mediate effects of NF on behavior. In addition, associations of learned self-regulation of a distinct EEG parameter with improvements in outcome measures can provide evidence for specific effects of different NF protocols (Gruzelier, 2013). So far, self-regulation has more consistently been examined in peak performance (for a review, see Gruzelier, 2014) than in clinical studies.

The aim of the present randomized controlled investigation in "healthy" adult participants was to examine the specificity of the effects of a theta/beta, and an SCP training on attention as well as on motor system excitability. The focus of the study was to gain further insights into the neurophysiological mechanisms underlying these two NF training protocols by also assessing ERP (P3 and CNV) and TMS (SICI and ICF) measures.

Regarding attention, on the performance level, larger training-related increases in attention were expected for the two NF groups compared to the control group, while no differential effects were expected between theta/beta and SCP protocols. At the level of ERP measures, pre–post increases were expected to be larger in the two NF groups compared to the control group. The largest pre–post increase in P3 amplitude was expected after theta/beta training, and the largest increase in CNV amplitude after SCP training. Good self-regulation skills during theta/beta and SCP training were expected to be associated with pre–post P3 amplitude changes and with a larger pre–post increased in CNV amplitude, respectively.

In comparison to the control group, theta/beta and SCP training were expected to have effects on motor system excitability. As the present study was the first examination of motor system excitability by means of TMS after a complete NF training, we had no directed hypotheses regarding differential effects of the two NF training protocols on SICI and ICF.

MATERIALS AND METHODS

PARTICIPANTS

Fifty-nine subjects (aged 19–31 years) participated in this randomized, controlled study. Exclusion criteria were: a psychiatric or neurologic diagnosis, a cardiovascular disease, a pathological EEG or ECG, pregnancy, estimated IQ below 80 (based on the Verbal Comprehension Index and the Perceptual Reasoning Index of the German version of the Wechsler Adult Intelligence Scale), values above norm values of the Symptom Checklist-90-R: SCL-90-R (Derogatis and Savitz, 2000). Two subjects dropped out of the study due to schedule problems directly after the pre-assessments, one subject had to be excluded due to German-language difficulties and one subject due to a personal crisis which occurred in the course of training. Thus, the final sample comprised 55 adults who have completed the study.

These participants were randomly assigned (randomized list without any stratification) to one of three groups: theta/beta frequency band training (T/B: $n = 19$), training of SCPs (SCP: $n = 19$), or control training (CON: $n = 17$). **Table 1** provides an overview over the demographic and psychological characteristics of the final sample.

Written informed consent was obtained from all participants. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty of the University Hospital of Erlangen.

DESIGN

All trainings including pre- and post-assessments were conducted in the Department of Child and Adolescent Mental Health at the University Hospital of Erlangen. The participation in the study extended for about 2 months per person and participants received an expense allowance. All three training programs were administered by the same trainers.

Neurofeedback

The two NF trainings (T/B and SCP) consisted of 20 sessions à 50 min each which were conducted as 10 double sessions mostly taking place twice per week. Visual feedback information was provided. Both theta/beta and SCP training included about 40% transfer trials during which participants received no feedback about their current brain state. Subjects in the T/B and SCP groups were instructed to develop individual (intuitive or cognitive) strategies in order to achieve the desired brain state. Starting with the fifth double session, subjects of both NF groups applied their strategies to attention-demanding tasks (in turn a game of darts or a continuous performance test) in the last 10 min of a double session – as a first step toward a transfer to other relevant situations. Moreover, participants were instructed to practice the transfer of their strategies at least once each day in daily life situations in which they wanted to improve their attention or well-being.

During theta/beta self-regulation blocks, subjects were asked to reduce their theta activity (4–8 Hz) and simultaneously increase their beta activity (13–20 Hz) relative to a baseline assessed at the beginning of a training session and received feedback by means of changing bars which had to be reduced and increased, respectively. The aim was to achieve an attentive but relaxed state. To calculate theta and beta activity, Buttworth filters (48 dB/octave) were applied and feedback information was determined 10 times per second by means of a moving time window of 2 s length. In

Table 1 | Demographic and psychological characteristics of the sample.

	Age (years)	Sex m/f	Estimated IQ	SCL-90: GSI
T/B ($n = 19$)	24.62 ± 2.56	7/12	105.95 ± 6.19	0.23 ± 0.18
SCP ($n = 19$)	25.08 ± 2.47	10/9	105.24 ± 7.67	0.14 ± 0.10
CON ($n = 17$)	23.59 ± 3.06	7/10	103.65 ± 9.31	0.33 ± 0.20
ANOVA	$F(2,52) = 1.33$, n.s.	$F(2,52) = 0.49$, n.s.	$F(2,52) = 0.41$, n.s.	$F(2,51) = 3.62$, $p < 0.05$

For each group demographic and psychological characteristics are depicted (mean value and standard deviation). T/B, theta/beta frequency band training group; SCP, SCP training group; CON, control training group; m, male; f, female. Estimated IQ: based on the Verbal Comprehension Index and the Perceptual Reasoning Index of the German version of the Wechsler Adult Intelligence Scale. GSI, Global Severity Index of the Symptom-Checklist-90-R (SCL-90) self-report measure. ANOVA, analysis of variance with the between-subject factor GROUP. Significant effects for the GSI were related to higher scores in the CON group.

the first few training sessions, most self-regulation blocks lasted for 5 min, while in the course of training, self-regulation blocks were extended to 10 min in order to train staying focused for a longer time period.

During SCP training, feedback was provided in the form of a ball that subjects were to direct upwards in negativity trials and downwards in positivity trials (equal number of positivity and negativity trials, randomized order). A trial lasted for 8 s and consisted of a 2 s baseline period and a 6 s feedback period (intertrial interval: 5 ± 1 s). Training was performed in blocks of 40–60 trials. The training aimed at enhancing an activated / attentive state during negativity trials as well as a deactivated/relaxed state during positivity trials. Feedback was provided based on the mean SCP amplitude based on a moving time window of 1 s length which was calculated 10 times per second.

For theta/beta and SCP training, the NF system Self-regulation and Attention Management (SAM; developed by our group) was used. Brain electrical activity (recorded via sintered Ag/AgCl electrodes) was calculated from Cz (reference: one mastoid, sampling rate: 250 Hz, bandwidth T/B: 1–30 Hz, bandwidth SCP: 0.01–30 Hz). Two additional EOG electrodes were placed above and below one eye in order to record blinks and vertical eye movements and the time course of the EOG channel was depicted on the trainer's monitor. These ocular artifacts were corrected online using a regression-based algorithm (T/B: Semlitsch et al., 1986; SCP: Kotchoubey et al., 1997). When artifacts exceeded ±100 μV in the EEG channel or ±200 μV in the EOG channel, for these segments no feedback was provided to the subject.

Control training

The control training was no NF training and was only designed to parallel the transfer tasks included in the NF trainings (but not the amount of time) in order to control for both practice effects due to repeated testing (pre- and post-assessments) and for unspecific training effects related to developing and applying strategies to daily life situations. It comprised six sessions of about 20 min each which on average took place twice per week. Similar to the NF groups, before performing the transfer tasks (in turn a game of darts or a continuous performance test), subjects developed individual cognitive strategies that helped them to achieve an attentive state, a relaxed state or a state in which they were in a positive mood. Subjects were then instructed to activate these strategies before starting the transfer task. As in the NF groups, participants were instructed to practice their strategies in relevant daily life situations.

LEARNING OF SELF-REGULATION SKILLS

Self-regulation of the theta/beta ratio during T/B training as well as differentiation between negativity and positivity trials during SCP training was analyzed. Self-regulation in the first two training sessions (average value of sessions one and two) was compared to self-regulation of the last two training sessions (average value of sessions nine and 10). Self-regulation measures presented here do not differentiate between trials with contingent feedback and transfer trials.

Associations of self-regulation abilities (good vs. poor performers) and pre–post changes in ERP measures (T/B: P3 amplitudes, SCP: CNV amplitudes) were calculated. For the analysis related to CNV amplitudes, self-regulation abilities were analyzed based on regulation abilities in negativity trials due to the close relation of negative SCPs and the CNV.

ASSESSMENTS AND NEUROPHYSIOLOGICAL RECORDINGS

Participants of all three groups performed pre- and post-training assessments which took place before the start of training and in the week after the end of training, respectively. The laboratory assessments included the performance of an attention-demanding task while brain electrical activity was recorded, and a measurement with TMS.

Attention task and event-related potentials

As an attention-demanding task the Attention Network Test (ANT; Posner and Petersen, 1990; Fan et al., 2002) was selected. Subjects performed the ANT while brain electrical activity was recorded.

The ANT version used in the present study (Rueda et al., 2004) was realized in Presentation (Version 11.0; Neurobehavioral Systems, Albany, CA, USA) in a similar same way as described in Kratz et al. (2011) but with an additional variant including the presentation of a noise sound. The variant with the noise sound, in the following referred to as WithStress condition, was added in order to include a condition with higher demands. The test itself consisted of four blocks of 48 trials each, two blocks of each variant (with noise sound, without noise sound).

Subjects were presented five fish in a row (a middle fish surrounded by two flanking fish on each side) and were instructed to respond with a left- or right-mouse click depending on the direction in which the middle fish (target fish) was pointing. The target fish was presented 100 ms after the four flanking fish. Trials were congruent (resp. incongruent) if the fish flanking the middle fish were pointing in the same (resp. opposite) direction. Three cue conditions were included in the task and cues were presented 1400 ms before the target fish: no cue was presented (NoCue condition), a cue was presented in the center of the screen (NeutralCue condition), a cue was presented above or below the center of the screen, i.e., at the location where the target fish was to appear (SpatialCue condition). The performance measures number of hits, mean RT, and variability of RT (RTV).

EEG was recorded from 23 sites (10–20 system with FPz and Oz; recording reference: FCz; ground electrode: CPz; bandwidth: 0.016–120 Hz; sampling rate: 500 Hz) with sintered silver/silver-chloride (Ag/AgCl) electrodes and Abralyt 2000 electrolyte using the BrainAmp amplifier (Brain Products, Munich, Germany). In addition, vertical and horizontal EOG were recorded. Impedances were kept below 20 kΩ.

The data were analyzed with the Vision Analyzer software (Brain Products, Munich, Germany). Encephalogram was downsampled to 256 Hz, re-referenced to the mastoids, and filtered offline (resting EEG: 0.1–30 Hz, ERPs: 0.05–30 Hz; 12 dB/octave Butterworth filter; 50-Hz notch filter). Ocular artifacts were corrected using the Gratton and Coles algorithm (Gratton et al., 1983). If EEG amplitude exceeded ±80 μV at any electrode a section of −500 to +500 ms around the artifact was removed in all channels. For the analysis of the interval between cue and target presentation, segments of 1800 ms length were formed, which

started 230 ms before cue presentation. The CNV was determined at Cz as the mean amplitude in the time window 1000–1300 ms after cue onset. Target processing was analyzed based on segments of 1250 ms length, which started 125 ms before target presentation. The P3 was determined as the most positive peak at Pz in the time window 280–450 ms after target presentation. For ERP analysis, only trials with correct responses were considered and averaged responses of a participant were required to be based on at least 20 artifact-free segments. In order to avoid distortion of the ERP topography, no baseline correction was applied.

TMS

Transcranial magnetic stimulation measurements based on the double-pulse paradigm (Kujirai et al., 1993) were performed, while subjects remained in a resting state. Electromyogram (EMG) activity was recorded at the musculus abductor digiti minimi of the right hand.

For the TMS measurements, recording settings of the amplifier were adjusted accordingly (bandwidth: 8–1000 Hz, sampling frequency: 5 kHz). A figure-of-eight coil (diameter of one wing: 70 mm) connected to a Magstim Bistim unit with two Magstim 200^2 stimulators (Magstim, Whitland, UK) was used for the measurements. The stimulation position was determined as the position of the coil on the scalp which elicited the largest motor evoked potential (MEP). The resting motor threshold (RMT) was determined as the minimal stimulus intensity that did not elicit an MEP larger than 50 μV in five consecutive trials. The suprathreshold stimulus intensity was determined such that MEP amplitude was about 1 mV (peak-to-peak) and the intensity of the conditioning stimulus was set to 75% of RMT. During measurement, paired pulses were used for stimulation which consisted of the conditioning stimulus followed by the suprathreshold stimulus. The inter-stimulus interval of these two pulses was set to 2, 3, 4, or 5 ms for inhibitory trials and to 7, 9, 12, or 18 ms for facilitatory trials. The task consisted of 50 trials that were pseudo-randomized in blocks of five trials, which consisted of a single-pulse trial (without a conditioning stimulus), two inhibitory and two facilitatory trials. The task was performed twice with a short break in between.

Data were segmented into trials. If in a time window of 40 ms before stimulation, peak-to-peak amplitude exceeded 45 μV, this trial was discarded due to initial muscle tension. The MEP amplitude was determined as the peak-to-peak amplitude of the most positive and most negative peak in a window of 65–100 ms after stimulation. If the MEP amplitude of the single-pulse trial was below 400 or above 2000 μV, the whole block of five trials related to this single-pulse trial was discarded. The relative MEP amplitude was determined by dividing the MEP amplitudes of double-pulse trials by the MEP amplitude of the single-pulse trial of the corresponding block of five trials. For inhibitory and facilitatory trials, the average relative MEP was calculated per subject reflecting SICI and ICF, respectively. A subject was excluded from further analysis, if less than 14 trials with sufficient data quality remained for inhibitory or for facilitatory trials in the pre or post measurement.

STATISTICAL ANALYSIS

Statistical data analysis was performed using the software PASW Statistics (v.18). Repeated-measure ANOVAs with the between-subject factor GROUP (T/B, SCP, CON), the within-subject factor TIME (pre, post) were performed for all measures. For all ANT analyses, an additional within-subject factor STRESS (NoStress, WithStress) was included. For the CNV analysis, a factor CUE (NeutralCue, SpatialCue), and for the target-P3 analysis a factor CUE (NoCue, NeutralCue, SpatialCue) were added (as in the NoCue condition no CNV is elicited, this condition had to be excluded for the CNV analysis). Results were reported if at least a trend was revealed in the ANOVA.

Statistical analyses were based on data for which extreme values (larger/smaller than 2.5 standard deviations) had been excluded. For the self-regulation analyses, extreme values were not excluded due to very small group sizes resulting from the application of a median split.

An exploratory analysis was performed based on pre–post change scores between groups. Effect sizes (Cohen's d) were reported where at least medium effect sizes were revealed. Effects were interpreted following the notion that $d = 0.20$ indicates a small, $d = 0.50$ a medium, and $d = 0.80$ a large effect (Cohen, 1988).

In addition, for all-measures ANOVAs were calculated for pre-training data and results were only reported if significant pre-training differences were observed.

Self-regulation analyses performed for the SCP and theta/beta groups were based on Student's t-tests. As we had directed hypotheses regarding associations of SCP negativity regulation and CNV amplitudes, one-sided, t-tests were applied. For the associations of theta/beta self-regulation and P3 amplitudes two-sided, t-tests were used, as we did not have directed hypothesis regarding the direction of P3 amplitude changes.

RESULTS

LEARNING OF SELF-REGULATION SKILLS

For the SCP group ($n = 17$), a trend was obtained for a change in differentiation from the beginning to the end of training (pre: $M = -1.02$ μV, SD = 1.43 μV, post: $M = -0.20$ μV, SD = 2.63 μV; $t(15) = -1.40$, $p < 0.10$, Cohen's $d = 0.32$). When comparing the change in self-regulation of good and poor performers from the beginning to the end of training (see **Figure 1A**), good performers based on negativity self-regulation during SCP training were able to produce, e.g., significantly more pronounced negative potential shifts in the course of training than poor performers ($t(14) = 3.81$, $p < 0.01$).

For theta/beta training ($n = 16$), theta/beta ratio did not significantly change in the course of training (pre: $M = 1.72$, SD = 0.31, post: $M = 1.75$, SD = 0.34; $t(16) = -1.05$, n.s.). When comparing the change in self-regulation of good and poor performers from the beginning to the end of training (see **Figure 1C**), a significant difference was obtained for good compared to bad performers based on self-regulation of the theta/beta ration during theta/beta training ($t(15) = 4.14$, $p = 0.001$).

ATTENTIONAL PROCESSES

Performance measures

With respect to attention as measured by the ANT (see **Table 2**), RT ($n = 51$) significantly decreased from pre- to post-assessment [TIME: $F(1,48) = 15.58$, $p < 0.001$] and training type showed

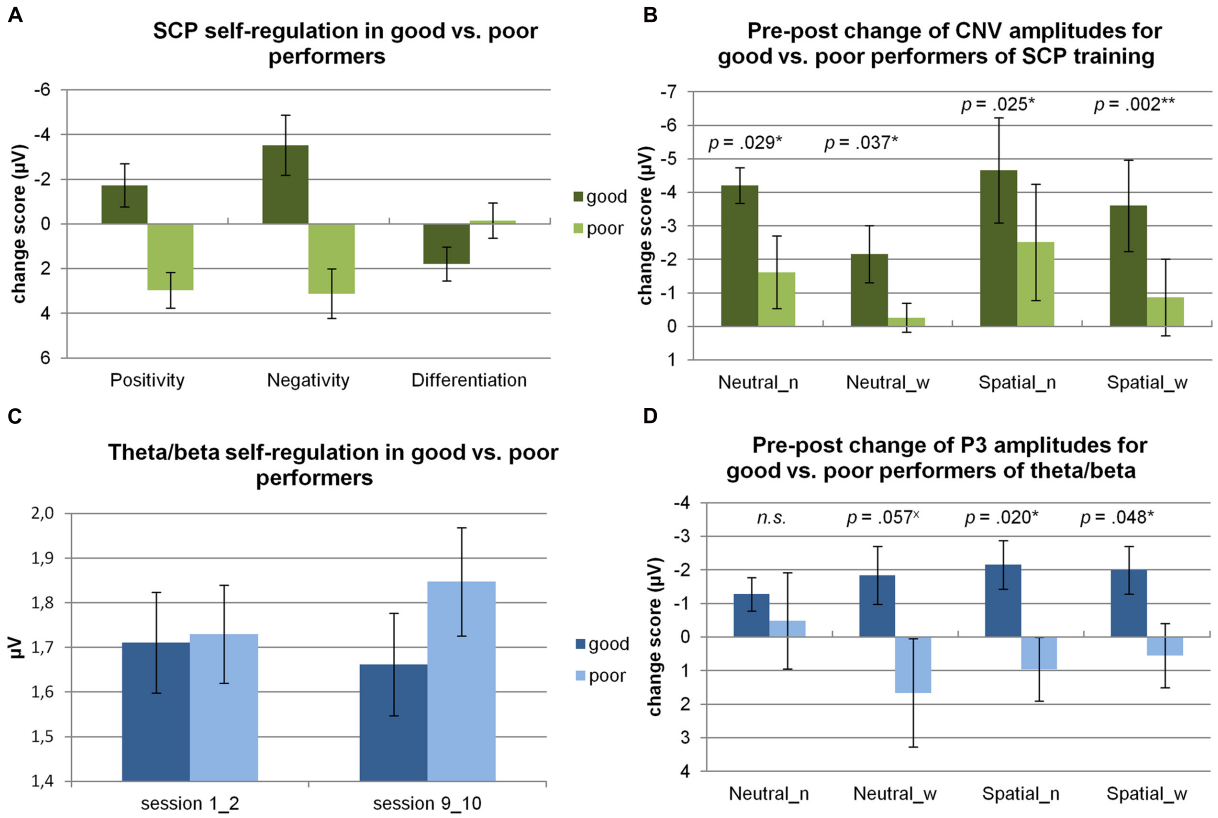

FIGURE 1 | Self-regulation skills. (A) Changes in SCP self-regulation skills from the beginning (first two double sessions) to the end of training (last two double sessions) are depicted for good vs. poor performers. Self-regulation is shown for positivity and negativity trials, and for the differentiation between positivity and negativity trials. The group of good and poor performers is based on the median split of negativity regulation performance. **(B)** Pre–post changes in CNV amplitudes (at Cz) are depicted for good vs. poor performers of negativity regulation for the NoStress (n) and WithStress (w) conditions during NeutralCue and SpatialCue trials. In addition, *p* values of the one-sided, Student's *t*-tests performed to compare CNV amplitudes of good and bad performers are depicted. **(C)** Changes in theta/beta self-regulation skills (theta/beta ratio) from the beginning (double sessions 1 and 2) to the end of training (double sessions 9 and 10) are depicted for good vs. poor performers based on the median-split of theta/beta ratio self-regulation. **(D)** Pre–post changes in target-P3 amplitudes (at Pz) are depicted for good vs. poor performers of theta/beta regulation for the NoStress (n) and WithStress (w) conditions during NeutralCue and SpatialCue trials. In addition, *p* values of the two-sided, Student's *t*-tests performed to compare P3 amplitudes of good and bad performers are depicted. ^{x}trend; *significant result, i.e., $p < 0.05$, **result remains significant after Holm–Bonferroni correction due to multiple comparisons.

a tendency to have an effect on this pre–post decrease in RT [TIME × GROUP ($F(2,48) = 2.84$, $p < 0.10$)]. These group differences were mainly related to larger decreases in the T/B group in the range of medium to large effect sizes (see **Table 3**).

Regarding the number of correct responses ($n = 48$), no significant pre–post changes were observed [TIME: $F(1,45) = 2.43$, n.s.; TIME × GROUP: $F(2,45) = 0.42$, n.s.]. While the variability of RTs ($n = 51$) significantly decreased from pre to post [TIME: $F(1,48) = 9.23$, $p < 0.01$], no significant effect of training type could be observed [TIME × GROUP: $F(2,48) = 0.41$, n.s.].

For the performance measures, no group-specific effects including the factor STRESS were observed.

CNV

Grand average ERPs during the preparation phase of the ANT are depicted in **Figures 2A,B**. A significant interaction of TIME and GROUP was obtained [$F(2,42) = 3.89$, $p < 0.05$] indicating that type of training differentially affected attentional processing during anticipation as measured by CNV amplitudes during the ANT. This effect was related to a pre–post increase in CNV amplitude in both NF groups and a decrease in the control group. Effect size measures revealed medium to large effects for the T/B vs. CON and for the SCP vs. CON group, but no effect for the SCP vs. T/B group (see **Table 3**).

In addition, a significant effect of GROUP was observed [$F(2,42) = 3.61$, $p < 0.05$] which was related to higher overall CNV values in the SCP group.

No group-specific effects including the factor STRESS were observed.

In line with our hypotheses, good compared to poor negativity regulation during SCP training was associated with significantly larger pre–post increases of CNV amplitudes for all four stress/cue conditions according to one-sided, Student's *t*-tests (see **Figure 1B**). Cohen's *d* revealed large effects for all four conditions (NeutralCue_NoStress: $d = 1.24$;

Table 2 | Attention Network Test performance.

	Theta/beta		SCP		Control	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Hits_n	95.0 ± 1.2	95.4 ± 0.7	94.8 ± 1.1	94.9 ± 1.6	94.4 ± 1.4	95.1 ± 0.9
Hits_w	94.9 ± 0.9	94.8 ± 1.4	94.5 ± 1.2	94.6 ± 1.2	94.5 ± 1.5	94.6 ± 1.6
RT_n (ms)	426.1 ± 32.1	400.2 ± 33.3	415.1 ± 41.4	408.9 ± 46.4	419.1 ± 36.8	404.5 ± 29.2
RT_w (ms)	417.2 ± 32.8	392.4 ± 27.7	407.4 ± 39.2	402.8 ± 43.7	409.5 ± 36.1	401.5 ± 29.9
RTV_n (ms)	72.8 ± 16.9	60.0 ± 19.8	75.6 ± 22.1	62.7 ± 23.9	74.0 ± 19.7	67.1 ± 15.8
RTV_w (ms)	64.4 ± 14.0	55.9 ± 9.6	63.3 ± 15.2	64.4 ± 21.3	69.8 ± 20.7	64.6 ± 20.0

For each group, the mean score (±SD) of each measure of the ANT are depicted at both pre- and post-assessment. SCP, slow cortical potential training group; RT, reaction time; RTV, variability of reaction time; ms, milliseconds; n, NoStress condition; w, WithStress condition.

Table 3 | Effect sizes (Cohen's *d*).

	Theta/beta vs. control	SCP vs. control	Theta/beta vs. SCP
Attention Network Test (ANT)			
Reaction time (RT) total score	**0.61**	−0.21	**0.82**
Contingent negative variation (CNV)			
NoStress/WithStress	**0.66/1.01**	**0.57/0.84**	0.00/0.06
Transcranial magnetic stimulation (TMS)			
SICI	| **1.08**|	| 0.44|	**| 0.65|**
ICF	| −0.17|	**| −0.78|**	**| 0.64|**

Effect size measures (Cohen's d) are depicted for the comparison of pre–post change scores between groups. Positive values of effect sizes indicate a larger improvement (or smaller decline) in the group mentioned first compared to the group mentioned second. Black numbers indicate small effect sizes, black bold numbers medium effect sizes, and black bold underlined numbers large effect sizes, while gray numbers indicate no effect. SCP, slow cortical potential training group; total score: based on data averaged over NoStress and WithStress conditions; TMS: for this measure effect sizes are depicted in brackets since it is not clear a change in which direction constitutes an improvement; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation.

NeutralCue_WithStress: $d = 1.15$; SpatialCue_NoStress: $d = 1.30$; and SpatialCue_WithStress: $d = 2.17$).

Target-P3

Grand average ERPs during target processing in the ANT are depicted in **Figures 2C,D**. Attentional resource allocation during target processing as measured by target-P3 amplitudes did not significantly change from pre- to post-training [TIME: $F(1,40) = 0.02$, n.s.; TIME × GROUP: $F(2,40) = 0.56$, n.s.].

Regarding self-regulation of the theta/beta ratio, good performance was associated with significantly larger pre–post decreases of target-P3 amplitudes in the SpatialCue_WithStress and SpatialCue_NoStress condition and with a trend in the NeutralCue_WithStress condition, but not in the NeutralCue_NoStress condition according to two-sided, Student's *t*-tests (see **Figure 1D**).

Cohen's *d* revealed large effects for both SpatialCue conditions (NoStress: $d = 1.38$, WithStress: $d = 1.14$) and for the NeutralCue_WithStress condition ($d = 1.05$), but not for the NeutralCue_NoStress condition ($d = 0.29$), indicating large pre–post decreases in P3 amplitudes in good compared to poor performers in three out of four task conditions.

MOTOR SYSTEM EXCITABILITY

For safety reasons, TMS measurement had not been performed in all subjects and data quality was not sufficient in some subjects which was related to the high variability of single-pulse MEP amplitudes. Thus, 28 subjects (T/B: $n = 10$, SCP: $n = 9$, CON: $n = 9$) could be included in further analyses (for more information see Studer, 2011). Relative MEP amplitudes for SICI and ICF measures are depicted in **Figure 3**.

The repeated-measure ANOVA calculated for the SICI measure resulted in a trend for the interaction of TIME × GROUP [$F(2,25) = 2.83$, $p < 0.10$]. This result was mainly related to differences between the T/B and the CON group, for which a large effect size was obtained and also to differences between T/B and SCP for which a medium effect size was observed (see **Table 3**).

A trend for pre-training group differences was obtained [GROUP: $F(2,25) = 3.37$, $p < 0.10$], related to higher SICI in the control group at pre-training.

Regarding ICF, no significant change from pre- to post-training was observed [TIME: $F(1,25) = 1.49$, n.s.; TIME × GROUP: $F(2,25) = 1.52$, n.s.]. Effect sizes for this ICF measure revealed medium effects for SCP vs. CON, and for T/B vs. SCP (see **Table 3**).

DISCUSSION

The present randomized, controlled investigation in "healthy" adult participants aimed at examining the specificity of the effects of a theta/beta, and an SCP NF training on attention both at the performance and neurophysiological level (ERPs) as well as on motor system excitability (TMS). To our knowledge, the present study was the first study to examine motor system excitability by means of TMS after a complete NF training, and it was one of few studies which has examined the effects of SCP training in "healthy" adults and which has examined the neurophysiological mechanisms mediating the NF effects of both theta/beta and SCP training in a controlled design.

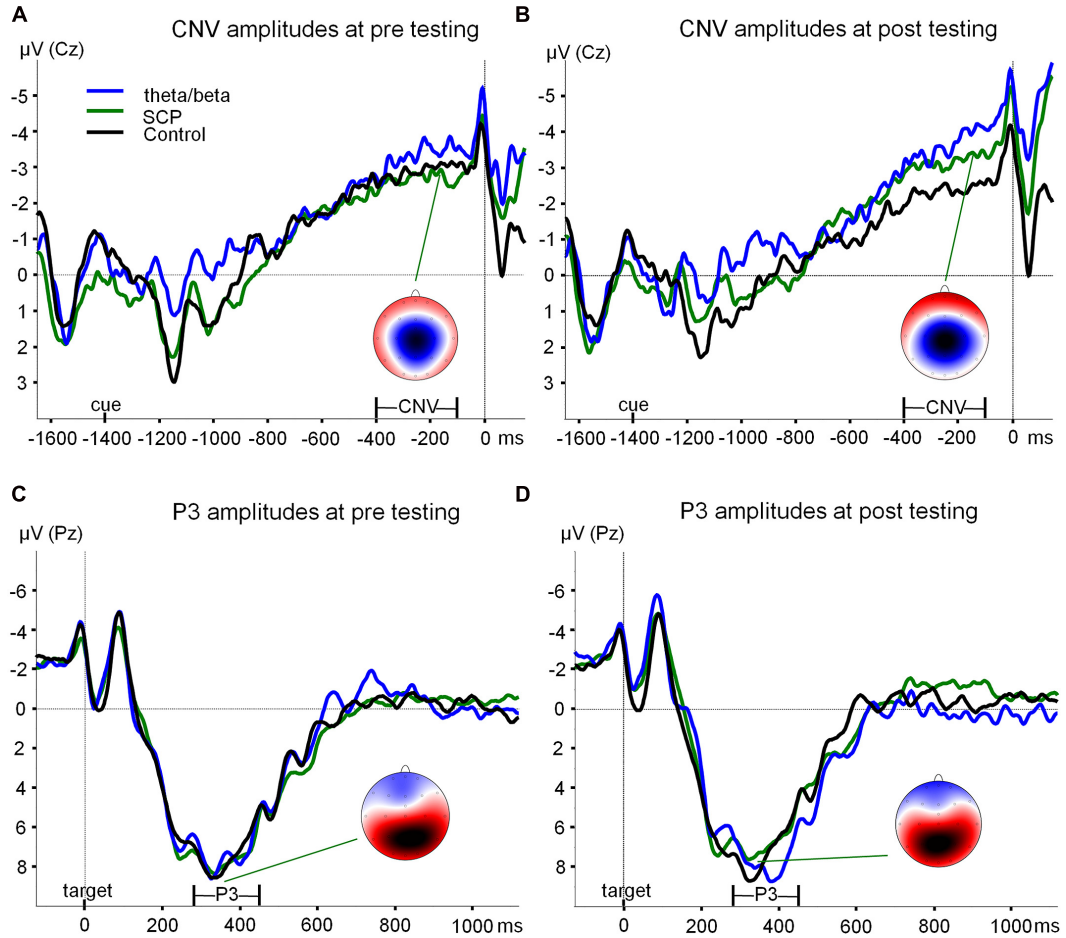

FIGURE 2 | ERPs during the ANT. (A) Grand average ERPs (at Cz) during the preparation phase in the ANT at pre-testing are depicted exemplary for SpatialCue trials (averaged over the NoStress and WithStress conditions) for each training group (theta/beta: blue line, SCP: green line, control: black line). At −1400 ms a cue was presented, flanking fish appeared at −100 ms, and the target fish appeared at 0 ms. Contingent negative variation was determined as the mean area between −400 and −100 ms. Spline-interpolated maps illustrate the topography of the CNV exemplary for the SCP group, with blue and red colors indicating negative and positive amplitude values, respectively in a range from −4 to 4 µV. **(B)** Grand average ERPs (at Cz) during the preparation phase in the ANT at post-testing. **(C)** Grand average ERPs (at Pz) during target processing in the ANT at pre-testing are depicted exemplary for SpatialCue trials (averaged over the NoStress and WithStress conditions) for each training group (theta/beta: blue line, SCP: green line, Control: black line). At 0 ms, the target fish appeared. P3 amplitude was determined as the most positive peak at Pz in the time window 280–450 ms after target presentation. Spline-interpolated maps illustrate the topography of the P3 exemplary for the SCP group, with blue and red colors indicating negative and positive amplitude values, respectively in a range from −8 to 6 µV. **(D)** Grand average ERPs (at Pz) during target processing in the ANT at post-testing. SCP, slow cortical potential training group; CNV, contingent negative variation; ANT, Attention Network Test.

LEARNING OF SELF-REGULATION SKILLS

Self-regulation skills of the theta/beta ratio as well as differentiation between negativity and positivity trials were not sufficiently learned in our study. This constitutes a limitation of our study and needs to be considered for the interpretation of the results. At the same time, regarding the self-regulation analysis, methodological aspects concerning training design and self-regulation analysis need to be considered and self-regulation results of our study need to be discussed in the light of NF literature.

One reason for the non-sufficient learning of self-regulation may be related to the training design of double sessions, which lasted for about two hours, which is much longer than the design commonly applied in adult NF studies. In addition, many of the participants had very packed time schedules and the demands of being attentive for such a long time may have been too long. This is supported by observations of the trainers that many participants became very tired in the course of training. In addition, the number of training sessions (10 double sessions) may not have been sufficient to acquire reliable self-regulation and the instruction of using cognitive strategies may have interfered with the processing of the contingent feedback signal.

Regarding methodological aspects of self-regulation analysis, so far there is no standardized analysis method in the literature. In our training design, within the first two sessions, the duration of most self-regulation blocks was much shorter than for the following sessions in order to allow subjects so accommodate to the training programs. Thus, self-regulation during shorter self-regulation blocks at the beginning of the training was compared to

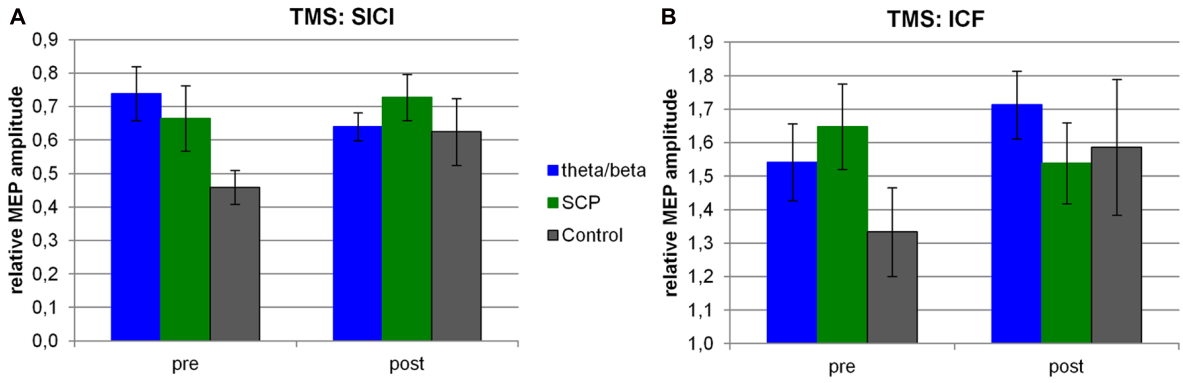

FIGURE 3 | TMS. For each group, the relative MEP amplitude is depicted for SICI **(A)** and ICF **(B)** measures both at pre- and post-assessment. SCP, slow cortical potential training group.

self-regulation during longer self-regulation blocks at the end of the training which required keeping up successful self-regulation for a longer period in a row.

In children with ADHD, some studies have reported on self-regulation abilities. Self-regulation abilities were acquired during theta/beta and SCP training (Leins et al., 2007), and learned self-regulation in the course of SCP training was associated with larger reductions in ADHD symptomatology in two studies (Strehl et al., 2006; Drechsler et al., 2007). However, comparability to our study remains limited as applying these NF protocols in patients may leave more room for improvements. Also the theta/beta training was realized in a different way including much shorter trials, a continuous updating of the baseline and activation as well as deactivation blocks.

Regarding studies in healthy adults, with respect to self-regulation abilities across sessions, mixed results are reported in the literature for different NF protocols (e.g., Raymond et al., 2005b; Doppelmayr and Weber, 2011; Weber et al., 2011; De Zambotti et al., 2012). In a comprehensive review of self-regulation abilities acquired in healthy adults, it is concluded that SMR learning has mainly been successful (Gruzelier, 2014), e.g., SMR learning was observed after 30 sessions by Doppelmayr and Weber (2011), but in a recent study by Gruzelier et al. (2014), across-session SMR learning was only observed by linear trends, and it was not observed in a study by Vernon et al. (2003). So far, SCP training has hardly been applied in healthy adults, but it has been shown, that adults are able to learn self-regulating their SCPs (Birbaumer, 1999). Regarding theta/beta training, Doppelmayr and Weber (2011) did not observe theta/beta theta/beta (4.5–7.5/17–21 Hz) learning after 30 training sessions, while they observed SMR learning in the SMR training group. Due to the differences in training protocols with respect to, e.g., frequency bands (we used a broader beta band ranging from 13 to 20 Hz), training implementation (duration of training sessions, including transfer trials, using cognitive strategies for self-regulation) limits comparability of the described results in addition to differences in the parameterization of self-regulation.

Despite the discussed limitations related to self-regulation, the study was able to indicate both some effects at the group level and differential effects between good and poor performers and thus indicating some specific effects of theta/beta and SCP training.

ATTENTIONAL PROCESSES

Regarding attentional performance during the ANT, our study did not reveal any advantages of NF on the number of correct responses, mainly due to ceiling effects as performance in all groups was very good at pre-testing (e.g., nearly 100% correct responses). Faster responding and lower variability of responses during the ANT were observed over all groups, which constitute general learning effects related to the repeated task performance.

More specifically, a trend for a larger increase in response speed which was related to the type of training was observed. Effect sizes measures revealed a large effect for the theta/beta compared to the SCP group indicating a specific effect for theta/beta training.

While such an effect was not observed to be specific for theta/beta training in children with ADHD (Wangler et al., 2011), comparability of this finding to studies in healthy adults remains difficult as we used a broader beta band (13–20 Hz) and also due to the non-consistent findings in the literature. While faster responding in attention tasks was observed after beta training (15–18 Hz) and reduced variability of responding after SMR training (Egner and Gruzelier, 2004), a more recent study reported faster responding only after SMR but not after theta/beta (4.5–7.5/17–21 Hz) training (Doppelmayr and Weber, 2011). These mixed results may be related to differences in training protocols as has been discussed above, as well as to the different attention tasks employed in the different studies.

On the neurophysiological level, attentional resource allocation during the preparation phase of the ANT was improved after NF compared to CON training as indicated by medium to large effect sizes for each of the NF groups compared to the CON group. Contrary to our hypotheses, no differential effect between the SCP and theta/beta training groups was obtained. However, self-regulation abilities of good performers during SCP training were associated with a larger increase in CNV amplitudes compared to poor performers. In addition, it has to be taken into account that overall CNV amplitudes were highest in the SCP group (sign. effect for GROUP), and that despite higher CNV amplitudes at

pre-assessment a pre–post increase in CNV amplitudes comparable to the one after theta/beta training was observed for SCP training. Overall, these results indicate a small specific effect for SCP training on attentional resource allocation as measured by CNV amplitudes.

Our findings of some specific effects of SCP training are in line (but less pronounced) with those of Wangler et al. (2011) who, in children with ADHD, have found the pre–post increase in CNV amplitude to be specific for SCP training. In children with ADHD, increased CNV amplitudes after SCP training compared to a waiting-list group had also been reported previously (Heinrich et al., 2004). Even though in a study by Doehnert et al. (2008) in children with ADHD a decrease in CNV amplitudes was observed after both SCP training and group therapy, this decrease was less pronounced in those children who successfully learned SCP self-regulation. Also in adults with ADHD, preliminary results after 15 SCP sessions indicated a trend toward a CNV amplitude increase (Mayer et al., 2012a,b). However, it has to be considered that in several studies in children with ADHD (Sartory et al., 2002; Banaschewski et al., 2003), and also in adults with ADHD (Mayer et al., 2012a,b), reduced CNV amplitudes have been observed compared to normal controls, which may have left more room for improvement than in "healthy" adults. Overall, in line with previous literature our results provide further evidence for specific effects of SCP training on resource allocation as assessed by CNV amplitudes.

Our findings of no overall pre–post change in P3 amplitudes after NF fits into the mixed results reported in the literature. No change in P3 amplitudes has been observed after an SMR training, while an increase in P3 amplitudes was observed after a beta1 (15–18 Hz) training in healthy adults (Egner and Gruzelier, 2004), and after an SMR training in six patients with ADHD who were considered responders of SMR training (Arns et al., 2012). As already discussed in a previous section, comparability of the results of the different studies is limited by the differences in NF protocols that were used as well as by the different attention tasks during which P3 amplitudes were assessed.

Based on self-regulation analysis measures, in our study a specific effect of theta/beta training on attentional resource allocation as assessed by P3 amplitudes was observed. Good performance during theta/beta training (theta/beta ratio) was to some extent (for some but not for all cue conditions) associated with reduced target-P3 amplitudes. Our results were in contrast to Egner and Gruzelier (2001) who observed regulation abilities of SMR as well as beta training in healthy adults to be positively correlated with increased P3 amplitudes. However, it remains to be questioned in how far larger P3 amplitudes are indicators of improved processing abilities. In children with ADHD, target P3 amplitudes during the ANT were observed to decrease from pre- to post-training (combined theta/beta and SCP NF or attention skills training) while at the same time performance improved and in addition, larger decreases in P3 amplitudes after training were reported for more intelligent children (Wangler et al., 2011). Moreover, repeated task performance had been associated with decreased P3 amplitudes (Howells et al., 2010). Thus, the hints for decreased P3 amplitudes observed after theta/beta training in our study may also be seen as indicating more efficient stimulus processing.

In summary, in our study differential effects of theta/beta and SCP training on attention were less pronounced than expected. While increased attentional resource allocation was observed for both NF protocols compared to the control group, successful SCP regulation was associated with increased CNV amplitudes suggesting a specific effect for SCP training. Theta/beta training was associated with a larger increase in response speed and successful theta/beta regulation was associated with reduced P3 amplitudes suggesting a specific effect of theta/beta training on more efficient stimulus processing. These results can be seen as in line with the neurobehavioral model of NF (Gevensleben et al., 2012).

MOTOR SYSTEM EXCITABILITY

Regarding motor system excitability, our TMS results after a complete NF training schedule did not constitute an extrapolation of the TMS effects after a single-session NF study by Ros et al. (2010), which had also been performed with different NF protocols, but rather indicated a different pattern of results.

Our study revealed a trend for training effects on SICI, which was related to an increase in SICI after theta/beta training as indicated by a large effect size for the T/B vs. CON and by a medium effect size for T/B vs. SCP group. Thus, our data suggest a specific effect of theta/beta training on increasing SICI. This constitutes an interesting finding as the motivation for studying effects of NF on motor system excitability was derived from the application of NF training in children with ADHD. Reduced SICI is a common finding in ADHD literature, and methylphenidate has been reported to increase SICI in children with ADHD (Moll et al., 2002). Thus, in healthy adults, theta/beta training exerted similar effects on motor system excitability as methylphenidate in children with ADHD.

In an exploratory analysis solely based on effect size measures, our results suggested a specific effect of theta/beta training on increasing both SICI and ICF. A treatment leading to an increase in SICI in combination with an increase in ICF is a rare finding in the TMS literature. Kirschner et al. (2003) observed an increase of both SICI and ICF in healthy adults after a single-dose treatment with methylphenidate. Thus, in healthy adults, theta/beta training exerted similar effects on motor system excitability as methylphenidate.

However, limitations of the TMS analysis were the small group sizes, the trend for pre-training group differences for the SICI measure (trend for higher SICI in the CON group at pre-training) and results being mainly based on an exploratory effect size analysis. In addition, the functional significance of changes in motor system excitability during a resting state in healthy adults is not clear. Due to the small group sizes, the good–bad performer analysis based on theta/beta and SCP self-regulation could not be performed for the TMS measures.

Overall, our study was the first study to report effects of a complete NF training on motor system excitability. Changes in motor system excitability after theta/beta training paralleled the effects of methylphenidate in children with ADHD, i.e., an increase of SICI was observed. In an exploratory analysis, the increase in SICI and ICF observed after a theta/beta training also paralleled the effects of methylphenidate in healthy adults. Further research based on a larger sample is needed to validate these findings and studying motor system excitability during NF self-regulation may

allow to better evaluate the functional significance of observed changes.

METHODICAL ISSUES

The present investigation was conducted in "healthy" adults and not in children with ADHD due to the very comprehensive pre and post assessments, and in order to recruit a larger and more homogeneous sample. However, regarding the aim of a relatively homogeneous sample, it proofed difficult to recruit healthy adults who wanted to spend that much time for the comprehensive training sessions. Thus, adults with some kind of subclinical symptomatology (which according to the Symptom-Checklist-90 was more pronounced in the control group) were included in the study which may have affected the results.

The theta/beta protocol in our study included a broader beta band (13–20 Hz), which made comparability to some findings in healthy adults difficult, as in those studies training was based on separate and smaller SMR and beta bands. However, the theta/beta protocols used in our study has been successfully applied in children with ADHD and therefore can be considered a legitimate approach.

Regarding statistical analysis, due to the limited sample size medium effects did not reach the level of significance. A larger sample would have been needed in order to delineate robust results instead of reporting results based on effect size measures, despite the sample size of the present study being comparable to previous peak performance NF studies (e.g., Egner and Gruzelier, 2004; Ros et al., 2009; Logemann et al., 2010; Doppelmayr and Weber, 2011).

CONCLUSION

Self-regulation skills were not sufficiently learned during theta/beta and SCP training, which needs to be considered as a limitation of our study. Yet, based on the good–poor performer analysis, some specific training effects on ERP components were observed. In line with the literature of NF in ADHD, our study provided further support for the SCP-specific effects on attentional resource allocation (CNV amplitudes) during response preparation also in "healthy adults." Theta/beta training was associated with increased response speed and reduced attentional resource allocation (P3 amplitudes) during target processing, adding to the mixed results reported in both ADHD and peak performance literature. Moreover, motor system excitability measures suggested parallels of the effects of a theta/beta training to those of methylphenidate, constituting a new finding.

Future studies including larger sample sizes are needed to further evaluate the protocol-specific effects on attention and motor system excitability reported. Moreover, examining which factors mediate a more reliable acquisition of self-regulation skills, methodical issues of the parameterization of self-regulation as well as assessing motor system excitability during self-regulation can be considered as relevant topics for future research.

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EEG neurofeedback treatments in children with ADHD: an updated meta-analysis of randomized controlled trials

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Objective: We undertook a meta-analysis of published Randomized Controlled Trials (RCT) with semi-active control and sham-NF groups to determine whether Electroencephalogram-neurofeedback (EEG-NF) significantly improves the overall symptoms, inattention and hyperactivity/impulsivity dimensions for probably unblinded assessment (parent assessment) and probably blinded assessment (teacher assessment) in children with Attention Deficit Hyperactivity Disorder (ADHD).

Data sources: A systematic review identified independent studies that were eligible for inclusion in a random effects meta-analysis.

Data extraction: Effect sizes for ADHD symptoms were expressed as standardized mean differences (SMD) with 95% confidence intervals.

Results: Five identified studies met eligibility criteria, 263 patients with ADHD were included, 146 patients were trained with EEG-NF. On parent assessment (probably unblinded assessment), the overall ADHD score (SMD = −0.49 [−0.74, −0.24]), the inattention score (SMD = −0.46 [−0.76, −0.15]) and the hyperactivity/impulsivity score (SMD = −0.34 [−0.59, −0.09]) were significantly improved in patients receiving EEG-NF compared to controls. On teacher assessment (probably blinded assessment), only the inattention score was significantly improved in patients receiving EEG-NF compared to controls (SMD = −0.30 [−0.58, −0.03]).

Conclusions: This meta-analysis of EEG-NF in children with ADHD highlights improvement in the inattention dimension of ADHD symptoms. Future investigations should pay greater attention to adequately blinded studies and EEG-NF protocols that carefully control the implementation and embedding of training.

Keywords: attention deficit hyperactivity disorder, neurofeedback, randomized controlled trial, learning, practice guidelines

INTRODUCTION

The techniques of neurofeedback (NF) enable a patient to train him or herself to self-regulate a single measure of brain activity (Coben and Evans, 2011; Micoulaud-Franchi et al., 2014). Brain activity can be measured through electroencephalography (EEG); the technique is thus called EEG-NF. EEG-NF training aims to achieve self-control over specific aspects of electrical brain activity through real-time feedback and positive reinforcement and implement these self-regulation skills in daily life (Heinrich et al., 2007; Gevensleben et al., 2012). There is growing interest in the use of neurofeedback treatment in Attention Deficit Hyperactivity Disorder (ADHD) by providing strategies for better self-regulation and management of some disturbances of the disorder (Gevensleben et al., 2012; Arns et al., 2014; Vollebregt et al., 2014b). Nevertheless, NF effectiveness is one of the most debated subjects in this area at the moment

(Gevensleben et al., 2012; Arns and Strehl, 2013; Sonuga-Barke et al., 2013b; Arns et al., 2014; Cannon et al., 2014; Dagenais et al., 2014; van Dongen-Boomsma, 2014; van Dongen-Boomsma et al., 2014).

Despite the significant effects of probably not blinded assessment (i.e., an assessment made by an individual likely to be not blind to treatment, which was in most cases the parent assessment) (Arns et al., 2009), a recent meta-analysis by Sonuga-Barke et al. (2013a) reported a trend of only four Randomized Controlled Trials (RCT) with semi-active control (i.e., cognitive remediation or electromyographic (EMG)-biofeedback) and sham-NF groups (i.e., control conditions where everything is identical to the EEG-NF, except that in this case the feedback is not related to brain activity) (Arns et al., 2014), with "probably blinded assessment" (i.e., assessment made by an individual likely to be blind to treatment, which was in most cases assessment made by a teacher) (Gevensleben et al., 2009b; Bakhshayesh et al., 2011; Lansbergen et al., 2011; Steiner et al., 2011). Moreover, the effect of the total score on scale evaluating overall ADHD symptoms with probably blinded assessment was small (SMD = −0.29 [−0.61, 0.02], p = 0.07) (Sonuga-Barke et al., 2013a). This result was in line with the previous meta-analysis by Arns et al. (2009) that observed smaller effects in better-controlled studies (Arns et al., 2009).

Since this later meta-analysis, further RCTs were published (Arns et al., 2014); because of the methodological issues regarding blinded or unblinded assessment (by parents or teachers) (Arnold et al., 2013), we decided to further examine the efficacy of EEG-NF on ADHD in an updated meta-analysis. In addition, the meta-analysis by Sonuga-Barke et al. (2013a) did not analyze the inattention and hyperactivity/impulsivity dimensions separately, which define the three primary subtypes of ADHD: the predominately inattentive type, the predominantly hyperactive/impulsive type and the combined type (American Psychiatric Association, 2000; Polanczyk et al., 2007). Thus, we perform the present meta-analysis on overall ADHD symptoms as well as the inattention and hyperactivity/impulsivity dimensions for both probably unblinded assessment (parent assessment) and probably blinded assessment (teacher assessment). Thus, the aim of this study was to focus on recent major developments in the field of NF and ADHD in order to complete and update the meta-analysis of Sonuga-Barke et al. (2013a) by including further RCTs, published after this later meta-analysis with semi-active control and sham-NF groups to compare the NF intervention with an intervention that controls for the non-specific effects of EEG-NF (Arnold et al., 2013; Arns et al., 2014).

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations to undertake the search and analysis of the international scientific literature (Moher et al., 2009).

We searched PubMed, Embase and Google Scholar databases for publications between April 2012, the date of search finalization of the previous meta-analysis (Sonuga-Barke et al., 2013a) and August 2014. The following MESH terms were used: ("Neurofeedback" OR "EEG Biofeedback") AND ("ADHD" OR "attention-deficit/hyperactivity disorder"). We also examined the citation lists of identified publications for additional studies, used the related articles function of the PubMed database. English language publications reporting a RCT were eligible for inclusion. Studies were included if they met the following criteria:

1. Design: randomized controlled trials (RCT).
2. Intervention: standard protocol EEG-NF with Theta/Beta Ratio training—TBR (or likely to standard TBR training) or Slow Cortical Potentials (SCP) training.
3. Control group: semi-active (i.e., cognitive remediation and EMG-biofeedback) and sham-NF.
4. Participants: participants with an established clinical diagnosis of ADHD thanks to DSM or CIM criteria.
5. Evaluation of ADHD severity based on a validated scale with probably blinded assessment (teacher assessment) data available.
6. No secondary analyses of previously included trials.

Data was independently extracted into a standard electronic form by two authors (Jean-Arthur Micoulaud-Franchi and Pierre A. Geoffroy): first author name, date of publication, country, EEG-NF protocol, number of session, duration of session, electrode positions, manual or automatic threshold reward, session of transfer learning strategies in daily life, control protocols, sample size, mean age, percentage of ADHD males included, percentage of co-administration of methylphenidate, parent and teacher ADHD assessment (overall, inattention and hyperactivity/impulsivity scores).

We calculated a standardized mean difference (SMD) with 95% confidence intervals (CIs) for each study, defined as the difference in pre-post treatment mean changes between the two groups (ADHD with EEG-NF vs. control groups) divided by the pooled standard deviation of the measurements, as previously performed by Sonuga-Barke et al. (2013a). Random effects modeling for pooled effect sizes (ES) were used because it provides a more conservative ES estimate (Hedges and Olkin, 1985; DerSimonian and Laird, 1986). The SMDs were interpreted in a similar manner to Cohen's d (0.2 = small ES; 0.5 = medium ES; 0.8 = large ES). Confidence limit ratios (CLR = upper-to-lower confidence limit ratio) were calculated for significant CIs in order to estimate the precision and the random error (Poole, 2001). The I^2 statistic was used to quantify heterogeneity, with the values of 25%, 50% and 75% reflecting a small, medium or high degree of heterogeneity, respectively (Higgins et al., 2003). We used funnel plots to estimate by visual inspection the risk of bias (Borenstein et al., 2009). Forest plots were generated to show SMD with corresponding CIs for each study and the overall estimate of pooled random effects. We conducted two subgroups analyses to determine the impact of probably blinded assessment (teacher assessment) on ES estimates for EEG-NF effectiveness. Because sensitivity analysis to test for EEG-NF and clinical characteristics effects was not possible because of the small number of trials, we tested the correlation between ES and mean age, percentage of male, percentage of patient treated with methylphenidate with Spearman rank correlations. All analyses were performed

with Review Manager 5.2 software (Cochrane Collaboration, Copenhagen, Denmark) and SPSS software (Version 18, PASW Statistics).

RESULTS

RESULTS OF THE LITERATURE SEARCH

Twelve RCTs were published since April 2012. We excluded one study with a non-standard EEG-NF protocol (Arnold et al., 2013), five studies with non-semi-active or sham-NF control groups (i.e., treatment as usual or methylphenidate) (Li et al., 2013; Ogrim and Hestad, 2013; Bink et al., 2014; Meisel et al., 2014) and one study with no available probably blinded assessment data (Duric et al., 2012). Two studies were excluded because there were secondary analyses of already included RCTs (Steiner et al., 2014a; Vollebregt et al., 2014a).

Three studies from April 2012 to August 2014 (van Dongen-Boomsma et al., 2013; Maurizio et al., 2014; Steiner et al., 2014b) were eligible for inclusion. The previous meta-analysis by Sonuga-Barke et al. (2013a) included four RCTs (Gevensleben et al., 2009b; Bakhshayesh et al., 2011; Lansbergen et al., 2011; Steiner et al., 2011). We excluded studies that would lead us to pool data to avoid including the same patients more than once. Indeed, two studies eligible for inclusion in the present meta-analysis (van Dongen-Boomsma et al., 2013; Steiner et al., 2014b) were continuations of pilot studies included in the meta-analysis of Sonuga-Barke et al. (2013a) (Lansbergen et al., 2011; Steiner et al., 2011). These two pilot studies were not included in the present meta-analysis.

At the end of this RCT selection process, five studies were retained for quantitative analysis: two from the previous meta-analysis of Sonuga-Barke et al. (2013a) (Gevensleben et al., 2009b; Bakhshayesh et al., 2011) and three recently published RCTs (van Dongen-Boomsma et al., 2013; Maurizio et al., 2014; Steiner et al., 2014b).

RESULTS OF THE META-ANALYSIS

Studies and populations characteristics

Overall, 263 patients with ADHD were included vs. 179 in the meta-analysis of Sonuga-Barke et al. (2013a), the mean age range was 8.4–10.6 years, the range of the male percentages was 67.6–96.3% and the range of the children percentages taking methylphenidate was 0–50%. One hundred and forty-six patients vs. 103 in the meta-analysis of Sonuga-Barke et al. (2013a) were trained with EEG-NF. Four trials studied TBR training (Bakhshayesh et al., 2011; Maurizio et al., 2014; Steiner et al., 2014b) or likely to standard TBR training (van Dongen-Boomsma et al., 2013), one used the combination of both: TBR training and training of SCP (Gevensleben et al., 2009b). Sixty-nine controls received cognitive remediation (Gevensleben et al., 2009b; Steiner et al., 2014b) and 48 controls received sham-NF (van Dongen-Boomsma et al., 2013) or EMG biofeedback (Bakhshayesh et al., 2011; Maurizio et al., 2014). Three differents ADHD scales were used: the German ADHD Rating Scale, the ADHD Rating Scale and the Conners' Rating Scale. **Table 1** summarizes the characteristics of the included studies.

Effects of EEG-NF on parent assessment (probably no-blinded assessment)

The overall ADHD score (SMD = −0.49 [−0.74, −0.24], CLR = 3.08, $p < 0.001$), the inattention score (SMD = −0.46 [−0.76, −0.15], CLR = 3.04, $p = 0.003$) and the hyperactivity/impulsivity score (SMD = −0.34 [−0.59, −0.09], CLR = 6.55, $p = 0.007$) were significantly improved in patients receiving EEG-NF compared to controls. The three associated funnel plots were reasonably symmetrical excluding publication biases (**Figure 1**).

Effect of EEG-NF on teacher assessment (probably blinded assessment)

The inattention score was significantly improved in patients receiving EEG-NF compared to controls (SMD = −0.30 [−0.58, −0.03], CLR = 19.33, $p = 0.03$). No significant effect was found on the overall ADHD score (SMD = −0.18 [−0.42, 0.07], $p = 0.15$) and the hyperactivity/impulsivity score (SMD = −0.14 [−0.39, 0.10], $p = 0.26$). The three associated funnel plots were reasonably symmetrical excluding publication biases (**Figure 1**).

Sensitivity analysis to test for medication effects

A significant correlation was found between the ES on the overall ADHD score assessed by teacher and percentage of patient treated with methylphenidate ($rs[5] = 0.9$, $p = 0.037$). The more the effect size is negative (i.e., in favor of EEG-NF), the less the percentage of patient treated with methylphenidate. No other significant correlation between ES and EEG-NF and clinical characteristics was found.

DISCUSSION

The major findings of this updated meta-analysis are that: (i) EEG-NF significantly improves the ADHD total score on a parent-assessment scale with a medium effect size of −0.49; (ii) EEG-NF significantly improves both the inattention and hyperactivity/impulsivity dimensions on a parent-assessment scale with medium effect sizes of −0.46 and −0.34, respectively; and (iii) EEG-NF significantly improves the inattention dimension on a teacher-assessment scale with a smaller effect size of −0.30.

Our results confirmed the findings provided by the meta-analysis of Sonuga-Barke et al. (2013a) on the overall ADHD score with a medium effect size of −0.59 on a probably blinded assessment and of −0.29 on a probably unblinded assessment. Note that for overall scores on a probably unblinded assessment, the CLR was 3.08 similar as in Sonuga-Barke et al. (2013a). In our study, CLR was 3.04 for the inattention dimension with a probably unblinded assessment, and was higher with a probably blinded assessment (19.33). This result indicates that probably blinded assessment is influenced more by random error and is more unstable than unblinded assessment. Thus, the evidence supporting EEG-NF interventions was influenced by the probable blindness status of the assessor (probably unblinded parent vs. probably blinded teacher). These results suggest that EEG-NF should be evaluated by at least one probably blinded assessor.

Table 1 | Summary of characteristics of studies included in the meta-analysis of randomized controlled trials of EEG-NF treatments in ADHD.

		EEG-NF characteristics							*N*		Clinical characteristics			
	Country	Number of sessions	Duration of sessions	Electrode positions	Protocol	Rewards	Transfer learning strategies in daily life	Control	EEG-NF	Control	Age (years; mean, SD, [range])	Male %	Methyphenidate %	ADHD measures
Gevensleben et al. (2009b)	DE	36	50	Cz	TBR and SCP	Manual	Yes	Cognitive remediation	59	35	9.1 (1.3) [8–12]	89.1	0	FBB-HKS
Bakhshayesh et al. (2011)	DE	30	30	FCz-CPz	TBR	Manual	No	EMG biofeedback	18	17	9.6 (2.2) [6–14]	72	22	FBB-HKS
van Dongen-Boomsma et al. (2013)	NL	30	45	F3-F4 Fz C3-C4 or P3-P4	Likely to standard TBR protocol	Manual	Yes	Sham neurofeedback	22	19	10.5 (2.2) [8–15]	86.4	50	ADHD-RS
Steiner et al. (2014b)	USA	40	45	Close to Cz	TBR	Automatic	No	Cognitive remediation	34	34	8.4 (1.1) [Not available*]	67.6	44.4	Conners-RS
Maurizio et al. (2014)	SW	36	12–32	Tomographic EEG on ACC	TBR	Manual	Yes	EMG biofeedback	13	12	10.6 (1.3) [8.5–12.9]	96.3	7.6	FBB-HKS

*EEG-NF = EEG Neurofeedback; TBR= Theta/Beta Ratio; SCP = Slow Cortical Potential; ACC = Anterior Cingulate Cortex; FBB-HKS = German ADHD Rating Scale (Parent and Teacher); ADHD-RS = ADHD Rating Scale (Parent and Teacher); Conners-RS = Conners' Rating Scale (Parent and Teacher). *Second and fourth grade students in public elementary schools.*

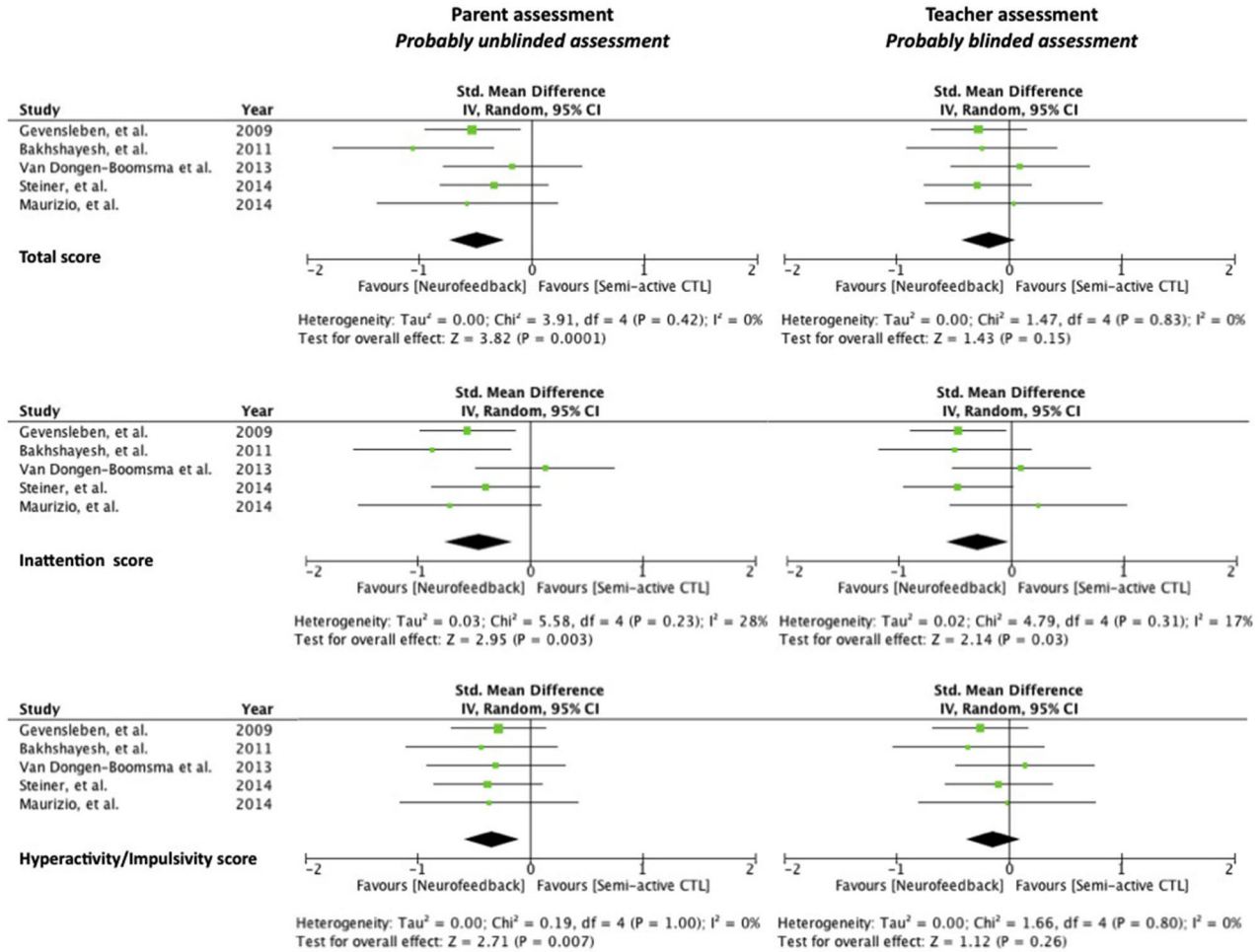

FIGURE 1 | Forest plots with Standardized Mean Difference (SMD), effect size, and homogeneity statistics for the meta-analysis examining total scores of ADHD symptoms, inattention dimension and hyperactivity/Impulsivity dimension assessed by parent (left) and by teacher (right).

The methodological strength and novelty of the present updated meta-analysis was to combine stringent inclusion criteria similar to the meta-analysis of Sonuga-Barke et al. (2013a) with the additional consideration of the inattention and hyperactivity/impulsivity dimensions. These precautions allow us to observe the effects of evidence-supporting EEG-NF on inattention symptoms in ADHD in both probably unblinded parents and probably blinded teacher assessments with similar effect sizes. On the contrary, EEG-NF was found to be effective in hyperactivity/impulsivity only in probably unblinded parent assessments. These results emphasize those of Arns et al. (2009), who observed a smaller size effect for the hyperactivity dimension than for the inattention dimension. Though moderate, the effect size remains significant in our meta-analysis compared to the large effect size observed by Arns et al. (2009). It could be explained by the fact that some trials included in our meta-analysis attempt to blind parents to treatment allocation by using sham NF (van Dongen-Boomsma et al., 2013) or EMG biofeedback with comparable electrode placement to EEG-NF (Bakhshayesh et al., 2011; Maurizio et al., 2014). This improved blinded methodology can diminish the risk of rater bias concerning the placebo effect of electronic devices (Schwitzgebel and Traugott, 1968; Stroebel and Glueck, 1973) and should thus be encouraged in further studies (Arnold et al., 2013; Arns et al., 2014).

The effect size in favor of EEG-NF to treat the inattention dimension of ADHD confirms the standard target of the EEG-NF protocol. EEG-NF, through the TBR or SCP training provides immediate feedback on how the brain is focusing. Thus, these protocols are classically known to reinforce the state of attention (focused and attentive but relaxed) (Monastra et al., 2005; Sherlin et al., 2011; Arns et al., 2014). The significant correlation between the teacher-assessed overall ADHD score and methylphenidate treatment could also be explained by the fact that methylphenidate decreases the TBR in children, exhibiting a positive medication response (Loo et al., 1999). As it was determined that low TBR at baseline was a negative predictor for EEG-NF (Gevensleben et al., 2009a; Arns et al., 2012), this

pharmacological EEG enhancement could reduce the possibility of training on this parameter during a session of EEG-NF (Sherlin et al., 2011). Thus, further studies should analyze the relationship between TBR at baseline and the enhancement of inattention after an EEG-NF intervention and the effect of methylphenidate on performance during EEG-NF training in children with ADHD.

The principal limitations of our meta-analysis include the small number of studies, the relatively small number of subjects enrolled in the individual studies, and the heterogeneous methodology concerning the characteristics of the EEG-NF protocols (**Table 1**). As we conducted an updated meta-analysis of Sonuga-Barke et al. (2013a) by including further RCTs according to similar criteria of inclusion and exclusion, we included only a small number of studies insufficient in order to explore potential reasons of heterogeneity between other studies with less conservative inclusion criteria. Moreover, the inclusion of the van Dongen-Boomsma et al. (2014) study in our meta-analysis could be discussed in line with the debate concerning the inclusion of the Lansbergen et al. (2011) study in the meta-analysis of Sonuga-Barke et al. (2013a) (Arns and Strehl, 2013; Sonuga-Barke et al., 2013b; Arns et al., 2014; Cannon et al., 2014; van Dongen-Boomsma, 2014; van Dongen-Boomsma et al., 2014). The EEG-NF protocol of the pilot study of van Dongen-Boomsma et al. (2013) was considered to be non-standard (Arns and Strehl, 2013; Arns et al., 2014; Cannon et al., 2014). However, we decided to include the van Dongen-Boomsma et al. (2013) study because two changes were made (manually adjusted reward thresholds and transfer learning strategies in daily life) that bring their EEG-NF protocol closer to a standard TBR protocol (Sherlin et al., 2011).

The inclusion of the Maurizio et al. (2014) study in our meta-analysis could be also a subject of discussion because it uses a tomographic EEG-NF that is rarely used in a clinical context. However, we decided to include this study because this training protocol was very close to standard TBR protocol on scalp-level EEG-NF. The main difference was the higher spatial resolution with tomographic EEG-NF. Such studies should be encouraged because it targeted more precisely the brain region known to be affected in ADHD and could increase the efficacy of EEG-NF (Micoulaud-Franchi et al., 2014).

Lastly, the non-inclusion of Arnold et al. (2013) study in our meta-analysis could be criticized. Nonetheless, as the authors highlighted in their limitation (Arnold et al., 2013), the protocol used was not based on the basic learning theory (in particular by the type of reinforcement) used in standard EEG-NF protocol (Sherlin et al., 2011).

This debate, concerning the choice of studies included in EEG-NF meta-analysis, highlights the importance of investigating the efficacy of EEG-NF in children with ADHD with adequately blinded studies as well as EEG-NF protocols that carefully control the implementation and embedding of training concerning the EEG target, reward feedback, learning during the sessions and transfer learning in daily life (Sherlin et al., 2011; Vollebregt et al., 2014b).

Another possible limit of our approach was to link probably blinded assessments to teacher assessments and probably unblinded assessments to parent assessments. Bralten et al. (2013) observed that the associations with genetics were stronger for parent assessment of ADHD symptoms than for teacher assessments. Because of the few number of studies using EMG-biofeedback or sham-NF as control group, we lacked the possibility to provide the meta-analysis with probably blinded parent assessments. Such studies are to be strongly encouraged and could afford more reliable and valid assessments than probably blinded teacher assessments to evaluate the efficacy of EEG-NF (Bralten et al., 2013).

In conclusion, this meta-analysis using stringent inclusion criteria is the third EEG-NF intervention that confirms the efficacy of EEG-NF when ADHD symptoms are assessed by parents (e.g., with a unblinded assessment). This is also the first meta-analysis that suggests the persistence of EEG-NF efficacy only for the inattention dimension of ADHD when considering recent well-controlled studies that include semi-active and sham-NF controls, as well as probably blinded assessment of inattention symptoms.

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Differential effects of theta/beta and SMR neurofeedback in ADHD on sleep onset latency

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Recent studies suggest a role for sleep and sleep problems in the etiology of attention deficit hyperactivity disorder (ADHD) and a recent model about the working mechanism of sensori-motor rhythm (SMR) neurofeedback, proposed that this intervention normalizes sleep and thus improves ADHD symptoms such as inattention and hyperactivity/impulsivity. In this study we compared adult ADHD patients (N = 19) to a control group (N = 28) and investigated if differences existed in sleep parameters such as Sleep Onset Latency (SOL), Sleep Duration (DUR) and overall reported sleep problems (PSQI) and if there is an association between sleep-parameters and ADHD symptoms. Secondly, in 37 ADHD patients we investigated the effects of SMR and Theta/Beta (TBR) neurofeedback on ADHD symptoms and sleep parameters and if these sleep parameters may mediate treatment outcome to SMR and TBR neurofeedback. In this study we found a clear continuous relationship between self-reported sleep problems (PSQI) and inattention in adults with- and without-ADHD. TBR neurofeedback resulted in a small reduction of SOL, this change in SOL did not correlate with the change in ADHD symptoms and the reduction in SOL only happened in the last half of treatment, suggesting this is an effect of symptom improvement not specifically related to TBR neurofeedback. SMR neurofeedback specifically reduced the SOL and PSQI score, and the change in SOL and change in PSQI correlated strongly with the change in inattention, and the reduction in SOL was achieved in the first half of treatment, suggesting the reduction in SOL mediated treatment response to SMR neurofeedback. Clinically, TBR and SMR neurofeedback had similar effects on symptom reduction in ADHD (inattention and hyperactivity/impulsivity). These results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD.

Keywords: ADHD, neurofeedback, theta, SMR, theta/beta, sleep, sleep onset insomnia, EEG

INTRODUCTION

Humans spend about one third of their lives in a sleeping state, yet the function and implications of this "inactive state" are to date not fully understood, especially in relation to psychiatric problems such as depression and attention deficit hyperactivity disorder (ADHD). A well known, validated and accepted model in sleep medicine is the two-process model by Borbély (1982). This model postulates a sleep-wake dependent Process-S and the circadian Process-C. Process-S can be quantified by the build-up of Electroencephalogram (EEG) slow activity (delta and theta) during the day, often referred to as sleep homeostatic drive, and is thus a function of duration of prior waking (Achermann et al., 1993). Also, this slow EEG activity is considered the hallmark of drowsiness (Arns et al., 2010), and shows a gradual decline with subsequent sleep stages. Interestingly, this type of EEG pattern is also seen in a subgroup of ADHD patients (excess theta, or greater theta/beta ratio (Arns et al., 2013a)). Process-C can be quantified by assessing the different circadian measures such as melatonin (using the Dim Light Melatonin Onset (DLMO: Van der Heijden et al., 2005) or core-body temperature. Both Process-S and Process-C, and especially their interaction, play a crucial role in sleep-wake regulation and optimal vigilance regulation. This model also helps explain many sleep related problems, such as jetlag (by a misalignment of Process-C with Process-S) and the effects of sleep deprivation or sleep restriction (Increased sleep pressure or Process-S). Often sleep problems are regarded as a comorbidity in psychiatric disorders. However, recent studies challenge this notion and implicate a causative role in the etiology of circadian and sleep problems in for example Depression (McClung, 2013) and ADHD (Arns and Kenemans, 2014). In the following, we will focus mainly on the role of sleep in ADHD (subgroups).

SLEEP AND COGNITION IN CHILDREN

In a recent large meta-analysis in 35.936 healthy children, Astill et al. (2012) demonstrated clear associations between sleep duration and executive function and school performance (positive), and between sleep duration and inernalizing and externalizing

behavior (negative). In addition, a meta-analysis in 690.747 children recently confirmed that, today, children sleep 1 h and 15 min less than a 100 years ago (Matricciani et al., 2012). Interestingly, several recent studies demonstrated that when morning school-time was delayed by 25–30 min, a 29–45 min *increase* in sleep duration occurred, with subsequent reductions in daytime sleepiness, depressed mood and caffeine use (Owens et al., 2010; Boergers et al., 2014). In a recent multicenter study among 9.000 students, it was even shown that when school start times were shifted from 7.35 AM to 8.55 AM, the number of car crashes among teen drivers was reduced by 70% (Wahlstrom et al., 2014). These studies further support the above trend that children and adolescents today have a too short sleep duration, further supported by a trend for increased signs of drowsiness in healthy children across the last 10 years, as measured with the more objective Electroencephalogram (EEG) Theta/Beta ratio (Arns et al., 2013a), which can be regarded as a measure of drowsiness (as per above, reflective of Process S, or increased homeostatic sleep drive). The question arises if this trend of reduced sleep duration for children has any repercussions in daily life, and/or could possibly be associated with complaints often reported in the ADHD spectrum, given the reported relation between reduced sleep duration and impaired executive functioning and higher levels of internalizing/externalizing behavior (Astill et al., 2012), as well as attentional (Belenky et al., 2003; Van Dongen et al., 2003; Axelsson et al., 2008) and mood problems (Owens et al., 2010; Boergers et al., 2014).

SLEEP, SLEEP RESTRICTION AND ADHD

Sleep deprivation is known to have detrimental effects on cognitive functioning. However, as was demonstrated by Van Dongen et al. (2003), a sleep *restriction* to six hours for 14 days had comparable effects on cognitive functioning (sustained attention and working memory) as two nights of full sleep deprivation, in line with predictions the authors made from the above 2-process model of sleep. Moreover, people submitted to this regimen of sleep restriction were unaware of their cognitive deficits. Similar findings have been reported after 5–7 days of sleep restriction (Belenky et al., 2003; Axelsson et al., 2008). Interestingly, these studies also showed that these cognitive impairments, most specifically inattention, took more days of normal sleep to recover than the initial sleep restriction (Belenky et al., 2003; Axelsson et al., 2008). Sleep restriction studies have also been conducted in children, albeit not as extensively as in adults. In general, sleep restriction studies in healthy children have demonstrated impairments of attention (Fallone et al., 2001, 2005; Sadeh et al., 2003; Beebe et al., 2008) and increased externalizing behavior (impaired behavioral regulation) after one week of sleep restriction (Belenky et al., 2003). Thus, core symptoms of ADHD such as inattention and externalizing behavior can be induced in healthy children through sleep restriction (Fallone et al., 2001; Golan et al., 2004), suggesting a role for sleep in the etiology of ADHD.

Several sleep disorders, such as sleep apnea and restless legs syndrome, are more prevalent in ADHD. Substantial improvements in ADHD complaints have been reported, when such specific sleep disorders were treated (for review also see (Arns and Kenemans, 2014; Cortese et al., 2013)). These sleep disorders most likely impact on Process-S, resulting in an impaired sleep homeostasis and thus sustained sleep restriction, expressed in more signs of drowsiness EEG or theta.

Other studies have investigated the occurrence of idiopathic "sleep-onset insomnia" (SOI), also called "delayed sleep phase syndrome", in ADHD (Van der Heijden et al., 2005). The main symptom in SOI is a difficulty falling asleep at a desired bedtime and/or a sleep onset latency (SOL) of more than 30 min (Smits et al., 2001; Van Veen et al., 2010). SOI is present in 72–78% of unmedicated children and adults with ADHD and in this subgroup of patients with SOI, a delayed DLMO has been found (delayed melatonin onset), suggestive of a circadian phase delay (Van der Heijden et al., 2005; Van Veen et al., 2010). In further agreement with these findings, Rybak et al. (2007) reported that adult ADHD is characterized by a higher prevalence of "evening types", characterized by a delayed circadian phase. Also consistent with this, Arns et al. demonstrated an association between high sunlight intensity and low ADHD prevalence, which could indicate an involvement of circadian clock disturbances Arns et al. (2013c) in ADHD etiology.

In this subgroup, a delayed Process-C causes Process-S and Process-C to intersect at a later time, thus explaining an inability to fall asleep at an age appropriate bedtime. The cause of this delayed circadian phase in ADHD has been attributed to a combination of genetic factors and environmental factors, especially evening exposure to blue-light sources such as LED lights and tablets (Baird et al., 2011; Bijlenga et al., 2011; Chaste et al., 2011; Arns et al., 2013d). Since children all have to go to school at the same time, a delayed sleep onset can cause a reduced sleep-duration and hence result in sleep restriction and associated complaints, such as inattention and/or externalizing behavior. Conversely, as noted above, when morning school times are delayed, overall improvements are seen on mood, alertness and a lower incidence of car crashes (possibly reflective of reduced inattention) (Owens et al., 2010; Boergers et al., 2014; Wahlstrom et al., 2014).

NEUROFEEDBACK AND SLEEP

Several studies have demonstrated that Sensori-Motor Rhythm neurofeedback (SMR) results in increased sleep spindle density during sleep (Sterman et al., 1970; Hoedlmoser et al., 2008), decreased sleep latency (Hoedlmoser et al., 2008) and increased total sleep time (Hoedlmoser et al., 2008; Cortoos et al., 2010). Research has also demonstrated that melatonin results in an increased sleep spindle density (Dijk et al., 1995) and decreased sleep latency (Van der Heijden et al., 2007), suggesting overlap in the working mechanisms of SMR neurofeedback and melatonin.

Sleep spindles are generated by the GABA-ergic thalamic reticular neurons and are synchronized through glutamatergic cortico-thalamic projections (De Gennaro and Ferrara, 2003). The spindle oscillation generated in the reticular neurons is transferred to thalamocortical relay cells in the dorsal thalamic nuclei through GABAergic synapses, producing inhibitory postsynaptic potentials (IPSPs) and these IPSPs travel through glutamatergic thalamocortical axons to generate rhythmic excitatory

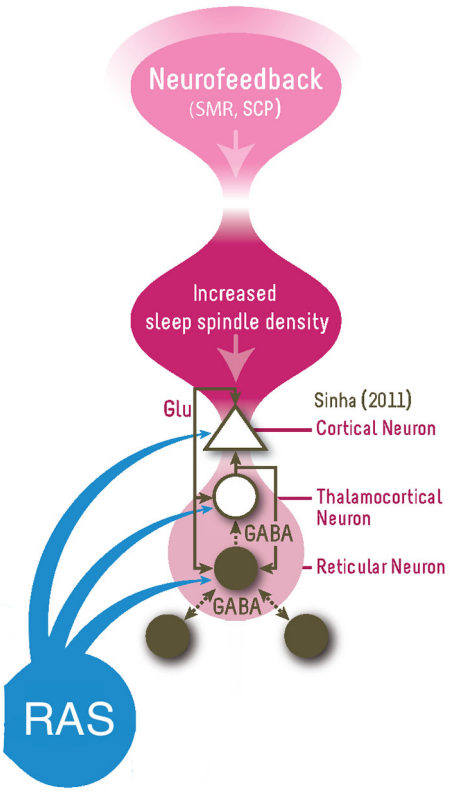

FIGURE 1 | This figure summarizes the proposed model for how neurofeedback (right top) impact on the vigilance system (responsible for sleep-wake regulation). SMR Neurofeedback is thought to train the Reticular-Thalamocortical-Cortical network by increasing the synaptic strengths within this network via the three-way glutamatergic (Glu) connections, resulting in long-term potentiation (LTP) which increases synaptic sensitivity and the probability of future activation in this network, namely by increased sleep spindle density during sleep (Sterman and Egner, 2006). This increased sleep spindle density results in decreased sleep latency and increased total sleep time, resulting in vigilance stabilization (or improved sleep homeostatis). The RAS (Reticular Activating System) also has an influence on this circuitry (Figure adapted from Sinha (2011)).

postsynaptic potentials (EPSPs) in the cortex (Sinha, 2011), also see **Figure 1** for a summary. Therefore, SMR neurofeedback is hypothesized to directly train the sleep spindle circuit given the overlap in frequency and location and as evidenced by studies demonstrating an increase in sleep spindle density after SMR neurofeedback (Sterman et al., 1970; Hoedlmoser et al., 2008). It was proposed that training this network function using neurofeedback results in long-term potentiation (LTP) which increases the synaptic strengths within this network and increase the likelihood of future activation of this network (Sterman and Egner, 2006; Arns and Kenemans, 2014), which was seen as increased sleep spindle density during sleep (Sterman et al., 1970; Hoedlmoser et al., 2008).

The influence of SMR neurofeedback on sleep spindles (Sterman et al., 1970; Hoedlmoser et al., 2008), and effects of SMR neurofeedback on SOL and sleep duration have been demonstrated (Hoedlmoser et al., 2008; Cortoos et al., 2010), however this has not been reported yet in ADHD. Another well-investigated neurofeedback protocol for ADHD is Theta/Beta ratio (TBR) neurofeedback (Arns et al., 2013b), and in earlier work we had observed that patients treated with both SMR and TBR neurofeedback improved on sleep (Arns, 2011; Arns et al., 2012), however no further studies have specifically looked at the effects of TBR neurofeedback on sleep. Furthermore, the TBR neurofeedback we apply aims at training beta frequencies above the SMR band (e.g., 15–20 Hz), so a further reason for including this protocol is to investigate the specificity of training a lower beta band or SMR (12–15 Hz) vs. a higher beta band (e.g., 15–20 Hz) in relation to sleep. Alternatively, Gevensleben et al. (2012), have hypothesized that the effects of TBR neurofeedback are mainly explained by learned self-regulation over brain activity associated with attention, which suggests another working mechanism for the efficacy of neurofeedback in ADHD. Therefore, in this study we employed an open-label design based on data from our clinic where sleep parameters as well as ADHD rating scale (RS) data were collected at different time points through neurofeedback treatment (using either SMR or TBR protocols) as well as data collected in healthy controls.

The primary aims of this study thus were to (1) compare our ADHD patients to a control group in order to substantiate differences on sleep parameters such as SOL, Sleep Duration (DUR) and overall reported sleep problems (PSQI) as well as establish a correlation between sleep-parameters and ADHD symptoms; and (2) investigate the effects of SMR and Theta/Beta (TBR) neurofeedback on ADHD symptoms, sleep parameters such as SOL, DUR and PSQI score and investigate if these sleep parameters mediate treatment outcome. We hypothesize that both SMR and TBR will demonstrate similar improvements on sleep parameters (SOL and DUR) and that these improvements mediate clinical improvement on inattention and hyperactivity/impulsivity. In addition in our analysis we will test for differential effects of protocol.

METHODS

PARTICIPANTS

This study is an open-label pilot study. Twenty-eight healthy controls (age: 21–64 yrs.; 13 male) and 51 patients with ADHD (age: 6–53 yrs; 35 male; 32 children) were included in this study. All files from patients seen in our clinic (Psychology Practice Brainclinics, Nijmegen, The Netherlands) between August 12th 2008 and December 4th 2013 were screened (The patients reported here overlap with the patients reported earlier by Arns et al. (2012)). Patients were screened for ADHD or ADD by a clinical psychologist using a structured interview (MINI Plus Dutch version 5.0.0, for adults or MINI KID for children) during intake. For inclusion in this study all data were screened and inclusion was based on DSM 5 criteria (American Psychiatric Association, 2013). During intake, every 10th session and outtake a self-report scale for ADHD symptoms (Kooij et al., 2005) was assessed (with a maximum score of 9 per sub-scale), as well as a self-report scale for quality of sleep (Pittsburgh Sleep Quality Index (PSQI); (Buysse et al., 1989) that also included questions about SOL and sleep duration (DUR). Only subjects with a primary diagnosis of

ADHD/ADD were included in the study. All patients signed an informed consent form before treatment was initiated.

CONTROLS

Twenty-eight healthy adult controls were included between August 31st 2012 and August 9th 2013, specifically for the purpose of this study. Participants were screened for physical conditions and psychiatric disorders. Participants reporting psychiatric disorders on the MINI plus interview were excluded from the study, as well as participants suffering from major physical illnesses. All controls completed the same questionnaires as the patients (ADHD-RS and PSQI). All controls signed an informed consent form before data collection.

NEUROFEEDBACK TREATMENT

Treatment of patients was identical to the methods published in Arns et al. (2012). In summary, all patients were assessed on a Quantitative EEG (QEEG) and an individualized neurofeedback treatment protocol was derived in line with the QEEG-informed decision rules reported in Arns et al. (2012). For this study only patients that were treated with an SMR or Theta/Beta protocol were included. In the SMR group all patients received a reward on 12–15 Hz at central locations (C3, Cz or C4); and the TBR group received mostly beta rewards outside the SMR frequency range (e.g., 20–25 Hz; 15–20 Hz) only at midline sites (Fz, FCz or Cz) in addition to theta inhibits. The locations for C3 and C4 for the SMR protocol were established using Transcranial Magnetic Stimulation (TMS) to individually localize the area where a visible response of the musculus abductor pollicis (thumb movement) was elicited (i.e., these were individualized "C3" and "C4" sites). In all protocols EMG inhibits were employed, meaning that the EMG (55–100 Hz) had to be kept below 5–10 μV.

Treatment was carried out by a masters level psychologist specialized in neurofeedback, supervised by the first author. Sessions took place 2–3 times a week, for 20–30 min provided in several 5-minute blocks, with 2 min pauses between successive blocks. The wireless Brainquiry PET 4.0 (Brainquiry B.V.) and BioExplorer software (CyberEvolution, Inc.) were used to provide visual feedback (bargraphs or neuropuzzles) and auditory feedback. Thresholds were set to achieve a 25–40% effective reinforcement. In addition for discrete SMR neurofeedback a time-above-threshold was set at 0.15–0.5 s.

ANALYSIS

Differences between groups were tested using One-Way ANOVA's or non-parametric Mann-Whitney U test (gender). Furthermore, for quantifying the effects of neurofeedback on ADHD symptoms and sleep, a repeated measure ANOVA was used with within-subject factor Time (pre-treatment, mid-way treatment and post-treatment) and between subject factor Neurofeedback Protocol (SMR and TBR). In addition partial correlations covarying for age were used to further correlate changes in ADHD symptoms and sleep variables. Effect sizes (ES) reported are between-group or within-group pre-post-treatment Cohen's D (*d*).

Mediator analysis will be performed in line with the MacArthur definitions and guidelines (Kraemer et al., 2002, 2008). The McArthur guidelines for mediator analyses require: (a) temporal precedence of the treatment; (b) an association between the mediator and treatment; and (c) a main effect of the mediator or an interaction between mediator and treatment (Kraemer et al., 2002, 2008). As mediator, the change in the significant sleep variables that change as a result of treatment will be correlated with improvement in inattention and hyperactivity/impulsivity.

Sleep Onset Latencies were log-transformed in order to meet a normal distribution, and for change across sessions a difference score (T_{intake}–$T_{outtake}$) was used rather than a percentage improvement score, since the latter resulted in non-normally distributed data.

RESULTS

Twenty-eight healthy controls (age: 21–64 yrs.; 13 male) and 52 patients with ADHD (age: 6–53 yrs; 37 male) were included in this study. For the comparison between controls and ADHD only adults will be included. For the within subject analysis of the effects of neurofeedback the whole ADHD group will be included.

HEALTHY CONTROLS VS. ADULT ADHD

For the comparison between healthy adult controls (n = 28) and ADHD, only adults with ADHD (N = 19) were included and these groups did not differ in age (p = 0.990; F = 0.000; DF = 1, 46) and gender (p = 0.445; Z = −0.763). The adult ADHD group had significantly higher scores on the ADHD-RS inattention ($p < 0.001$; F = 345.246, DF = 1, 46), ADHD-RS hyperactivity/impulsivity (Hyp/Imp: $p < 0.001$; F = 36.108; DF = 1,46) and PSQI ($p < 0.001$; F = 47.090; DF = 1,46). Furthermore, on the PSQI, adults with ADHD reported a significantly longer SOL of 37 min compared to 14 min for controls (SOL: p = 0.011; F = 7.047; DF = 1, 46) and a significantly shorter sleep duration of 6.8 hrs. compared to 7.4 hrs. for controls (p = 0.014; F = 6.562; DF = 1,46), also see **Table 1** for further details.

Correlations between ADHD complaints and sleep variables for the adult group yielded a significant correlation between age and sleep duration, hence partial correlations correcting for age were performed. Partial correlations with age as covariate yielded significant correlations between Inattention and PSQI score ($p > 0.001$; r = 0.789; DF = 44) for the whole group and performing this analysis separately for the ADHD group also resulted in a significant effect (p = 0.035; r = 0.499, DF = 16) but not for controls (p = 0.208; r = 0.250; DF = 25). Correlations between Inattention and Sleep Duration (p = 0.006; r = −0.401; DF = 44) and SOL (p = 0.004; r = 0.414; DF = 44) and between Impulsivity/Hyperactivity vs. PSQI score (p = 0.001; r = 0.464; DF = 44) and Sleep Duration (p = 0.027; r = −0.326; DF = 44) were only significant for the whole group, but not within the ADHD and control groups, suggesting these effects are driven only by the group differences. **Figure 2** visualizes these correlations further.

Using the criterion from previous studies that a SOL latency of ≥30 min (both in children and adults) can be considered sleep onset insomnia (SOI), 29/51 (57%) of the whole sample of ADHD subjects vs. 5/28 (18%) of the controls met this definition, which was also significantly different between groups (p = 0.001; Chi-Square = 11.218). This analysis was conducted on the whole

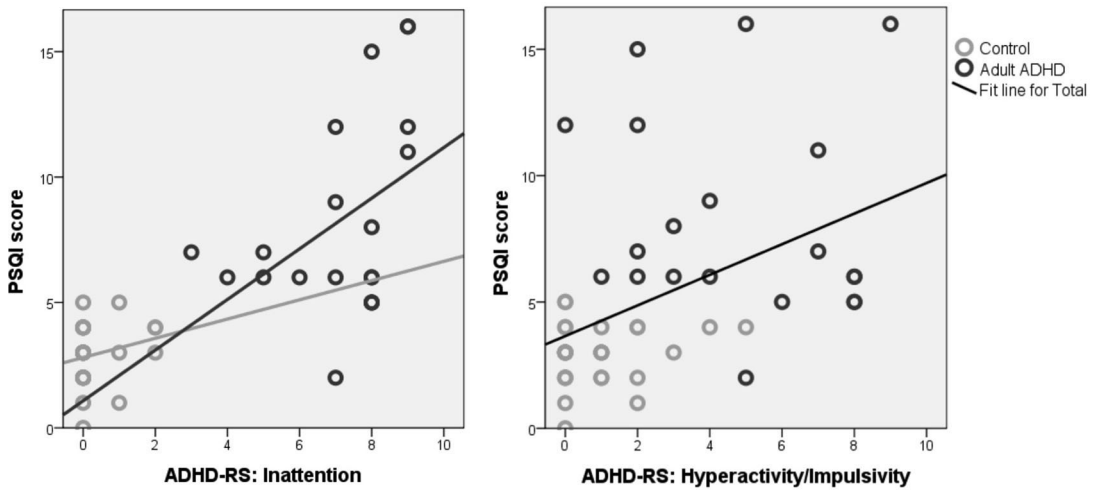

FIGURE 2 | Correlations between the PSQI score and inattention (left) and hyperactivity/impulsivity (right). Note the strong correlation for inattention, where the association between sleep problems (PSQI score) and ADHD symptoms was found for the whole group and also within the ADHD group, suggesting these almost seem to form a continuum from healthy controls (gray) to adults with ADHD (black), and for the whole group this association explained 59% of the variance for inattention. For Hyperactivity/Impulsivity the correlation was only significant for the whole group and not for the subgroups, suggesting this is only driven by group differences.

Table 1 | Differences between the control group and adult ADHD group on ADHD and sleep complaints.

	Control group (N = 28)	Adult ADHD group (N = 19)	Cohen's D
Age (yrs.)	34.1 (9.72)	34.1 (11.33)	
ADHD-RS: Inattention	0.3 (0.67)	7.1 (1.76) ***	5.2
ADHD-RS: Hyp/Imp	0.9 (1.33)	4.5 (2.74) ***	1.7
PSQI	2.9 (1.18)	8.5 (4.05) ***	1.8
Sleep duration (hrs.)	7.4 (0.61)	6.8 (0.90) *	0.7
Sleep onset latency (min.)	13.8 (9.29)	37.2 (41.73) *	0.7

sample including the children, since the criterion used for SOI (>30 min) is the same for children and adults and thus independent of age (Van der Heijden et al., 2005; Van Veen et al., 2010).

NEUROFEEDBACK TREATMENT EFFECTS: SMR VS. TBR

Of the 51 ADHD patients included, 10 were treated with TBR Neurofeedback and 27 with SMR Neurofeedback (The remaining 14 patients were treated with combined SMR and TBR neurofeedback ($N = 9$) or only had intake data ($N = 5$)). There were no differences between these 2 groups on age, gender, ADHD-RS and PSQI measures (all $p > 0.193$), see **Table 2**. There were also no differences in the average number of sessions for the SMR (31 sessions) and TBR (29 sessions) groups ($p = 0.656$).

A repeated measures ANOVA with within-subject factor Time (pre-treatment, mid-way treatment and post-treatment) and between-subject factor Protocol (SMR vs. TBR) yielded significant Time effects (improvement) for Inattention ($p < 0.001$; $F = 82.631$; DF = 2,34; $d = 2.6$), Hyp/Imp ($p < 0.001$; $F = 51.529$; DF = 2,34; $d = 1.8$), PSQI score ($p > 0.001$; $F = 11.417$; DF = 2, 34; $d = 0.9$) and no significant Time X Protocol nor a main effect of Protocol, suggesting that both protocols had similar effects on main ADHD symptoms and PSQI score. For sleep duration no main effect of Time or Protocol, or Time X Protocol interaction were found.

Table 2 | Baseline levels of ADHD and sleep complaints between the SMR neurofeedback treated group and TBR neurofeedback treated group and MSE (mean square error) and *p*-values.

	SMR (N = 27)	TBR (N = 10)	MSE	*p*-value
Age (yrs.)	23.5 (14.5)	17.8 (12.8)	197.895	$p = 0.280$
ADHD-RS: Inattention	7.0 (1.8)	7.0 (1.6)	3.056	$p = 0.955$
ADHD-RS: Hyp/Imp	4.8 (2.6)	6.0 (2.1)	6.190	$p = 0.193$
PSQI	7.3 (4.1)	5.9 (2.5)	14.072	$p = 0.322$
Sleep duration (hrs.)	7.9 (1.8)	8.4 (1.3)	2.802	$p = 0.517$
Sleep onset latency (min.)	38.8 (35.7)	25.8 (13.8)	0.108#	$p = 0.350$#
Number of sessions	31.5 (13.0)	29.5 (7.8)	138.871	$p = 0.656$

Note that # means statistics based on log-transformed data.

For SOL a near significant Time X Protocol interaction ($p = 0.076$; $F = 2.795$; DF = 2, 32) and a Time effect ($p = 0.002$; $F = 7.365$; DF = 2, 32) were found, but not of Protocol (note that for 2 patients in the SMR group there were missing data explaining the lower DF values). **Figure 3** visualizes this interaction further. As can be seen, the time effect (post-minus pre-treatment) is substantially larger for the SMR group than it is for the TBR group. This was further confirmed by paired sample t-test that found a significant decrease in SOL from pre-treatment to post treatment for TBR ($p = 0.036$) and SMR ($p < 0.001$), but only a significant decrease from pre-treatment

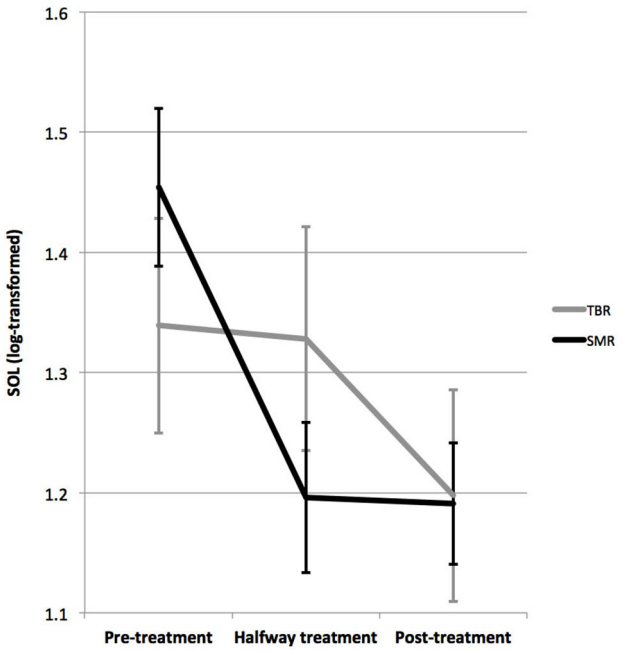

FIGURE 3 | This figure demonstrates the interaction between the SMR and TBR treated groups on SOL. The SMR treated group demonstrated a decrease in SOL from pre-treatment to post-treatment from 40 to 19 min, where this effect was most pronounced within the first half of treatment ($p < 0.001$), whereas for TBR this effect was not significant ($p = 0.921$) and only a significant pre-treatment to post-treatment (26 to 19 min) effect was found ($p = 0.036$). The time effects were significant for both groups.

to halfway treatment for SMR ($p < 0.001$) and not for TBR ($p = 0.921$).

Repeating the analyses separately for SMR and TBR, yielded a significant time effect for each: For SMR ($p < 0.001$; $F = 12.337$; DF = 2, 23; $d = 0.9$), where SOL decreased from 40.1 min pre-treatment to 19.1 min post-treatment; for TBR ($p = 0.036$: $F = 5.153$; DF = 2, 8; $d = 0.5$) where SOL decreased from 25.8 min to 18.8 min post-treatment. Repeating this analysis in children only or adults only resulted in similar effects and a similar trend for interaction.

Mediator analysis

Age did not correlate with change in inattention ($p = 0.980$, $r = 0.004$) and hyperactivity/impulsivity ($p = 0.879$, $r = -0.026$), and there was no difference between males and females in change in inattention ($p = 0.636$) and hyperactivity/impulsivity ($p = 0.885$) suggesting these variables do not moderate treatment outcome to neurofeedback treatment.

Given the above interaction between SOL and treatment protocol, mediator analyses were conducted for TBR and SMR separately.

The change in SOL from pre- to post-treatment was larger for the SMR group (21 min) as compared to the TBR group (7 min), however this difference was not significant ($p = 0.132$; $F = 2.378$; DF = 1, 36), and this change in SOL occurred earlier for the SMR group as compared to the TBR group (see **Figure 3**), thus the criterion of temporal precedence is fulfilled.

A significant correlation between the change in inattention and change in PSQI score was found for the SMR group ($p = 0.006$; $r = 0.518$; DF = 27) and not for the TBR group ($p = 0.206$; $r = 0.437$; DF = 10), also see **Figure 4A**. No correlation was found for change in hyperactivity/impulsivity. A significant correlation between the change in inattention and change in SOL was found for the SMR group ($p = 0.001$; $r = 0.625$; DF = 26) and not for the TBR group ($p = 0.653$; $r = 0.163$; DF = 10), also see **Figure 4B**. No correlation was found for change in hyperactivity/impulsivity ($p > 0.358$). Therefore, the criterion of association is also met.

When repeating the repeated measures ANOVA for inattention, including SOL change as a between subject factor, did not result in a main effect of SOL change ($p = 0.880$; $F = 0.541$; DF = 19,10), a Time X Protocol X SOL change ($p = 0.649$; $F = 0.778$; DF = 10,20) or Protocol X SOL Change interaction ($p = 0.874$; $F = 0.345$; DF = 5,10), whereby the third criterion for mediation is officially not met.

LEARNING

Figure 5 below depicts the SMR power during the first 10 min of neurofeedback intake, outtake and sessions 5, 10, 20 and 25 for the group treated with SMR neurofeedback. As can be seen SMR power during sessions starts to increase at session 10. A repeated measures ANOVA with average SMR at the beginning (intake and session 5) and average SMR at the end (session 15 to outtake) yielded a significant effect of time ($p = 0.010$; $F = 7.663$; DF = 1, 26; $d = 0.2$), also see **Figure 5B**. Of the 27 people that underwent SMR neurofeedback, 20 (74%) were able to increase their SMR from begin to end. Learners had a smaller decrease in PSQI score ($p = 0.024$, $F = 5.801$; DF = 1,26) as compared to non-learners. No differences were found for inattention, hyperactivity/impulsivity, SOL and sleep duration.

The TBR group was too small to conduct proper statistics. Visually, for beta a U-shaped distribution over sessions was found, where the decrease in beta from intake to session 15 paralleled the decrease in EMG, and when EMG remained flat beta increased from session 15 to outtake.

POST-HOC TESTS

In the SMR neurofeedback group, for 8 of the 27 patients a theta inhibit was used, whereas for the other 19 patients only SMR was trained. Repeating the above repeated measure ANOVA's did not yield any interactions between these 2 groups. Of the 27 patients treated with SMR neurofeedback, 12 were treated at C4 and 13 were treated at C3 (the remaining 2 were trained at Cz), also when repeating the above analysis with left vs. right SMR neurofeedback yielded no interactions with laterality.

DISCUSSION

In this study we found that adults with ADHD, reported more sleep problems (PSQI score), a shorter sleep duration (36 min less sleep on average) and a longer sleep onset latency (SOL: 23 min more to fall asleep) than adults without ADHD. When

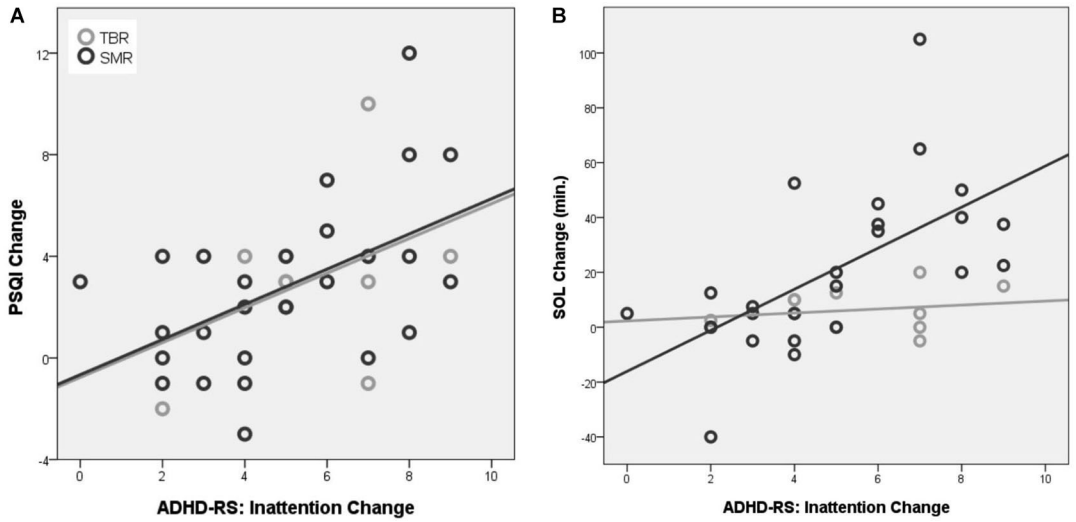

FIGURE 4 | Correlation between the change in ADHD-RS inattention and change in PSQI (A) and change in SOL (B). Note that only for the SMR treated group a significant association between improvement on PSQI change and inattention and SOL and inattention was observed that explained 34% and 39% of the variance respectively.

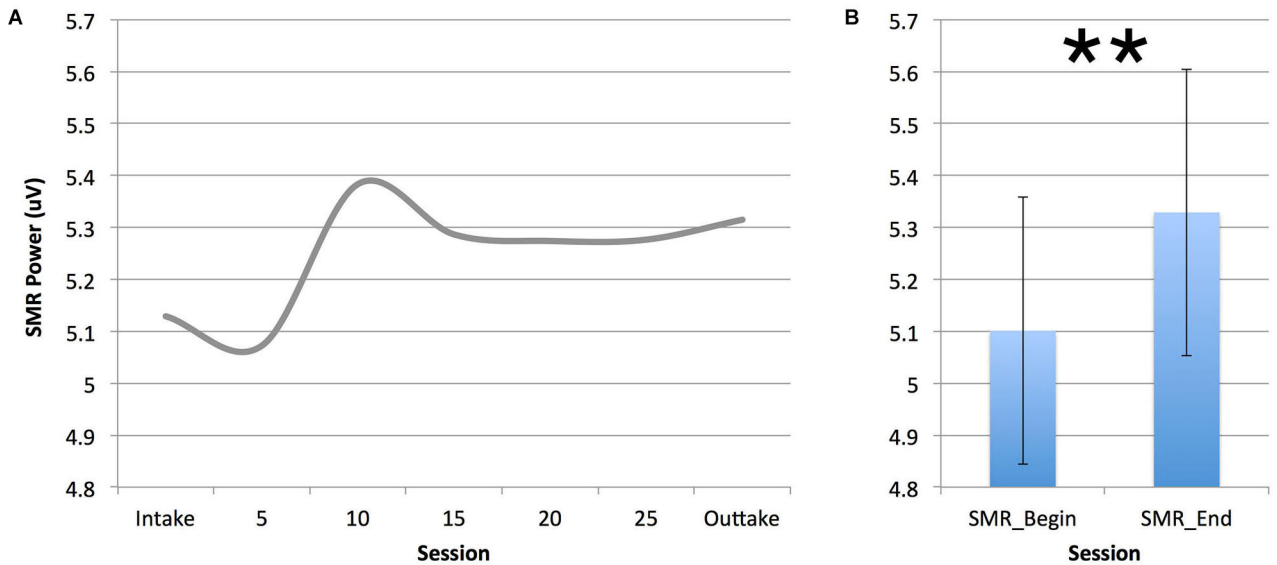

FIGURE 5 | This figure demonstrates the increase in SMR power across training sessions (A). Note that the SMR neurofeedback group was able to increase SMR power after 10 sessions, confirmed by comparing SMR power between the beginning and end of treatment (** $p \leq 0.01$).

using a cut-off of 30 min for SOL (Smits et al., 2001; Rybak et al., 2007) we found that 57% of the ADHD adults and children had sleep-onset insomnia (SOI) as compared to 18% of the control group, which is in line with previous studies that reported 72–78% of SOI in ADHD adults and children (Van der Heijden et al., 2005; Van Veen et al., 2010). Furthermore, for the adult group of ADHD patients and controls, strong correlations were found between reported sleep problems and inattention, explaining 59% of the variance. This correlation was also significant in the ADHD group, and had the same direction (albeit non-significant) in the control group, suggesting this relationship is not simply driven by group differences. **Figure 2** visualizes this association further, and it looks like the relation between reported sleep problems and inattention constitutes a continuum, where problems of inattention are strongly related to reported sleep problems. This overall PSQI score likely reflects a multitude of possible sleep problems that are likely to affect both Process S directly (e.g., RLS, Sleep apnea) as well as via Process C (delayed circadian phase), therefore the strength of this effect mainly suggests sleep disruptive processes explaining

impaired attention, albeit this does not implicate *specific* effects.

Both SMR and TBR neurofeedback had similar clinical effects on inattention, impulsivity/hyperactivity and reported sleep problems in this study. On the other hand, SMR neurofeedback had its most specific effect on decreasing SOL (specifically in the first half of treatment, see **Figure 3**), further demonstrated by the strong correlations between inattention improvement and SOL improvement (39% explained variance; see **Figure 4B**) suggesting the change in SOL could be considered a mediator of treatment response for SMR neurofeedback. These data are in agreement with the proposed working mechanism as presented in the introduction, and suggest that the effects of SMR neurofeedback could results in increased sleep spindle density, which would explain the decreased SOL. The association between SOL improvement and behavioral improvement were most specifically found for inattention but not for hyperactivity/impulsivity, which is in line with our earlier proposal where inattention is a direct result of sleep problems (vigilance dysregulation), whereas the hyperactivity and impulsivity are considered to be vigilance autostabilization behavior, or an indirect compensatory mechanism (Arns and Kenemans, 2014).

The McArthur guidelines for mediator analyses require: (a) temporal precedence of the treatment; (b) an association between the mediator (SOL change) and treatment (inattention change); and (c) a main effect of the mediator or an interaction between mediator and treatment (Kraemer et al., 2002, 2008). The mediator analysis fulfilled criteria (a) and (b); but not criterion (c) (a main effect for SOL change or a Protocol X SOL Change interaction), thereby formally not meeting the definition of the McArthur guidelines. However, since this study was not a randomized controlled trial, the TBR group also demonstrated improvements in SOL (albeit not correlated to improvement on inattention) and the limited sample size of the TBR group might explain this lack of a main effect or interaction with SOL change. Therefore, future randomized controlled trials, such as for example the trial by the Collaborative Neurofeedback Group (The Collaborative Neurofeedback Group, 2013), should conduct such mediator analysis to further demonstrate that clinical effects of SMR neurofeedback are mediated by SOL.

For TBR neurofeedback no association between clinical improvement and change in SOL or PSQI were found. Given that patients treated with TBR neurofeedback were mainly trained at midline sites (Fz, FCz or Cz) and at frequencies above the SMR frequency band and the clinical effects were the same, suggests at least a differential effect of these two neurofeedback protocols. Furthermore, this suggests that the proposed working mechanism of SMR neurofeedback as discussed in the introduction and in Arns and Kenemans (2014) might not generalize to TBR neurofeedback. Along these lines, maybe the effects of TBR neurofeedback can be better explained by the model put forward by Gevensleben and colleagues (Gevensleben et al., 2012), where the effects of TBR and SCP neurofeedback are mainly explained by learned self-regulation over brain activity associated with attention (decreased theta and increased beta as an indication of a desynchronized brain state).

For the SMR group a significant increase in SMR power was observed across training sessions, demonstrating that indeed learning took place on SMR power and 74% of patients were able to increase their SMR across sessions. However, there were no differences in clinical outcome between learners and non-learners, only an effect on PSQI score, where learners had a smaller decrease in PSQI score. Therefore, the question also arises how SMR neurofeedback really exerts its clinical effect. In most studies the assumption is that uni-directional training, in this case SMR uptraining, is required for clinical effects. However, in Slow Cortical Potential (SCP) neurofeedback bidirectional training is employed in order to learn patients to self-regulate the SCP. In a previous study we investigated bidirectional SMR neurofeedback, and found that some people learn to control their SMR mostly by upregulating SMR, whereas another group learned to control SMR mostly by downregulating SMR (Kleinnijenhuis et al., 2008). In Arns and Kenemans (2014) it was also stated that . . . *SMR neurofeedback is not about increasing the EEG power in a specific frequency range, but rather about regulating activity within a functional network (reticulo- thalamocortical network, also see Section 2.6), thereby increasing the synaptic strength within this network, resulting in long-term potentiation (LTP) which increases synaptic sensitivity and the probability of future activation in this network*. . .” Arns and Kenemans (2014). In this view it could thus be that some patients are more successful in up- and others in down-regulating SMR, and either approach resulting in increased sleep spindle density. Future studies should investigate this in more detail by employing bi-directional SMR training in patient populations.

Limitations of the study include: (1) In this study we did not assess Dim Light Melatonin Onset (DLMO) and our results on SOI are based on self-report using the PSQI whereby we could not formally define SOI in line with (Smits et al., 2001; Van Veen et al., 2010). However, interestingly our percentage of 56% SOI in adults with ADHD seems in line with previous studies. (2) In this study only self-report of sleep parameters was used. Future studies should further investigate these effects with more objective measures such as actigraphy, polysomnography or DLMO. (3) The mediator analyses did not yield a main effect nor an interaction with treatment, whereby formally based on the MacArthur guidelines, baseline SOL cannot be regarded as a mediator (Kraemer et al., 2002, 2008). The lack of this significant interaction is possibly explained by the comparison of two active conditions (SMR and TBR) and not an active vs. placebo condition, hence future randomized controlled trials should more specifically investigate this.

Concluding, in this study we found a clear continuous relationship between self-reported sleep problems (PSQI) and inattention in adults with- and without-ADHD, that explained 59% of the variance, prompting researchers and clinicians to pay more attention to identify sleep problems in patients suspected of ADHD to—in line with DSM 5—rule out other causes of inattention. If confirmed, such sleep problems might require treatment first, before treatment is focused on ADHD treatments in line with other studies (Cortese et al., 2013; Miano et al., 2012). TBR neurofeedback resulted in a small reduction of SOL, this change in SOL did not correlate with the change in ADHD symptoms

and the reduction in SOL only happened in the last half of treatment, suggesting this is an effect of symptom improvement not specifically related to TBR neurofeedback. SMR neurofeedback specifically reduced the SOL and PSQI score, and the change in SOL and change in PSQI correlated strongly with the change in inattention, and the reduction in SOL was achieved in the first half of treatment, suggesting the reduction in SOL mediated treatment response to SMR neurofeedback. Clinically, TBR and SMR neurofeedback had similar effects on symptom reduction in ADHD (inattention and hyperactivity/impulsivity), therefore these results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD. Future studies should investigate and replicate these findings in more controlled studies using more objective measures of SOL and sleep duration.

AUTHOR CONTRIBUTIONS

MA initiated this study, conducted the statistical analyses and initiated a first version of the manuscript. Ilse Feddema was responsible for the data collection and management, and assisted in writing the manuscript. J. Leon Kenemans assisted in writing the manuscript.

DISCLOSURES

Martijn Arns reports research grants and options from Brain Resource Ltd. (Sydney, Australia), equipment support from Deymed Diagnostic and is a paid consultant for United BioSource Corporation (UBC), Bracket and Vivatech and is a co-inventor on 3 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents.

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Slow cortical potential neurofeedback and self-management training in outpatient care for children with ADHD: study protocol and first preliminary results of a randomized controlled trial

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Background: Treatment for children with attention deficit/hyperactivity disorder (ADHD) today is predominantly pharmacological. While it is the most common treatment, it might not always be the most appropriate one. Moreover, long term effects remain unclear. Behavior therapy (BT) and non-pharmacological treatments such as neurofeedback (NF) are promising alternatives, though there are no routine outpatient care/effectiveness studies yet that have included children with medication or changes in medication.

Methods/design: This paper presents the protocol of a randomized controlled trial to compare the effectiveness of a Slow Cortical Potential (SCP) NF protocol with self-management (SM) in a high frequent outpatient care setting. Both groups (NF/SM) receive a total of 30 high frequent therapy sessions. Additionally, 6 sessions are reserved for comorbid problems. The primary outcome measure is the reduction of ADHD core symptoms according to parent and teacher ratings.

Preliminary Results: Untill now 58 children were included in the study (48 males), with a mean age of 8.42 (1.34) years, and a mean IQ of 110 (13.37). Conners-3 parent and teacher ratings were used to estimate core symptom change. Since the study is still ongoing, and children are in different study stages, pre-post and follow-up results are not yet available for all children included. Preliminary results suggest overall good pre-post effects, though. For parent and teacher ratings an ANOVA with repeated measures yielded overall satisfying pre-post effects (η^2 0.175–0.513). Differences between groups (NF vs. SM) could not yet be established ($p = 0.81$).

Discussion: This is the first randomized controlled trial to test the effectiveness of a NF protocol in a high frequent outpatient care setting that does not exclude children on or with changes in medication. First preliminary results show positive effects. The rationale for the trial, the design, and the strengths and limitations of the study are discussed.

Trial registration: This trial is registered in www.clinicaltrials.gov as NCT01879644.

Keywords: ADHD, neurofeedback, self-management, slow cortical potential training, behavior therapy, effectiveness

BACKGROUND

For children with Attention Deficit/Hyperactivity Disorder (ADHD) the European guidelines recommend a multimodal treatment (Graham et al., 2011), as well as the new German guidelines that recommend a treatment with medication only if other treatments are not effective.[1] While this is recommended, this seems not be the reality in clinical practice. The treatment for children with ADHD today is predominantly pharmacological, with increasing prescription rates for psycho-stimulants (Barbaresi et al., 2002; Dalsgaard et al., 2013; Steinhausen and Bisgaard, 2014). it is the most common treatment and with respect to short terms the most effective one for the majority of children with ADHD (Van der Oord et al., 2008), it might not always be the most appropriate one, due to possible non-response, side-effects, or parental preferences (Lofthouse et al., 2012). Moreover, long term effects remain unclear. About one third of the children treated with stimulants does not respond (Du Paul et al., 1998; Monastra et al., 2005; Lofthouse et al., 2012), adverse medication

[1] http://www.awmf.org/leitlinien/detail/ll/028-019.html

side effects such as insomnia, and decreased appetite are often reported (U.S. Department of Health and Human Services, 1999; Schachter et al., 2001; Graham et al., 2011), and improvement often seems not to be maintained after treatment discontinuation (Swanson et al., 2001; Abikoff et al., 2004a,b; Molina et al., 2009). Of the children treated with psycho-stimulants, 44–75% do not satisfactorily profit from this treatment in long-term follow-up (MTA Cooperative Group, 1999; Swanson et al., 2001; Molina et al., 2009; Nieweg, 2010), and protective long-term effects, i.e., on substance abuse (Molina et al., 2009, 2013), or on academic achievement, social and interpersonal skills could not consistently be established (Whalen and Henker, 1991; Greenhill et al., 1999; Molina et al., 2009; van de Loo-Neus et al., 2011; Mrug et al., 2012). Accordingly, some families are hesitant about medication treatment (Visser and Lesesne, 2003; Berger et al., 2008), and treatment alternatives are warranted.

Behavior therapy (BT) and non-pharmacological treatments such as neurofeedback (NF) are promising and supposedly side effect free alternatives (Molina et al., 2009; Moriyama et al., 2012). Evidence suggests positive short-term effects for different NF protocols (Arns et al., 2009; Lofthouse et al., 2012), and there is also some, though sparse evidence for long-term effects (Arns et al., 2009; Lofthouse et al., 2012). While the efficacy as well as the need for these approaches are still discussed controversely (Jensen et al., 2007; Swanson et al., 2008; Fabiano et al., 2009), recent quantitative reviews and meta-analyses have shed light on the efficacy of non-pharmacological treatments for ADHD (Van der Oord et al., 2008; Arns et al., 2009; Fabiano et al., 2009; Lofthouse et al., 2012; Moriyama et al., 2012; Sonuga-Barke et al., 2013; Hodgson et al., 2014). Overall, those reviews and meta-analyses report robust medium to large effect sizes for non-pharmacological interventions on ADHD (Fabiano et al., 2009; Hodgson et al., 2014) as well as for NF protocols (Arns et al., 2009, 2014; Lofthouse et al., 2012; Moriyama et al., 2012; Hodgson et al., 2014; Liew, 2014). The meta-analysis by Sonuga-Barke et al. (2013) differentiates findings for NF and behavioral interventions, demonstrating larger and significant effects by raters closest to the therapeutic setting, but diminishing and non-significant effects for both interventions when probably blinded assessment (i.e., teacher ratings) was employed. Since blinded assessment was overall rare in the studies included, and reduced the already small numbers of studies subjected to meta-analysis further (from $k = 8$ NF studies to $k = 4$ with probably blinded assessment; and from $k = 9$ behavioral intervention studies to $k = 5$ with probably blinded assessment), those results should be interpreted with respect to this. More studies with higher quality and more objective outcome measures are thus warranted, though subjective improvements of parents and children are not unimportant, since an association between a positive parent-child interaction and a better outcome has been observed previously (Schachar et al., 1987; Taylor et al., 1991, 1996; Tully et al., 2004; Drabick et al., 2006; Christiansen et al., 2010).

As Lofthouse et al. (2012, p. 366) admit, blinding in psychotherapy studies is harder compared to medication studies, since knowledge of the treatment is required for a therapist and makes a placebo condition virtually impossible (see also Zuberer et al. in this Frontiers Research Topic). Nevertheless, two pilot-studies report on EEG NF double-blind randomized placebo controlled trials. Both demonstrated feasibility, but no differences between the active and placebo condition, yet (Lansbergen et al., 2011; Arnold et al., 2012). The eight existing studies using triple blinding in NF protocols are also inconclusive. Four of them report significant positive effects of medium to large size (DeBeus, 2006; Leins et al., 2006; Picard et al., 2006; DeBeus and Kaiser, 2011), whereas the four more recent ones report negative results (Logemann et al., 2010; Perreau-Linck et al., 2010; Lansbergen et al., 2011; Arnold et al., 2012). Moriyama et al. (2012, p 592), criticize, that the negative findings of those four studies "might have been determined by the use of suboptimal NF, because all of these studies used very experimental protocols and in none of them, the principals of learning theory were applied to ensure that subjects were really under conditioning procedures". This is a key element, though, since in NF protocols operant conditioning procedures are applied to help participants learn to gain self-control over EEG patterns that are associated with attentional processes (Heinrich et al., 2007; Gevensleben et al., 2009b). Conditioning failures will thus be related to negative outcomes, since core principals of the therapy are then in question (for the combination of NF and behavioral therapeutic aspects see also Vollebregt et al. in this Frontiers Research Topic).

One study compared a NF slow cortical potential (SCP) protocol with BT (Drechsler et al., 2007). In the study, NF SCP in a single setting (20 high frequent 90 min sessions in 2 weeks with a further 5 weekly/twice weekly 90 min sessions after a 5 week break) is compared with a group therapy (total of 15 ninety minute sessions weekly to twice weekly) based on behavioral interventions such as self-management (SM) and parent training, demonstrating more pronounced treatment effects for the NF SCP group. But the total number of sessions (NF SCP: 25 vs. BT: 15), the setting (NF SCP: single vs. BT: group), frequency (NF SCP: dayly vs. BT: weekly/twice weekly), and duration of the two interventions are not comparable, hampering conclusions with respect to the efficacy of the interventions. A more recent study by Garcia et al. (see this Frontiers Research Topic) compares 57 children with ADHD that were randomly assigned to three different treatments: NF theta/beta training sessions, methylphenidate treatment, and BT. Their results reveal specific changes in EEG variables, specifically related to NF theta/beta training; results on ADHD symptoms are not reported, yet.

AIMS OF THE TRIAL

The aim of the present study is to establish whether a NF protocol under outpatient care conditions is at least as effective as an approved and established behavioral treatment (SM), as results in the Drechsler et al. (2007) study suggest. The current study is designed to compare a SCP NF training with a behavioral SM training (SM: Lauth and Schlottke, 2009). To date, NF is not yet approved as a psychotherapeutic intervention by health care providers in Germany, and to our knowledge there is no effectiveness study investigating the feasibility and effects of NF under regular outpatient care conditions.

We are thus interested in whether NF (SCP training) is a true treatment alternative to behavioral interventions that are approved by health care providers. Since the studies so far were experimental ones establishing effects of NF protocols that did not allow medication or changes in medication, this question is not answered, yet.

The primary research question is:

1. Is a SCP NF protocol under outpatient care conditions at least as effective as an approved and established behavioral treatment (SM) at the end of treatment, and at six and twelve months follow-up?

Further examination of secondary research questions

1. EEG-patterns:
   Does NF result in specific changes of EEG patterns compared to SM? Are there specific associations between neuroregulation skills and clinical outcomes?
2. Child outcomes:
   Do both treatments (NF and SM) improve children's executive functions, quality of life, self-concept and school grades? And is treatment response in both treatments moderated by children's perceived social support?
3. Parent outcomes:
   Do both treatments (NF and SM) improve parenting skills, parental perceived social support and expressed emotion (EE)? Does the parent group with additional social support (PE + SU) show enhanced social support after treatment and more positivity and warmth towards the child compared to the group with PE only? Is this moderated by comorbidity?

METHODS

PARTICIPANTS

Inclusion criteria

The study is performed with children either newly diagnosed with ADHD or with verified diagnoses. Participants are children referred for ADHD treatment either by their parents, pediatricians, or psychiatrists. To be eligible for the study, the children have to meet the following inclusion criteria: aged seven to eleven, full command of the German language, current DSM-IV diagnosis of ADHD (either combined, predominantly inattentive or predominantly hyperactive/impulsive subtype), IQ $\geq$80 (short version of the WISC; information, picture arrangement, similarities and block-design; Sattler, 2008, p. 186). Children with comorbid disorders are not excluded from the study, and behavioral treatment of comorbid conditions is included in the treatment plan. The rational for this is based on the effectiveness design of the study. The majority of the children with ADHD presents with comorbid disorders (Kadesjö et al., 2003; Willcutt et al., 2005; Gadow et al., 2006; Jakobson and Kikas, 2007; Anney et al., 2008; Semrud-Clikeman and Bledsoe, 2011; Stein et al., 2011; Vakil et al., 2012), and parents and children seeking help in our outpatient clinic request treatment of all impairing problems, and not just ADHD (please refert to the preliminary result section for information on comorbidities). The children under stimulant medication are also not excluded from the study, but dose and possible changes will be recorded.

Exclusion criteria

Children with symptoms of inattention, hyperactivity or impulsivity due to other medical reasons such as hyperthyreosis, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalizing behavior.

DESIGN AND PROCEDURE

Recruitment and consent

The Psychotherapeutic Outpatient Clinic of the Department of Psychology, Clinical Psychology, at the University of Marburg treats children, adolescents and adults with psychological disorders. Patients can refer themselves or are referred by their pediatricians, psychiatrists, or general practitioners. Parents and children interested in the study are sent a full study description with separate information for parents, teachers, and children, and Conners-3 questionnaires for parents and teachers as well as questions on demographics and therapy expectations. Screen positive patients are invited for a semi-structured diagnostic interview (Kiddie-Sads-Present and Lifetime Version; K-SADS-PL; Kaufman et al., 1996) with a licensed child and adolescent psychotherapist to assess ADHD and possible comorbid disorders. If ADHD is diagnosed, the patient and his/her parents are informed about the treatment options and receive oral information based on the written information already sent out to the families. If the child fulfills diagnostic criteria and the family wants to participate in the study, informed consent is signed by the parents and their children, and further diagnostic assessments are scheduled.

Randomization and treatment allocation

The children are randomized to receive either NF or SM training. Parents of children are randomized to parent training groups with either psychoeducation only (PE), or PE enhanced with additional social support (PE+SU). Treatment allocation is performed by computer programming stratified for gender and stimulant medication. In this way, we aim to ensure that trial arms are balanced with respect to the baseline characteristics gender and use of ADHD medication. Patients, parents, therapists, and investigators were not blinded for the treatment allocation. Teachers are blind with respect to treatment allocation.

Procedure

Both the NF and SM interventions are manualized, equal in setting (single), duration, frequency, parental involvement, and supporting token economies (for details on this please refer to treatment protocols of this article). The rationale for those treatment parameters is based on the results of the available meta-analyses (Arns et al., 2009; Esser and Blank, 2011; Zwi et al., 2011; Lofthouse et al., 2012; Moriyama et al., 2012; Sonuga-Barke et al., 2013; Hodgson et al., 2014). The SM training is approved and refunded by insurance providers in Germany for ADHD therapy (for the efficacy of SM trainings for ADHD see the reviews by Saile, 1996; Fabiano et al., 2009); NF is only refunded in health care settings that also do research in the field. Since our department is a university

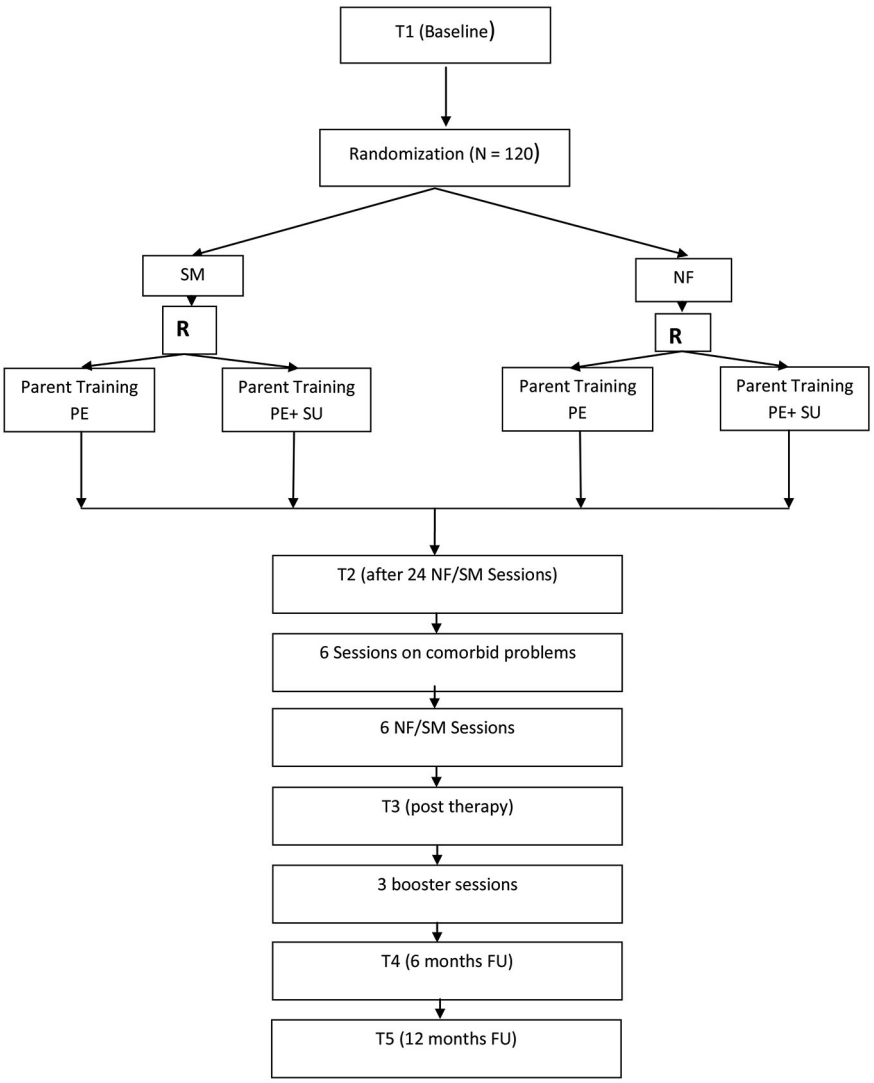

FIGURE 1 | Flow-chart of the study. **R** = Randomization of parents to either PE or PE+SU.

one, it is possible to get NF training refunded by in such a setting.

Figure 1 provides an overview of the trial flow. After informed consent and baseline assessment (T1), a diagnostic assessment of ADHD and possible comorbid disorders with the K-SADS-PL follows. During T1 all primary and secondary outcome measures, neuropsychological tests, and quantitative EEGs are scheduled. Children are off medication 48 h prior to all diagnostic assessments to not distort results due to treatment. The same procedure is applied for all further assessments. After confirmation of ADHD diagnosis, randomization takes place. The children in both groups then receive 24 high frequent therapy sessions (NF or SM) over twelve weeks with up to three 1 h sessions per week, since such an intensive training has proved to be highly effective (Strehl et al., 2011). After the first twelve sessions in 4 weeks, there is a 1 week break followed by the next 4 weeks with high frequent training. After 24 sessions only Conners-3 parent ratings are used for T2 assessment and there is another break for 1 week. Additionally for both groups 6 individualized BT sessions are reserved for comorbid problems after T2 assessment. Depending on the disorder and treatment selected, those sessions might be high frequent or scheduled only weekly. After the comorbid sessions, six high frequent NF or SM follow that end the therapy. T3 assesses post-treatment effects (all primary and secondary outcomes). Five months after end of treatment, all children are offered three booster training sessions (either NF or SM according to allocation). Six (T4) and twelve months (T5) after treatment termination follow-up assessments with all primary and secondary outcome measures are scheduled. Parent groups are accompanying children's therapy. **Table 1** gives a detailed overview of the treatment plan.

Table 1 | Overview of all assessment and treatment sessions of the study.

Session	Content	Duration
1	Outpatient assessment and informed consent; information on study participation	100 min
	Diagnostic assessment	
2–4	Pre-assessments of all primary and secondary outcome measures (T1)	50 min per session
	Randomization of children and parents	
5	Feedback of test results	50 min
6	Psycho-education children	50 min
	Intervention	
	Accompanying Parent Training	
7–18	***Block I:*** High frequent NF/SM treatment over 4 weeks (12 sessions)	50 min per session
	Break (1 week)	
19–30	***Block II:*** High frequent NF/SM treatment over 4 weeks (12 sessions)	50 min per session
	Break (1 week) and T2 assessment*	
31–36	***Block III—part 1:*** Behavior therapy of comorbid problems (6 sessions)	50 min per session
37–42	***Block III—part 2:*** High frequent NF/SM treatment (6 sessions)	50 min per session
43	**Post assessment (T3)**	**50 min**
	Follow-up assessment and booster sessions	
44–46	3 Booster sessions ca. 5 months after treatment discontinuation	50 min per session
47	6-months follow-up (T4)	50 min
48	12-months follow-up (T5)	50 min

**T2 assessment: only Conners 3© parent rating scales.*

TREATMENT PROTOCOLS

Neurofeedback

Before treatment all children receive standardized PE on ADHD (Lauth and Schlottke, 2009). For NF training in this study we use the Thera Prax® (NeuroConn©) NF system. It offers several different feedback animations and the option to upload pictures which keeps the training diversified and motivates children. During training sessions, the children take seat in a comfortable chair with a head- and armrest in front of a computer screen and are introduced to the training as kind of a computer game that helps them learn to modulate their brain activity.

We use the feedback protocol of SCP training that has been incorporated in many NF studies (Strehl et al., 2006; Heinrich et al., 2007; Gevensleben et al., 2009a,b, 2010; Arns et al., 2014). The children's task is to generate negative and positive SCPs by getting into an attentive (negativity trials) or a relaxed state (positivity trials). The aim of the training is to steer a moving object (i.e., an airplane, a fish, a spaceship) that appears on the screen in front of them in the requested direction (arrow upwards indicates negativity trial; arrow downwards indicates positivity trial). The children can choose a training object at the beginning of each therapy session. In the transfer trials, the children do not see the object, but only the direction of the arrow. The children are instructed to sit as still as possible during the training, to avoid laughing and talking, but to concentrate on the screen in front of her/him. No specific instruction is given to the children on how to succeed in negativity or positivity trials, but just to be attentive to feedback and to find the most effective mental strategy to steer the object into the requested direction. As there is no unique strategy for NF training, the children are given examples that have been successful for some children (i.e., negativity trials: "Think of something you find exciting like sitting in a race car or standing on a diving board"; positivity trials: "Those strategies are used in situations requiring relaxation. Think of something you find calming and pacifying like listening to soothing music"). After a successful trial a sun appears on the screen (reinforcement). Additionally, a token plan is used that enables the children to earn up to 5 tokens per session if they stay attentive during the whole session. A full token plan of 15 tokens (every third session) can be exchanged into small rewards by parents that are agreed upon at the beginning of the training together with the parents and the child.

Participants in the NF condition receive a total of 30 sessions of SCP training. Each therapy session consists of three runs. One run consists of 40 trials (8 min) resulting in a total of 24 min NF training per session (see **Figure 2** for details). A trial lasts for 8 s (2 s baseline period, 6 s feedback period). Inter-trial interval is set to 5 ± 1 s. Between each of the three runs there is a short break of several minutes which can be used by the therapist to motivate and praise the child and to talk about problems and use of strategies (i.e., "What was your strategy for negativity/positivity trials?", "How did it work?", "What else could you try as a negativity/positivity trial strategy?"). The last 10 min of each session are reserved for joint play which is an important aspect of motivating the child and strengthening the therapeutic relationship. Feedback is calculated from the vertex (Cz) and is referenced against both mastoids (bandwidth 0.01–30 Hz, sampling rate: 256 Hz), and vertical as well as horizontal eye movements are corrected online with electrodes placed above and below the left eye, and electrodes on the right and left side of the face (4 electrooculography channels, EGO; for details of the protocol see Strehl, 2009). Ocular artifact removal is possible with DC-EEG as described in Schlegelmilch et al. (2004). The ratio of negativity to positivity is set to 1:1, and negativity/positivity trials are presented in random order. All sessions start with no threshold, but if the child has a hit rate (correct responses) of $\geq$70%, thresholds are introduced automatically. Those start with an initial 5% threshold, and are followed in steps of 5% if the child continuous to score $\geq$70%.

The first two runs in every therapy session include no transfer trials, i.e., the child gets continuous visual feedback, whereas the third run is set to 100% transfer (for this rationale see also Vollebregt et al. in this Frontiers Research Topic). Although no continuous feedback is given on transfer trials,

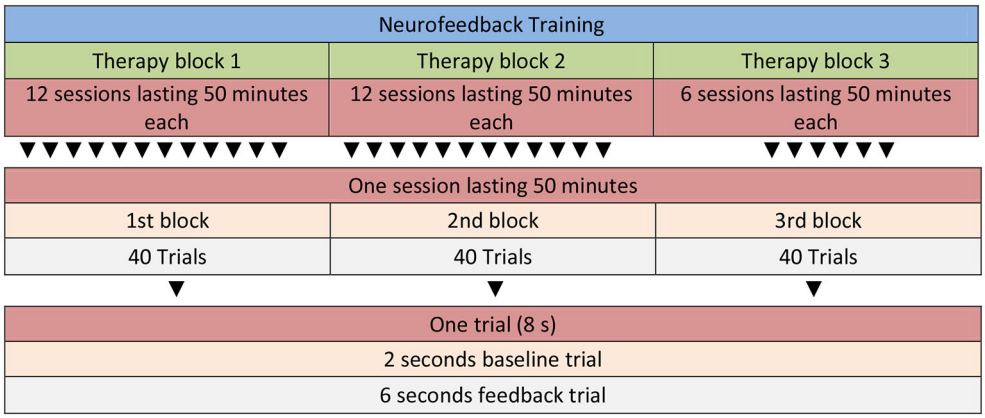

FIGURE 2 | Neurofeedback Protocol with three therapy blocks and a total of 30 sessions.

a sun appears at the end of the trials to provide information about success (reinforcement). Transfer trials are thought to support generalization to everyday life situations (Strehl et al., 2011). Additionally, starting with the second therapy block (12th session) children are asked to practice their mental strategies in specific situations at home or school for about 10 min each day. Together with the therapist children identify situations that require attention control (i.e., negativity strategies: before starting to do homework; positivity strategies: at night before going to bed). The children are asked to document practicing by keeping a log which is controlled by the therapist at the beginning of a session (see also Vollebregt et al. in this Frontiers Research Topic). If the child practices each day between sessions he/she can earn an extra token.

In the first and second therapy block the children complete twelve NF sessions each. After those two blocks (with a 1 week break to relieve families in between; see also Strehl et al., 2011) a block reserved for the treatment of comorbid problems follows (total of six sessions). In this block individual BT is applied for the specific comorbid conditions. Treatment of those is based on published intervention manuals. Then a final block with six NF sessions follows that ends the therapy. In this block, the ratio of negativity to positivity trials is set to 3:1.

Self-management

Before treatment all children receive standardized PE as described in the NF section above. The SM training addresses children aged 6–12 years (Lauth and Schlottke, 2009), and is based on the self-instruction training as described in Meichenbaum and Goodman (1971). Goal of the training is to enhance child development in the domains behavior regulation, planning, organization, and self-reflection. A meta-analysis with $k = 11$ studies provides empirical evidence of the training (Lauth and Schlottke, 2009; for the general efficacy of such treatments see the reviews by Saile, 1996; Fabiano et al., 2009). In the first therapy block the basic training (12 sessions) is completed. This consists of the sessions (1) precise looking; (2) precise describing; (3) precise listening; (4) precise listening and re-telling; (5) precise account of perceptions; (6) introduction of the stop-signal; (7) self-contained stopping and checking; (8) accompanying checking procedures; (9) transfer of checking techniques to school contexts; (10) self-instruction with the stop signal; (11) self-instruction with difficult tasks; (12) self-instruction under distraction. After 1 week break the second therapy block follows with the strategy training: (1) basic skills; (2) signal cards; (3) thinking loud; (4) flexible use of signal cards; (5) adaptation of learned strategies for new tasks; (6) cross-linking strategies; (7) discover systematic principles; (8) adaptation of learned strategies for complex tasks; (9) solving abstract problems; (10) organizing learning strategies; (11) development of strategies for complex school tasks; (12) application of strategies for complex school tasks.

Each session (except the first one) begins with the recapitulation of the last session and an introduction into the topic of the session (10 min). This is followed by modeling the behavior that the topic of the session requires (10 min) and the child trains this for 20 min. The last 10 min are reserved for joint play to motivate the child and to build a good therapeutic relationship. A token plan is installed together with the child and the parents. As in the NF group, the children can earn up to 5 tokens per session if they stay attentive during the training unit. A full token plan of 15 tokens (every third session) can be exchanged into small rewards by parents.

To keep both therapy groups balanced, quantity of homework is kept identical. Starting in the second therapy block, the children in the SM group are asked to practice self-instruction with the stop signal during homework each day for 10 min. As in the NF group, practicing is documented in a log which is controlled by the therapist at the beginning of a session and the children can also earn an extra token for doing the homework. Differing from the NF protocol, the children do not practice relaxation, since this is not part of the SM training.

Treatment of comorbid disorders

Depending on the comorbid disorder of the child, manualized behavior treatments are applied. The most common comorbid

disorder in our sample so far is Oppositional Defiant Disorder (ODD). The principles to reduce such problem behaviors are based on the training manuals used in the parent PE (see below). In addition, after PE with the child token economies are also introduced to reduce ODD symptoms. Other disorders such as Tic Disorder, Enuresis, Sibling Rivalry Disorder are also treated with BT, i.e., apart from token economies, habit reversal training, alarm therapy, one to one quality time with the child (Esser, 2011). For children without comorbid disorders, those sessions are used to resolve other conflicts that have an impairing quality, i.e., children without many friends receive social competence training.

Parent Training

Psycho-education only (PE). Since ADHD does not only affect the child, but is specifically characterized by impairments at home and school, the parent training supports the parents and the transfer into the home setting. It is part of the training by Lauth and Schlottke (2009). The core element is PE with respect to ADHD, as well as development of strategies that effectively support the child. Topics are: (1) information on ADHD; (2) handling problem behavior I and introduction of token economies; (3) joint parent-child play; (4) handling problem behavior II and introduction of timeout and 1-2-3-Magic (Phelan, 2003); (5) handling problem behavior in public. Between sessions, parents have to complete homework, training the strategies in everyday life. This homework is discussed in the following session. Therapists are the same as in the children's intervention. A meta-analysis supports parent trainings as this one for ADHD (Bachmann et al., 2008; Zwi et al., 2011). A total of five parent group sessions lasting 100 min each are scheduled accompanying children's therapy.

PE + social support (SU). Parents in this group receive PE as described above, with additional components on social support, based on network oriented interventions (Röhrle et al., 1998), since a study has shown positive effects of social support on parental EEs, with parents with high social support showing more positivity and warmth towards their children, that was related to reduced comorbid oppositionality (Christiansen et al., 2010). Parents are trained with network analyses to identify supporting social networks, and to possibly activate them. If non-supportive network characteristics are identified, modification is supported. Between sessions, parents have to complete homework as in the PE only group and additionally on individual social network analyses. For this they have to think of ways of how to activate positive social support. A total of five parent group sessions lasting 100 min each are scheduled accompanying the children's therapy.

THERAPISTS

All therapists are trained in both NF, SM, PE, and PE+SU and all therapists deliver all trainings based on intervention manuals. All interventions for comorbid conditions are also based on published intervention manuals. All therapists are therapists in training and receive regular supervision (every fourth session) by a licensed supervisor with more than 5 years experience in BT for the duration of the trial. To control implementation and fidelity, all sessions are videotaped and analyzed in the supervision sessions.

MEASUREMENTS

With the exception of parent and teacher questionnaires, all assessments are conducted in face-to-face contacts. Apart from the primary ADHD outcomes (change in psychopathology from baseline to post therapy) we are also interested in therapy related quantitative EEG patterns of response to NF/SM. In the existing NF studies, changes in EEG patterns have been reported after therapy (e. g.: Monastra et al., 2005; Heinrich et al., 2007; Gevensleben et al., 2009a; Arns et al., 2014; see also Garcia et al. in this Frontiers Research Topic). But, differing from the homogeneous results for parent and teacher ratings (primary outcomes), this change proved to be heterogeneous according to meta-analysis (Nestoriuc et al., 2011). Possible changes in EEG patterns before and after therapy will thus be compared for both the NF and SM group to establish whether changes are specific for the NF group.

Selection and diagnostic measurements

1. Screening for the presence of ADHD symptoms is performed with the Conners 3® parent and teacher ratings (German version: Lidzba et al., 2013). Clinical impairment is established with T-scores of $\geq$60.
2. The DSM-IV diagnosis of ADHD and possible comorbid disorders is based on the semi-structured diagnostic interview Kiddie-Sads-Present and Lifetime Version (K-SADS-PL: Kaufman et al., 1996).

The 3rd edition of the CRS (Conners 3®: Conners, 2008; German version: Lidzba et al., 2013) assess ADHD core symptoms as well as Learning Problems, Executive Functioning, Peer- and Family Relations, co-morbid conditions such as ODD and Conduct Disorder (CD) in children aged six (parent and teacher forms) and eight (self-report forms) to 18 years of age. The Conners 3® rating scales have been translated into German, back-translated, and norms for a German-speaking sample were established (Lidzba et al., 2013). A study on cultural comparability of the German Conners 3® resulted in good model-fits for confirmatory factor analyses (Christiansen et al., submitted), and cultural comparability for a large group of Germans with Turkish migration background could also be established (Schmidt et al., 2013), with satisfactory internal consistencies of the scales in both studies.

The K-SADS-PL (Kaufman et al., 1996; German adaptation Delmo et al., 2011) is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. Probes and objective criteria are provided to rate individual symptoms. The interview consists of two parts. The first part is a screening interview that screens for the psychological disorders. If an item is scored with "3" (0 = no information, 1 = nonexistent, 2 = below threshold, 3 = above threshold), the full interview of this section is carried out. Diagnoses are then based on DSM criteria that are listed and scored at the end of the

full interview. The K-SADS has been carefully constructed and is widely used.[2]

Outcome measures

Parent, and/or teacher ratings

1. The Conners 3® parent and teacher scales are used as the measure of change of children's ADHD symptoms (see above Conners, 2008; German adaptation Lidzba et al., 2013). The parent and teacher scales consist of 105 and 111 items respectively that are rated on a four point Likert scale with severity ratings from 0 (not at all/never) to 3 (very much/very frequently).
2. The Parental Stress Inventory (Eltern-Stress-Fragebogen (ESF); Domsch and Lohaus, 2010) assesses with 38 items the four subscales parenting stress, role restriction, social support, and partnership. Internal consistency is satisfactory (0.76–0.92) as well as re-test reliability (0.76–0.91). Convergent validity has been established with the Parenting Stress Index.
3. The Parenting Scale (PS: Arnold et al., 1993; German version: Miller, 2001) assesses parenting styles (reactions and strategies) for different problematic situations. The two subscales over-reacting and leniency have satisfactory internal consistency (0.75), as well as the total scale (0.76).
4. Start, stop and dosis of stimulant medication are monitored throughout the therapy. Since our clinic is a psychotherapeutic department, medication treatment is monitored by children's pediatricians or child and adolescent psychiatrist. Parents report what medication is given at what time and report on titration procedures, as well as on side-effects.

Child ratings

5. The Qb-Test is a combined continuous performance (CPT) and activity test for children aged 6–12 years (Ulberstad, 2012), which aims to objectively assess all three core symptoms of ADHD in one test, and has been approved by the Food and Drug Administration (FDA) in 2012. While performing a standardized CPT on a computer, the movements of the participant are recorded with an infrared camera following a reflective marker attached to a headband that the participant wears while performing the test. Factorial validity for the test and the three core ADHD symptoms (inattention, hyperactivity, impulsivity) has been established (Reh et al., 2013), as well as usefulness as a potential endophenotype assessment (Reh et al., 2014).
6. The children's test-battery of attention assessment (KITAP: Zimmermann et al., 2002) assesses different attention parameters that are administered with a computer. Psychometric properties of the KITAP have been reported in different studies (Renner and Irblich, 2007; Kaufmann et al., 2010; Röthlisberger et al., 2010; Sobeh, 2010; Dreisörner and Georgiadis, 2011; Renner et al., 2012) as well as clinical validity for seven to 10 year old children with ADHD (Drechsler et al., 2009). In our study the following subtests are included: sustained attention, Go/No-Go, and divided attention.
7. The Child and Adolescent Social Support Scale (CASSS: Malecki et al., 1999) is a 40-item multidimensional scale measuring perceived social support from four sources: parents, teachers, classmates, and friends. Frequency ratings consist of a 6-point Likert Scale from 1 (Never) to 6 (Always). Importance ratings consist of a 3-point Likert Scale ranging from 1 (Not Important) to 3 (Very Important). Each subscale corresponds to one of the sources of support (e.g., parent, teacher, classmate, and close friend) and consists of 10 items. Subscale scores are calculated by summing the frequency ratings on the 10 items on each subscale. Analyses revealed evidence of reliability, a four-factor structure (Parent, Teacher, Classmate, and Close Friend subscales), and construct validity. The CASSS co-varies with the clinically important constructs of self-concept, social skills, and behavioral indicators. There is evidence that the CASSS can be used to understand children's and adolescents' perceived social support (Malecki and Demaray, 2002).
8. The self-concept interview (Schöning et al., 2002) is a structured interview. Self-concept is assessed for school, family, and peer-relations. The following categories are rated and coping abilities are assessed: social interactions, perceived quality of life and self-worth. Items are formulated in a way that they do not confound with core ADHD symptoms. Internal consistency is satisfactory (range 0.70–0.83; overall 0.85).
9. The KINDL-R (Ravens-Sieberer et al., 2003) assesses health related quality of life of children and adolescents. Both parents and children rate the six dimensions physical well-being, emotional well-being, self-worth, family related well-being, peer related well-being and school related well-being. A total of 24 items is to be rated on a 5-point Likert scale from 0 = never to 4 = often. Internal consistency is satisfactory (0.85 for the total scale, all subscales $\geq$0.70), and the questionnaire has been used in various studies with children (Ravens-Sieberer and Bullinger, 1998a,b).
10. The Perceived Criticism Scale (PC) consists of the item "How critical is your spouse of you" to be rated on 10-point Likert scale from 0 = not at all critical to 10 = very critical indeed. Originally the item was used by Hooley (1990) to assess high EE, i.e., hostility, criticism, and emotional over-involvement, in spouses of patients with depression. With 40% variance explained, this item was the strongest predictor of relapse in a 9 months follow-up. The item has been translated into German and was adapted for children (How much does your mum/dad like you?). This version has already been successfully used with children with and without ADHD (Christiansen et al., 2010).
11. Quantitative EEGs are assessed for both NF and SM groups before therapy (T1), and post therapy (t3) as well as at six (t4) and twelve (t5) months follow-up to establish whether NF training results in changes specific for NF.

Primary and secondary outcome measures

The primary outcome measure is defined as the change of ADHD hyperacitivity, inattention, and impulsivity symptoms according to parent and teacher Conners 3® ratings (DSM-IV subscales

[2]http://www.psychiatry.pitt.edu/research/tools-research/ksads-pl

and Conners'-ADHD-Index; Conners, 2008; German version: Lidzba et al., 2013) at the end of the treatment (T3) compared to T1. To establish stability of effects, T3 assessments will be compared to six (T4) and 12 (T5) months follow-up assessments. T2 assessment (after the first therapy block) will be used to establish effects compared to T1 without the treatment of comorbid disorders.

Key secondary outcome measure is percentage of treatment responders (defined as a reduction of at least 30% of ADHD symptoms according to Conners-3 ratings of parents and teachers) at the end of treatment and at follow-ups. Qb-Test (Ulberstad, 2012; Reh et al., 2013), and KITAP (Zimmermann et al., 2002) scores objectively assessing core ADHD-symptoms and executive functions at follow-ups are further key secondary outcome measures at the end of treatment (T3).

Other secondary outcome measures are changes in quantitative EEG patterns as well as changes in scores of self-concept, the KINDL-R, PC, ESF, PS at the end of treatment and follow-ups.

STATISTICAL ANALYSES

Data will be analyzed according to the intent-to-treat (ITT) principle, thus patients will be analyzed according to the randomization scheme. When appropriate (data missing completely at random) the method "last observation carried forward" will be applied. The treatment effects will be analyzed with multivariate repeated measure ANOVAS with the within-subject factor "time" (five levels: T1 to T5) and the between-subject factor "group" (NF vs. SM; PE vs. PE+SU). Effect sizes will be reported with η^2 = 0.039 defining a small, η^2 = 0.110 a medium, and η^2 = 0.200 a large effect. Gender and stimulant medications are important control variables, as well as treatment response according to primary outcomes. All analyses will be performed with SPSS 20 (SPSS Inc, Chicago, Il, USA).

Sample size

The primary outcome is the difference in the severity of ADHD symptoms in the Conners 3© rating scales for parents and teachers between the four treatment conditions (NF+PE vs. SM+PE vs. NF+PE+SU vs. SM+PE+SU) at the end of treatment (T3) and follow-up assessments (T4 and T5). ITT analyses as described will be performed. Meta-analyses report medium to large effect-sizes for behavioral ADHD interventions (Fabiano et al., 2009; Sonuga-Barke et al., 2013) as well as for NF (Arns et al., 2009, 2014). Sonuga-Barke et al. (2013, p. 1) state that when the best probably blinded assessment is employed, effect sizes were substantially attenuated to non-significant levels for all treatments except for free fatty acid supplementation and artificial food color exclusion. On the other hand, the meta-analyses by Fabiano et al. (2009) and Arns et al. (2009) have demonstrated homogeneous and robust effects for behavioral treatments and NF protocols, so that we expect medium to large effect sizes for parent ratings of ADHD and somewhat smaller effect sizes for teacher ratings. Thus, with an assumed effect size of f = 0.25, a two-sided alpha of 0.05, a power of 0.80, four groups (NF+ PE/NF+PE+SU; SM+PE/SM+PE+SU) and five measurement time points, a total of 97 children needs to be included (GPower© λ = 18.18, critical F = 1.78, numerator df = 12.00, denominator df = 276, n = 97, power = 0.80, Pillai V = 0.17). In order to adjust for loss of power due to an anticipated dropout of 20%, 120 children will be included in the study. Since the study is quite time consuming and the follow-up assessment fairly extensive, it seems likely that not all families will follow through with the whole study.

ETHICAL REVIEW AND TRIAL REGISTRATION

This RCT has been reviewed and approved by the local review board of the Department of Psychology of the Philipps-University Marburg (AZ: 2010-04). It is registered at www.clinicaltrials.gov as NCT01879644.

PRELIMINARY RESULTS

From February 2011 till August 2014 a total of 74 children have been screened for the study so far. Of those, 69 fulfilled study entry criteria, but 11 dropped out of the study. Thus, a total of 58 children (83% boys) has completed the diagnostic study procedure (mean age 8.42 (SD 1.34), mean IQ 110 (SD 13.37); 23% on medication; 48% with comorbid diagnoses such as ODD, Tic Disorders, Enuresis, Sibling Rivalry Disorder, Separation Anxiety Disorder). Of those, n = 32 children have already completed the T3 and n = 17 the T4 assessments. Effects of parent training groups cannot be reported here, since number of participants of the four groups is overall too small for analyses (n < 10 per group). Thus, preliminary data is only reported on the whole sample and for a comparison of children in the NF vs. the SM group.

An ANOVA on the whole sample with repeated measures shows significant differences between T1 and T3 scores for the Conners' parent and teacher ratings: main effect time = $F_{(1,35)}$ = 17.31, $p < 0.001$, η^2 = 0.331. For details for the different subscales, please refer to **Table 2A**.

An ANOVA on the whole sample with repeated measures does not show significant differences between T3 and T4 scores for the Conners' parent and teacher ratings: main effect time = $F_{(6,11)}$ = 0.59, p = 0.73, η^2 = 0.244. For details for the different subscales, please refer to **Table 2B**.

Comparing the NF and SM group in a preliminary ANOVA with repeated measures, there is a multivariate significant main effect time ($F_{(2,27)}$ = 6.98, p = 0.004, η^2 = 0.34), but a multivariate non-significant main effect group ($F_{(2,27)}$ = 0.43, p = 0.64, η^2 = 0.03), and a multivariate non-significant interaction time*group ($F_{(2,27)}$ = 0.01, p = 0.81, η^2 = 0.01) for the Conners ADHD-index. **Table 2C** shows details of the two groups. The study continues and future results with respect to the measures outlined above and to group differences will be reported based on a larger sample.

DISCUSSION

In this trial, information is collected on acceptance, feasibility, and effectiveness of behavioral treatment with either NF or SM in a high frequent outpatient setting, to establish whether NF is a treatment alternative in such a setting. To collect such information is important, since the majority of studies comparing NF to other treatments are laboratory ones, making it difficult

Table 2A | Conners-3 T1 and T3 scores for parent and teacher ratings: means and standard deviations (SD) for Conners-3 raw scores, *F*- and *p*-values and η^2.

Conners-3	T1 *N* = 32**	T3 *N* = 32**	*F*-Value	*p*-Value	η^2
ADHD index parent	11.75 (5.53)	7.13 (5.11)	$F_{(1,31)} = 25.23$	$p < 0.001$	$\eta_p^2 = 0.449$
Inattention parent	29.56 (5.97)	15.16 (5.73)	$F_{(1,31)} = 21.79$	$p < 0.001$	$\eta_p^2 = 0.413$
H/I* parent	18.78 (7.97)	14.00 (6.79)	$F_{(1,31)} = 32.61$	$p < 0.001$	$\eta_p^2 = 0.513$
ADHD index teacher	10.59 (5.14)	7.09 (5.13)	$F_{(1,31)} = 13.74$	$p = 0.001$	$\eta_p^2 = 0.307$
Inattention teacher	17.69 (4.84)	14.78 (5.58)	$F_{(1,31)} = 8.54$	$p = 0.006$	$\eta_p^2 = 0.216$
H/I* teacher	16.03 (8.91)	12.69 (7.92)	$F_{(1,31)} = 6.55$	$p = 0.016$	$\eta_p^2 = 0.175$

**H/I = Hyperactivity/Impulsivity.*

***Both SM and NF together.*

Table 2B | Conners-3 T3 and T4 scores for parent and teacher ratings: means and standard deviations (SD) for Conners-3 raw scores, *F*- and *p*-values and η^2.

Conners-3	T3 *N* = 17**	T4 *N* = 17**	*F*-Value	*p*-Value	η^2
ADHD index parent	7.53 (6.23)	7.41 (5.87)	$F_{(1,16)} = 0.013$	$p = 0.91$	$\eta_p^2 = 0.001$
Inattention parent	15.41 (6.94)	14.88 (6.13)	$F_{(1,16)} = 0.172$	$p = 0.68$	$\eta_p^2 = 0.011$
H/I* Parent	14.24 (7.79)	14.06 (8.03)	$F_{(1,16)} = 0.26$	$p = 0.87$	$\eta_p^2 = 0.002$
ADHD index teacher	5.88 (5.52)	6.12 (5.48)	$F_{(1,16)} = 0.039$	$p = 0.84$	$\eta_p^2 = 0.002$
Inattention teacher	13.76 (5.82)	13.41 (5.98)	$F_{(1,16)} = 0.064$	$p = 0.80$	$\eta_p^2 = 0.004$
H/I* teacher	10.69 (6.32)	9.88 (8.08)	$F_{(1,16)} = 0.264$	$p = 0.61$	$\eta_p^2 = 0.016$

**H/I = Hyperactivity/Impulsivity.*

***Both SM and NF together.*

Table 2C | Conners-3 T1 and T3 scores for parent and teacher ratings: means and standard deviations (SD) for Conners-3 raw scores for the SM and NF group, *F*- and *p*-values and η^2 for the main effects time and time*group.

Conners-3	Group	T1	T3	*F*-Value	*p*-Value	η^2
ADHD index parent	SM	13.13	7.00			
	n = 15	(4.50)	(4.45)	Time*: $F_{(1,27)} = 23.11$	$p < 0.001$	$\eta_p^2 = 0.461$
	NF	10.64	7.71	Time*Group*: $F_{(1,27)} = 2.89$	$p = 0.101$	$\eta_p^2 = 0.097$
	n = 14	(6.35)	(6.28)			
ADHD index teacher	SM	10.06	6.69			
	n = 15	(5.48)	(5.37)	Time*: $F_{(1,27)} = 12.99$	$p = 0.001$	$\eta_p^2 = 0.325$
	NF	11.71	7.43	Time*Group*: $F_{(1,27)} = 0.273$	$p = 0.605$	$\eta_p^2 = 0.010$
	n = 14	(4.71)	(5.04)			

**Univariate effects for the ADHD index for time and time*group for the SM and NF group.*

to conclude whether such a treatment will be efficacious in a naturalistic setting. Further, the majority of studies so far was done with children either without comorbidities or stimulant treatment (Arns et al., 2009; Fabiano et al., 2009), but this is not the reality of families seeking help for their children with ADHD (see introduction). So far we were able to include 58 children and their parents in the study. About half the children present with comorbid disorders and 23% are on medication. Reasons for dropout of the study varied. For some families the setting was too time consuming, other families came from far away and were able to initialize support closer to home. The majority dropped out of the study at the beginning of the treatment. Detailed results on dropouts with respect to the NF and SM group, time points and an extensive discussion of the reasons will follow when the study is completed. So far, 32 children have completed the therapy, and 17 have completed the follow-up (T4) assessment according to the study protocol. Thus, our approach to recruit a natural sample and to treat this in the described setting was feasible so far.

First preliminary results of our study show positive training effects. Children in both groups (NF and SM) improve in their psychopathology ratings according to parent and teacher

Conners-3 scores over time. There is no significant difference between groups (NF and SM) in changes over time. Since we assumed that NF treatment will be at least equally effective, this assumption is met. So far, those effects are stable over time, since there is no significant change in Conners-3 scores from post treatment (T3) to 6 months after treatment (T4). Since this is an ongoing study we could only include 32 children in our preliminary analysis. Thus, those results should be perceived with caution. Results on primary and secondary outcomes with respect to our research questions (i.e., group differences, long-term effects, response rates, objective measures, changes in medication etc.; see above) and for all four groups (NF/SM, PE/PE+SU) will be presented when the full data set is available. But, if this treatment in a time limited, high frequent outpatient setting (three times a week over a period of 12 weeks) continues to be as effective as our preliminary results suggest, NF training might be an additional treatment alternative for other outpatient clinics and private practices. This would contribute to an improved patient centered care for this large group of impaired children (Christiansen and Röhrle, 2012).

The greatest challenge of the study so far is the high frequency of sessions. Today, the majority of children is involved in extracurricular activities and/or parental duties make appointments three times a week difficult. The total time frame (12 weeks) somewhat eased reservations towards participation though, especially the fairly fast positive experiences related to the treatment have proved to be very motivating for children and parents. Considering the many studies that demonstrated shortend delay reward gradients for children with ADHD, i.e., a preference for smaller but sooner rewards (Sagvolden, 2000; Kuntsi et al., 2001; Solanto et al., 2001; Sonuga-Barke, 2002, 2011; Dalen et al., 2004; Antrop et al., 2006; Hoerger and Mace, 2006; Bitsakou et al., 2009; Tripp and Wickens, 2009), this seems crucial for positive therapy effects, and indeed argues for short and frequent therapy time frames, while coming to the therapy sessions might not necessarily be perceived as rewarding.

LIMITATIONS

A limitation of the study is the lack of blinding. Even though randomization and stratification of study participants are carefully done, treatment allocation is not blinded, as are of course neither children, nor parents and therapists. To meet this limitation, we decided to include likely objective outcome measures as key secondary outcomes, i.e., the Qb-Test and the KITAP. Both are computer based and assess the three ADHD core symptoms (Qb-Test: Reh et al., 2013), and differential markers of inattention (KITAP; Drechsler et al., 2009). Further, the probably blinded assessment in the meta-analysis by Sonuga-Barke et al. (2013) were teacher ADHD ratings and those are also part of the primary outcome in our study. Those strategies, along with an a priori power analysis and assessment of participants with and without medication have been suggested to optimize designs in NF research (Vollebregt et al., this Frontiers Research Topic).

All parents receive parent training. This in itself is an evidence based intervention (Bachmann et al., 2008; Zwi et al., 2011), and could cause confounder effects, especially since the PE part includes strategies to manage problem behavior. But, children aged seven to eleven rarely refer themselves to therapy (Kazdin, 2003), and psychotherapy effects for children are larger, when parents are involved (Esser and Blank, 2011). Thus, not to include parents would be against the state of the art, and would not respect the needs of parents and caregivers.[3] It might be difficult to differentiate parent training effects for the two groups. But since the PE part is identical in both groups, and the SU does receive an addition on network-analyses, we do hope to be able to discriminate effects for the two different conditions in this study.

CONCLUSION

Despite these challenges and limitations, we think that this study is a first step in establishing effective interventions in primary psycho-therapeutic care for parents and children seeking help for ADHD. According to our preliminary results, NF and SM accompanied by parent training seem to be effective in a high frequent outpatient setting. Since 23% of the children are on medication, NF and SM training effects seem to result in additional improvement. While the efficacy of psychological treatments for children has frequently been shown, the dissemination in routine care is still a problem to be solved.

AUTHOR'S CONTRIBUTIONS

Hanna Christiansen designed the study and drafted the manuscript. Verena Reh and Martin H. Schmidt conduct the study and participated in the design of the study and performed the power analysis. Winfried Rief conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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[3]http://www.nice.org.uk/guidance/cg72 (retrieved August 18th 2014).

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Near-infrared spectroscopy (NIRS) neurofeedback as a treatment for children with attention deficit hyperactivity disorder (ADHD)—a pilot study

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In this pilot study near-infrared spectroscopy (NIRS) neurofeedback was investigated as a new method for the treatment of Attention Deficit-/Hyperactivity Disorder (ADHD). Oxygenated hemoglobin in the prefrontal cortex of children with ADHD was measured and fed back. 12 sessions of NIRS-neurofeedback were compared to the intermediate outcome after 12 sessions of EEG-neurofeedback (slow cortical potentials, SCP) and 12 sessions of EMG-feedback (muscular activity of left and right musculus supraspinatus). The task was either to increase or decrease hemodynamic activity in the prefrontal cortex (NIRS), to produce positive or negative shifts of SCP (EEG) or to increase or decrease muscular activity (EMG). In each group nine children with ADHD, aged 7–10 years, took part. Changes in parents' ratings of ADHD symptoms were assessed before and after the 12 sessions and compared within and between groups. For the NIRS-group additional teachers' ratings of ADHD symptoms, parents' and teachers' ratings of associated behavioral symptoms, childrens' self reports on quality of life and a computer based attention task were conducted before, 4 weeks and 6 months after training. As primary outcome, ADHD symptoms decreased significantly 4 weeks and 6 months after the NIRS training, according to parents' ratings. In teachers' ratings of ADHD symptoms there was a significant reduction 4 weeks after the training. The performance in the computer based attention test improved significantly. Within-group comparisons after 12 sessions of NIRS-, EEG- and EMG-training revealed a significant reduction in ADHD symptoms in the NIRS-group and a trend for EEG- and EMG-groups. No significant differences for symptom reduction were found between the groups. Despite the limitations of small groups and the comparison of a completed with two uncompleted interventions, the results of this pilot study are promising. NIRS-neurofeedback could be a time-effective treatment for ADHD and an interesting new option to consider in the treatment of ADHD.

Keywords: near-infrared spectroscopy (NIRS), fNIRS, neurofeedback, attention deficit hyperactivity disorder (ADHD), children, prefrontal cortex (PFC)

INTRODUCTION

Attention Deficit-/Hyperactivity Disorder (ADHD) is characterized by the main symptoms of inattention, hyperactivity and impulsivity, leading to deficits in social and/or academic functioning.

In the model of prefrontal lobe executive functions according to Barkley (1997), a deficit in behavioral inhibition in ADHD leads to deficits in executive functions, such as working memory, and in consequence to a deficient self control. Increasing behavioral inhibition should in consequence lead to an increased self control and symptom reduction. Deficits in executive functioning can be observed in children with ADHD compared to healthy controls (Martinussen et al., 2005; Willcutt et al., 2005). On a neurophysiological level, central nervous hypo-arousal during

working memory tasks measured with fMRI was found in children with ADHD compared to healthy controls (Dickstein et al., 2006; Paloyelis et al., 2007), as well as alterations in the prefrontal cortex (Brennan and Arnsten, 2008) (see also NIRS studies below).

Neurofeedback as a treatment for ADHD can be interpreted as a way to increase behavioral inhibition. Neurofeedback is commonly EEG-feedback of frequency bands or slow cortical potentials (SCP), measuring and feeding back electrical brain activity (Arns et al., 2013; Holtmann et al., 2014b). The training protocols are based on findings of hypoarousal in the resting state EEG (Barry et al., 2003a) or findings on divergent event-related potentials (Barry et al., 2003b). EEG-neurofeedback has been proven to be an effective treatment for ADHD as regards to the reduction of inattention, impulsivity and hyperactivity (Arns et al., 2009).

An alternative method to assess brain activity is functional near-infrared spectroscopy (NIRS), measuring hemodynamic correlates of neural activity. Light in the near-infrared spectrum is absorbed to different amounts by oxygenated and deoxygenated hemoglobin allowing to determine relative concentration changes on the cortical surface (Fallgatter and Strik, 1997; Obrig et al., 2000; for an overview on applications see: Ehlis et al., 2014). Higher brain activity is thereby reflected by concentration increases (decreases) of oxygenated (deoxygenated) hemoglobin.

In most of the few NIRS studies comparing children with ADHD to healthy controls in different executive functioning tasks, altered prefrontal activity was observed: some reported reduced activity in ADHD (Negoro et al., 2010; Inoue et al., 2012; Xiao et al., 2012), some reported increased activity in ADHD (Weber et al., 2005; Jourdan Moser et al., 2009). While a few studies suggest a more pronounced involvement of the right lateral prefrontal cortex (Xiao et al., 2012; Yasumura et al., 2014), most report no specific lateralization or even clear bilateral deficits (e.g., Ehlis et al., 2008; Negoro et al., 2010; Inoue et al., 2012). Based on these findings, neurofeedback of hemodynamic activity in the prefrontal cortex could lead to a more effective use of cognitive resources, similar to EEG-neurofeedback.

fMRI-neurofeedback of hemodynamic activity has been investigated in healthy adults, showing the possibility of acquiring self-regulation rapidly in only three to four sessions (Weiskopf et al., 2003, 2004; Caria et al., 2007, 2010). The same was observed for NIRS-neurofeedback in healthy adults (Ayaz et al., 2009). In comparison to EEG-neurofeedback requiring around 30 sessions to gain sufficient self-control, NIRS-neurofeedback could be an interesting alternative, possibly allowing changes in symptomatology in fewer sessions of feedback.

Based on these findings we wanted to investigate NIRS-neurofeedback as a new method of neurofeedback for children with ADHD, aimed at gaining control over prefrontal hemodynamics. Based on the above mentioned findings in fMRI- and NIRS-studies, the left and right dorsolateral prefrontal cortex was chosen as region of interest for the neurofeedback signal, representing also a key region of executive functioning. Concentration changes in oxygenated hemoglobin were used as feedback signal due to several (partly interrelated) reasons: First, oxygenated hemoglobin was found to show the strongest correlation with the fMRI BOLD signal, probably because of its superior signal-to-noise ratio as compared to deoxygenated hemoglobin (Strangman et al., 2002). Second, depending on the vascular characteristics of the brain tissue covered by the NIRS optodes, the signal course of deoxygenated hemoglobin can show considerable differences, with cortical activation leading to (the usually expected) decreases, increases or even no changes in HHb concentration. Oxygenated hemoglobin, on the other hand, consistently shows concentration increases during active task periods (Yamamoto and Kato, 2002) allowing for a more reliable interpretation of oxy-Hb data. Third, previous findings also suggest that the amplitude of change is always larger for oxygenated than for deoxygenated hemoglobin (Yamamoto and Kato, 2002), which is a critical point in feedback trainings that rely on single-trial NIRS data (as in our case).

Besides the general aim to investigate the feasibility of NIRS-neurofeedback especially for children with ADHD, the study was designed to assess as primary outcome if NIRS-neurofeedback leads to a reduction of ADHD in parents' ratings and if changes persist 6 months after the training. Additionally, decreased teachers' ratings of ADHD symptoms, decreased parents' and teachers' ratings of associated behavioral symptoms, improvements in children's self-rated quality of life and in the performance in a computer based attention task were expected. As an active control condition neurofeedback of SCPs was selected, as a semi-active control condition feedback of muscular activity of the left and right musculus supraspinatus was chosen (for an overview of control conditions in neurofeedback see Arns et al., 2013). We expected comparable changes in symptomatology compared to EEG-neurofeedback and greater changes in comparison to EMG-feedback after 12 sessions of training.

Additionally, the hemodynamic brain activity was measured during the NIRS-neurofeedback training sessions and a working memory task with parallel NIRS measurement was conducted to measure changes in prefrontal brain activity before and after the training. The hemodynamic data are not part of this paper and will be published separately.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Tuebingen and conducted according to the ethical guidelines and principles of the international Declaration of Helsinki. The multicentre study (ISRCTN76187185) was approved by all local Ethics Committees according to the Declaration of Helsinki. Written informed consent was obtained from parents and children.

MATERIALS AND METHODS

PARTICIPANTS

Inclusion criteria were age between 7;0 and 10;11 years and a full-scale intelligence quotient over 80 (percentile >9, assessed with the Colored Progressive Matrices CPM, Raven et al., 1998; German version: Bulheller and Häcker, 2006) and a pre-diagnosis of ADHD by a child psychiatrist, pediatrician or clinical psychologist. Exclusion criteria were an intelligence level under 80 (percentile ≤9), medical or neurological disorders, psychiatric

Table 1 | Description of the sample.

		NIRS-group $n = 9$	EEG-group $n = 9$	EMG-group $n = 9$	Kruskal-Wallis
Age	*Mdn*	8.92	9.17	8.83	$H(2) = 0.28$
	IQR	7.67–10.25	8.00–9.83	8.25–9.50	$p = 0.869$
CPM	*Mdn*	76.00	69.00	85.00	$H(2) = 1.94$
Percentile	*IQR*	61.50–97.50	32.00–90.00	72.50–93.50	$p = 0.380$
EFB-K total	*Mdn*	2.77	3.00	3.20	$H(2) = 0.78$
Score	*IQR*	2.23–3.56	2.75–3.50	2.70–3.30	$p = 0.678$
CBCL total	*Mdn*	47.00	36.00	35.00	$H(2) = 3.03$
Raw score	*IQR*	35.00–66.00	26.00–56.50	24.50–52.50	$p = 0.220$

Mdn = median, IQR = interquartile range, CPM = Colored Progressive Matrices, EFB-K = Parenting scale, CBCL = Child Behavior Checklist.

disorders other than oppositional defiant disorder and current participation in a psychotherapeutic treatment.

27 children with ADHD combined type (age $M = 8.90$ years, $sd = 1.02$; 9 female) participated in the study. The diagnosis was confirmed with the supplement for ADHD (German version: Delmo et al., 2000) of the semi-structured interview Kiddie-Sads-Present and Lifetime Version (Kaufman et al., 1997; Kaufman and Schweder, 2003), using DSM-IV criteria.

Nine children (3 female) with a mean age of $M = 9.00$ years ($sd = 1.26$) took part in the NIRS-feedback. For the EEG- and the EMG-group, 18 children were matched to the NIRS-group for gender, medication status and age (EEG-group: $M = 8.85$ years, $sd = 0.99$, 3 female; EMG-group: $M = 8.83$ years, $sd = 0.88$, 3 female). The children of these two groups were participants in a multicenter neurofeedback study (ISRCTN76187185, Holtmann et al., 2014a) with a total of 144 participants recruited with identical inclusion and exclusion criteria.

As additional screening instruments, all parents rated the child's behavior on the Child behavior checklist (CBCL, Achenbach, 1991; German version: Arbeitsgruppe Deutsche Child Behavior Checklist, 1998) and their own parenting behavior on the Parenting Scale (Arnold et al., 1993; German short version EFB-K: Miller, 2001). Medication status was assessed; seven children in each group with a medication of methylphenidate stopped medication at least 48 h before the pretest, the post test 2 and the follow-up test. There were no other medication agents (amphetamine, atomoxetine) prescribed in the NIRS-sample, so the matching included only children with a medication of methylphenidate. The groups did not differ significantly in age, IQ percentile, total score of parenting behavior and total score of child's behavior (see **Table 1**).

PROCEDURE AND MEASUREMENT INSTRUMENTS

The nine children in the NIRS-group were recruited in the same manner as the children of the two other groups through local advertisements and through pediatricians and child psychiatrists. For the matching of EEG- and EMG-group, 80 complete datasets were used and only gender, medication status, age and IQ were transferred. After matching, the complete dataset was provided. Main matching criteria were same gender and same medication status, followed by nearest age and nearest IQ. The NIRS-group received 12 sessions, the EEG- and EMG-group received 25 sessions of training. For the inter-group comparison, the FBB-ADHS was used after 12 sessions (see **Table 2**). As there are no NIRS-neurofeedback studies investigating children with ADHD so far, the amount of 12 sessions for the NIRS-group was based on the findings in fMRI- and NIRS-neurofeedback with healthy subjects using three to four sessions (see Introduction) and was adapted for practical reasons to the intermediate outcome of the multicentric study, to allow group comparison. The outcome of the full 12 session NIRS-training was thus compared to the intermediate 12 session outcome of the longer EEG- and EMG-training, in order to test for a more rapid clinical improvement with NIRS-neurofeedback.

For the pre-post comparison of the NIRS-group ADHD symptoms rated by parents and teachers in the Rating Scale for Attention Deficit Hyperactivity Disorder (Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, FBB-ADHS) were assessed as main dependent variables. The parent-rated FBB-ADHS was the primary outcome. The FBB-ADHS is part of the Diagnostic System for Mental Disorders in Childhood and Adolescence (DISYPS-II, Döpfner et al., 2008). The FBB-ADHS covers the diagnostic criteria for the combined

Table 2 | Measurement points and instruments for within- and between-group comparisons.

Measurement point	Measurement instruments		
	Parents	**Teachers**	**Children**
Pretest	**FBB-ADHS** SDQ	FBB-ADHS SDQ	KID-KINDL TAP 2.2 Go/NoGo and Flexibility
Post Test 1 (after session 12)	**FBB-ADHS**		
Post Test 2 (4 weeks after session 12)	FBB-ADHS SDQ	FBB-ADHS SDQ	KID-KINDL TAP 2.2 Go/NoGo and Flexibility
Follow up Test (6 months after session 12)	FBB-ADHS SDQ	FBB-ADHS SDQ	KID-KINDL TAP 2.2 Go/NoGo and Flexibility

Bold marked FBB-ADHS = measurements in all three groups for group comparison. FBB-ADHS = Rating scale for ADHD, SDQ = Strengths and Difficulties Questionnaire, KID-KINDL = Questionnaire for health-related quality of life, TAP 2.2 = Test Battery for Attentional Performance.

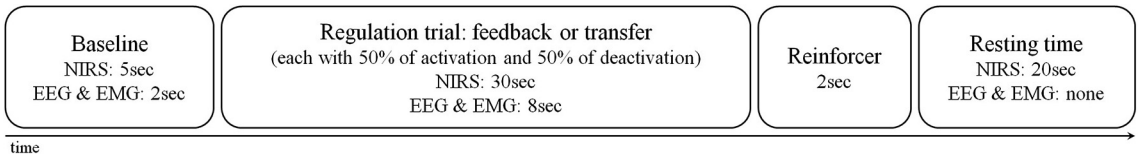

FIGURE 1 | Trial design of NIRS-, EEG- and EMG- blocks. One NIRS session consisted of 2 feedback blocks each with 12 trials and 1 transfer block with 8 trials. An EEG and EMG session consisted of 3 feedback blocks and 1 transfer block each with 40 trials.

type of ADHD according to the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition; DSM-IV, American Psychiatric Association, 2000) and can be regarded as the German equivalent of the SNAP-IV. Associated behavioral symptoms were assessed with the Strengths and Difficulties Questionnaire (SDQ, Goodman, 1997; German Version: Rothenberger and Woerner, 2004), rated by parents and teachers. Children rated their quality of life in the Kindl-Questionnaire for health-related quality of life (KID-KINDL, Ravens-Sieberer, 2003) and childrens' attention and impulsivity were measured with two subtests (Flexibility, Go/NoGo) of a computer based attention task (Test Battery for Attentional Performance, TAP, Zimmermann and Fimm, 2009). The TAP subtest Go/NoGo measures the ability to inhibit reactions (performance variables: median of reaction times, standard deviation of reaction times, omissions and commissions); the subtest Flexibility measures the ability to change the focus of attention (performance variables: median of reaction times, standard deviation of reaction times, commissions). All instruments were applied before training (pretest), 4 weeks (post test 2) and 6 months (follow-up test) after the training. **Table 2** gives an overview of measurement points and instruments.

The childrens' pediatricians or the childrens' psychiatrists were asked to rate severity of psychopathology and improvement after treatment on the Clinical Global Impression Scale (Guy, 1976). This data was not analyzed and will not be reported due to low return rates (pretest $n = 6$, post test $n = 3$, follow up $n = 2$).

NIRS-NEUROFEEDBACK

NIRS-neurofeedback training consisted of twelve sessions within 4–6 weeks, with 2–3 sessions per week. Each session comprised three blocks of NIRS-neurofeedback. After the 12 sessions, children were instructed to practice their strategy for 3 weeks in attention-requiring situations at home or school, to facilitate the transfer to everyday life. In order to motivate the children, the whole training was accompanied by a token system in which the children could gain points and swap them for small toys. Tokens were given for good cooperation during a training session, independent of achievement.

The basic parameters of the three trainings (NIRS, EEG, EMG) were comparable. Each session lasted approximately 1 hour with 32 min effective feedback time. The visual layout of the feedback was identical. Compared to electrical brain and muscular activity, changes in hemodynamic activity are somewhat delayed and need more time to return back to baseline. In consequence, hemodynamic neurofeedback trials were designed with longer regulation and resting times (see **Figure 1** for a comparison of the three training protocols).

One session comprised 2 feedback blocks each lasting 12 min and one transfer block lasting 8 min. A feedback block consisted of 12 regulation trials. One trial consisted of 20 s resting time, 5 s baseline measurement and 30 s regulation time (see **Figure 1** for trial design). The task was to increase or decrease the hemodynamic activity in the prefrontal cortex (in 50% of cases activation, in 50% deactivation, in a random order). As feedback the children saw an object on a screen (e.g., a fish), moving from left to right and depicting concentration changes in oxygenated hemoglobin. An arrow in the middle of the screen indicated if activation (pointing upwards) or deactivation (pointing downwards) was expected. In activation trials the concentration of oxygenated hemoglobin should increase in comparison to the baseline, in deactivation trials it should decrease. At the end of a successful trial (= the object was flying at least 7 s of the last 15 s regulation time in the expected direction) a sun was shown on the screen as a visual reinforcer. A transfer block consisted of 8 regulation trials in which the moving feedback object was not shown, but the sun at the end of the trial indicated whether the participant was successful. The transfer blocks were included in order to facilitate the transfer to everyday life.

The neurofeedback signal reflected relative concentration changes of oxygenated hemoglobin in the prefrontal cortex. A 52-channel NIRS system (Hitachi Optical Topography System ETG-4000) was placed over frontal and temporal areas and linked to a neurofeedback device (NeuroConn THERA-PRAX). For the measurement 46 optodes (44 NIRS channels) were used, arranged on two 3 × 5 probesets. The probesets were oriented along positions of the 10–20-system of electrode placement. The lowest row of both probesets was oriented frontally with Fpz as midpoint, while the second optode from occipital in the lowest row on each side was lying on T3 respectively T4 (see **Figure 2** for channel positions). The neurofeedback signal, that is the signal that controls the "flying" object on the computer's screen, was based on mean concentration changes in oxygenated hemoglobin measured over the right and left dorsolateral prefrontal cortex and computed using the following procedure: In a first step, for each sample in time, the average of the signals from four NIRS channels located over the left and right dorsolateral prefrontal cortex (see **Figure 2**, blue marking) was computed. This was followed by subtracting the average of the particular probeset (22 channels) per side (common average reference). In a last step, the resulting two signals (one corresponding to each side) were averaged and used to provide feedback. This method was adopted to minimize

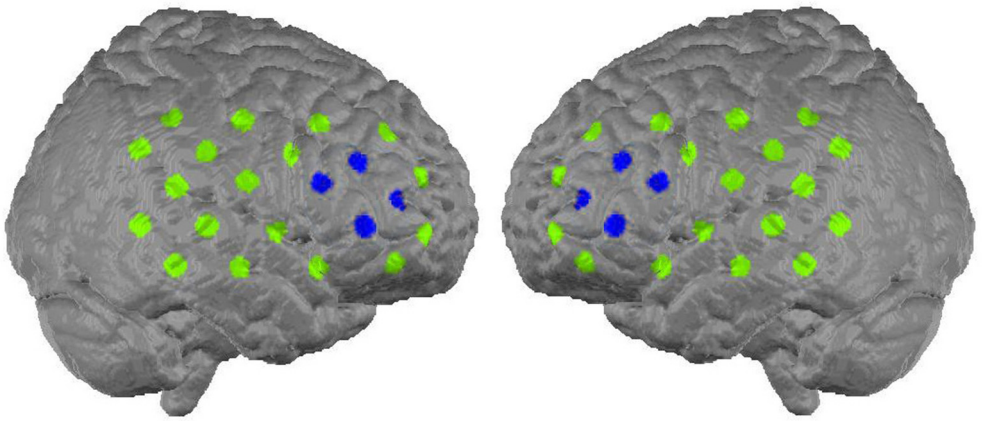

FIGURE 2 | Alignment of the 44 NIRS channels on the cortex surface (Marx, 2014). The eight channels from which the feedback signal was computed are marked with blue (figure buildt with MATLAB based on MNI coordinates, available: http://www.jichi.ac.jp/brainlab/virtual_registration/Result3x5_E.html, Tzourio-Mazoyer et al., 2002; Tsuzuki et al., 2007).

the effect of hemodynamic artifacts induced by breathing, head movements or skin blood flow.

The NIRS signals were transmitted to a personal computer via TCP/IP protocol for further processing. The feedback signal was computed online using a self-programmed MATLAB routine and it served as input signal for the neurofeedback device.

EEG-NEUROFEEDBACK AND EMG-FEEDBACK

The EEG- and EMG-group participated in 25 sessions, with a 3 week practice break including an intermediate outcome assessment using the FBB-ADHS after 12 sessions. One session consisted of 3 feedback blocks (with the same visualization as in the NIRS-group) and one transfer block (without feedback object) each lasting 8 min. The blocks consisted of 40 regulation trials. One regulation trial comprised 2 s baseline measurement and 8 s regulation time (50% of cases activation, 50% deactivation, in a random order, see **Figure 1** for trial design, a detailed description is provided in Holtmann et al., 2014a).

The feedback was conducted with the NeuroConn NEUROPRAX (identical software to THERA-PRAX, possibility to measure more EEG channels). Nine Ag/AgCl ring electrodes were used, one at Cz, two at the right and left mastoid (A1 and A2), two central over and under the left eye, two at the left and right corner of both eyes and two at the right and left musculus supraspinatus above the shoulders.

In the EEG-group the EEG-signal (slow cortical potentials at Cz referenced against A1, online corrected for eye movements, ground electrode at A2) was fed back, in the EMG-group the EMG-signal was fed back. The task in the EEG-group was to produce a positive or negative shift of the SCPs in comparison to the baseline. The task in the EMG-group was to increase muscle tension on the left side while decreasing it on the right side and vice versa in comparison to the baseline. At the end of a successful trial (= the object was flying at least 2 s of the last 4 s regulation time in the expected direction) a sun was shown on the screen as a visual reinforcer.

DATA ANALYSIS AND STATISTICS

For the FBB-ADHS, the SDQ and the KID-KINDL total scores were calculated according to the test instructions. A higher score in the FBB-ADHS implies more severe ADHD symptoms and a higher score in the SDQ implies a higher occurrence of associated behavioral symptoms, including hyperactivity. A higher score in the KID-KINDL implies a higher self-rated quality of life. For the two TAP subtests, medians of reaction times, standard deviations of reaction times and the numbers of commissions and omissions (only Go/NoGo) were assessed and analyzed. Higher medians of reaction times represent slower reactions; higher standard deviations of reaction times represent a higher variability of reaction times.

IBM SPSS Version 20 was used for statistical analysis. Due to small sample-size, non-parametric tests were applied. Significance level was set to $\alpha \leq 0.05$. Friedman's ANOVAS were conducted for comparisons within the NIRS-group (pretest, post test 2, follow-up test) for the dependent variables. For *post hoc* analysis Wilcoxon signed-rank tests were conducted. Additionally, effect sizes were calculated ($r = \frac{z}{\sqrt{N}}$).

For the comparison of the three groups the initial values of parents' and teachers' ratings of the FBB-ADHD and the SDQ, the child-rated KID-KINDL and the performance data of the TAP subtests were compared with Kruskal-Wallis-Tests and *post hoc* Mann-Whitney *U* Tests, to ensure the general comparability of the three groups. To assess the pre-post effects of the twelve training sessions for each group separately, three Wilcoxon signed rank tests were conducted for the total scores of the FBB-ADHS comparing pretest and post test 1 within each group. Additionally, differences of the scores were calculated for each group (total score at post test 1 minus total score at pretest, a higher difference implies a higher symptom reduction), and these differences were compared between groups in a Kruskal-Wallis-Test.

Table 3 | Medians and interquartile ranges for the dependent variables of the NIRS-group at all measurement points with test statistics.

		Pretest	Post test 2	Follow-up test	Friedman's ANOVAS
FBB-ADHS total score parents	*Mdn*	1.65	1.05	1.05	$\chi^2(2) = 6.59$
	IQR	1.33–2.15	0.68–1.33	0.88–1.25	**$p = 0.037$**
FBB- ADHS total score teachers	*Mdn*	1.10 ($n = 7$)	1.00 ($n = 8$)	1.03 ($n = 8$)	$\chi^2(2) = 6.33$
	IQR	0.80–2.15	0.44–2.05	0.66–1.51	**$p = 0.042$**
KID-KINDL total score	*Mdn*	4.13	4.46	4.17	$\chi^2(2) = 2.00$
	IQR	3.75–4.46	3.40–4.71	3.98–4.40	$p = 0.368$
SDQ total score parents	*Mdn*	18.00	16.00	14.00	$\chi^2(2) = 5.88$
	IQR	16.50–23.00	11.50–19.50	9.50–17.50	$p = 0.053$
SDQ total score teachers	*Mdn*	13.00 ($n = 7$)	10.00 ($n = 7$)	9.50 ($n = 8$)	$\chi^2(2) = 2.78$
	IQR	10.00–18.00	6.00–27.00	7.50–23.75	$p = 0.249$
TAP Go/NoGo median reaction time	*Mdn*	551.00	580.00	497.00	$\chi^2(2) = 6.91$
	IQR	450.50–600.00	470–606.50	440.00–520.00	**$p = 0.032$**
TAP Go/NoGo standard deviation reaction time	*Mdn*	150.00	122.00	89.00	$\chi^2(2) = 8.97$
	IQR	112.50–185.50	87.00–149.50	79.00–113.50	**$p = 0.011$**
TAP Go/NoGo commissions	*Mdn*	4.00	0.00	0.00	$\chi^2(2) = 12.96$
	IQR	1.50–11.50	0.00–2.00	0.00–3.50	**$p = 0.002$**
TAP Go/NoGo omissions	*Mdn*	0.00	0.00	0.00	$\chi^2(2) = 5.38$
	IQR	0.00–2.00	0.00–0.00	0.00–0.50	$p = 0.068$
TAP Flexibility median reaction time	*Mdn*	1276.00	929.00	1012.00	$\chi^2(2) = 6.22$
	IQR	843.00–1468.00	776.50–1092.50	719.50–1144.50	**$p = 0.045$**
TAP Flexibility standard deviation reaction time	*Mdn*	534.00	350.00	320.00	$\chi^2(2) = 6.22$
	IQR	272.00–630.00	285.00–409.00	227.00–384.50	**$p = 0.045$**
TAP Flexibility commissions	*Mdn*	12.00	9.00	5.00	$\chi^2(2) = 4.22$
	IQR	6.00–21.00	4.00–17.00	3.50–8.50	$p = 0.121$

Reaction times in milliseconds, Mdn = Median, IQR = interquartile range, bold = significant at $\alpha \leq 0.05$, FBB-ADHS = Rating scale for ADHD, SDQ = Strengths and Difficulties Questionnaire, KID-KINDL = Questionnaire for health-related quality of life, TAP = Test Battery for Attentional Performance; if not reported otherwise: n = 9.

RESULTS

WITHIN-GROUP COMPARISONS FOR THE NIRS-GROUP

For an overview of all medians and interquartile ranges for the dependent variables of the NIRS-group at all measurement points with test statistics see **Table 3**. Five teacher ratings were not included in the data analysis: one was not sent back (SDQ + FBB-ADHS), one was returned empty (SDQ + FBB-ADHS), three could not be assigned to a measurement point (2 SDQ + FBB-ADHS, 1 SDQ).

FBB-ADHS

There are significant differences in the measurement points of the FBB-ADHS total score for the NIRS-group in parents' and teachers' ratings (parents: $\chi^2(2) = 6.59$, $p = 0.037$; teachers: $\chi^2(2) = 6.33$, $p = 0.042$). In the *post hoc* analysis of parents' ratings, ADHD symptoms significantly decreased from pretest to post test 2 ($z = -2.49$, $p = 0.013$, $r = -0.587$) as well as from pretest to follow-up test ($z = -2.31$, $p = 0.021$, $r = -0.544$). There was no significant difference between parents' ratings from post test 2 to follow-up test ($z = -0.51$, $p = 0.611$, $r = -0.120$). The *post hoc* analysis of teachers' ratings revealed a significant decrease of ADHD symptoms in teachers' ratings from pretest to post test 2 ($z = -2.21$, $p = 0.027$, $r = -0.535$), but not from pretest to follow-up test ($z = -1.69$, $p = 0.091$, $r = -0.410$) or from post test 2 to follow-up test ($z = -0.34$, $p = 0.735$, $r = -0.080$). For medians and interquartile ranges of FBB-ADHS total scores see **Figure 3** and **Table 3**.

SDQ and KID-KINDL

There were no significant differences in parents' and teachers' ratings of associated behavioral symptoms (SDQ total scores) and in childrens' ratings of quality of life (KID-KINDL) for the three measurement points (parents' ratings SDQ: $\chi^2(2) = 5.88$, $p = 0.053$; teachers' ratings SDQ: $\chi^2(2) = 2.78$, $p = 0.249$; childrens' ratings KID-KINDL: $\chi^2(2) = 2.00$, $p = 0.368$). In the *post hoc* analysis there was a significant decrease in parents' ratings of the SDQ total score from pretest to follow-up test ($z = -2.55$, $p = 0.011$, $r = -0.602$). See **Figure 4** and **Table 3** for medians and interquartile ranges of the SDQ total scores.

TAP

Go/NoGo. For the subtest Go/NoGo significant differences were found for the three measurement points in standard deviations of reaction times ($\chi^2(2) = 8.97$, $p = 0.011$), commission errors ($\chi^2(2) = 12.96$, $p = 0.002$) and medians of reaction times ($\chi^2(2) = 6.91$, $p = 0.032$). In the *post hoc* analysis there was a significant difference in the medians of reaction times from post test 2 to follow-up test ($z = -2.52$, $p = 0.012$, $r = -0.595$), as shown in **Figure 5**. The children reacted faster 6 months after the training than 4 weeks after the training. In the *post hoc*

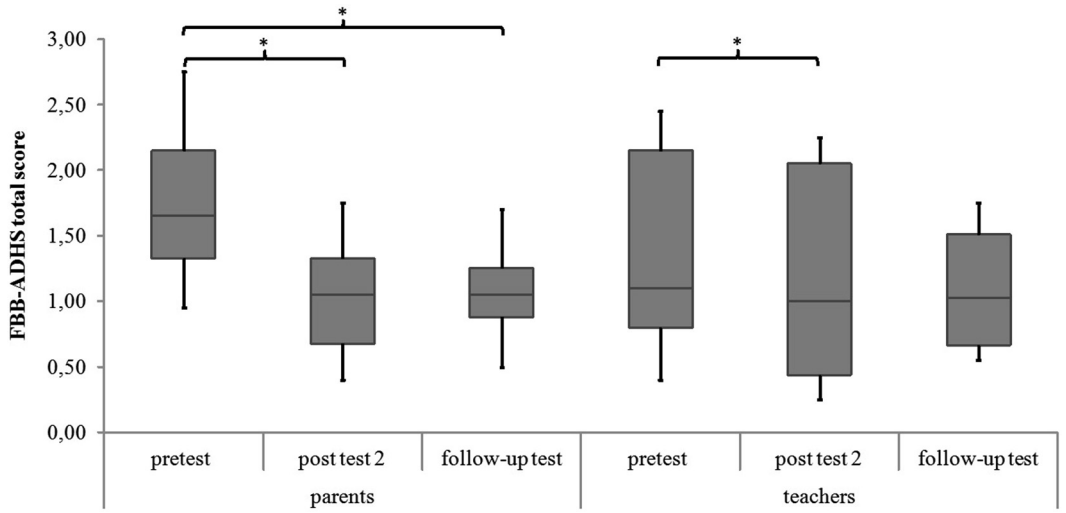

FIGURE 3 | FBB-ADHS total score of parents' and teachers' ratings for all meeasurement points. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

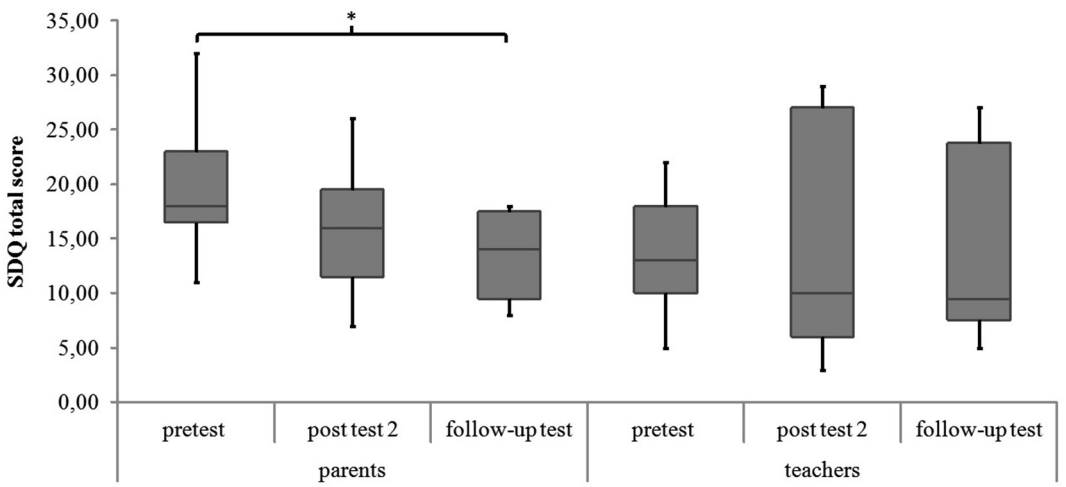

FIGURE 4 | SDQ total score of parents' and teachers' ratings for all measurement points. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

analyses of the standard deviations of reaction times there was a significant difference between pretest and post test 2 ($z = -2.38$, $p = 0.017$, $r = -0.561$) as well as between pretest and follow up test ($z = -2.55$, $p = 0.011$, $r = -0.600$, see **Figure 6**). The children reacted with less variability 4 weeks and 6 months after the training in comparison to prior to the training. There were significant differences in commission errors from pretest to *post test* 2 ($z = -2.53$, $p = 0.012$, $r = -0.596$) and from pretest to follow-up test ($z = -2.37$, $p = 0.018$, $r = -0.559$), as shown in **Figure 7**. The children made fewer commission errors after the training.

Flexibility. In the subtest Flexibility there were significant differences for the medians of reaction times ($\chi^2(2) = 6.22$, $p = 0.045$) and the standard deviations of reaction times ($\chi^2(2) = 6.22$, $p = 0.045$). In the *post hoc* analysis there were no significant differences for the medians of reaction times (see **Figure 5**). In the *post hoc* analysis of the standard deviations of reaction times there was a significant decrease of variability from pretest to post test 2 ($z = -2.31$, $p = 0.021$, $r = -0.544$) and from pretest to follow-up test ($z = -2.31$, $p = 0.021$, $r = -0.544$), see **Figure 6**. There was also a significant decrease of commission errors from pretest to follow-up test ($z = -1.96$, $p = 0.050$, $r = -0.462$), see **Figure 7**.

WITHIN AND BETWEEN GROUP COMPARISONS FOR EEG-, EMG- AND NIRS-GROUP

There were no significant differences between groups in the pretest values of parents' and teachers' rating of the ADHD

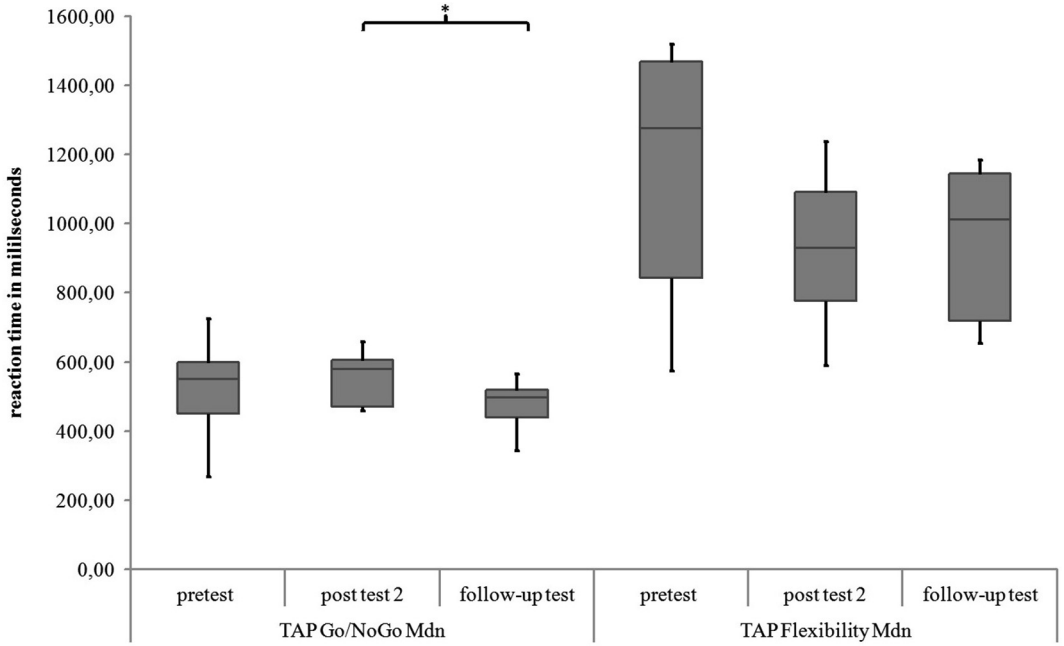

FIGURE 5 | Medians of reaction times for the TAP subtests Go/NoGo and Flexibility for all measurement points. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

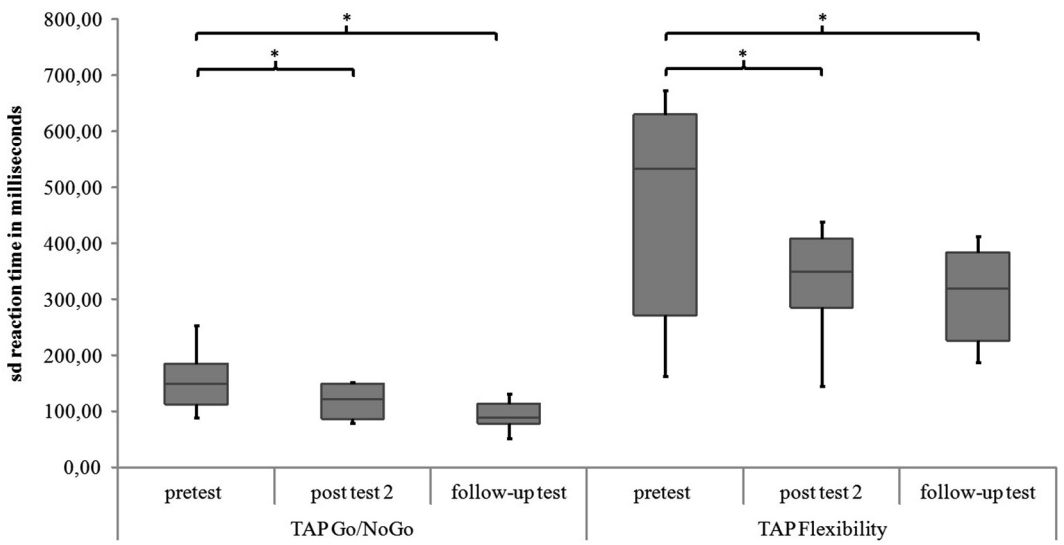

FIGURE 6 | Standard deviations of reaction times for the TAP subtests Go/NoGo and Flexibility for all measurement points. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

symptoms in the FBB-ADHS and in the teachers' rating of associated behavioral symptoms in the SDQ (see **Table 4**). Childrens' ratings of the quality of life in the KID-KINDL and parents' ratings of associated behavioral symptoms in the SDQ differed significantly between groups (see **Table 4**). *Post hoc* analyses for the SDQ revealed a significant higher score in the EMG-group in comparison to the NIRS-group (NIRS vs. EEG: $U = 21.50$, $z = -1.68$, $p = 0.094$; NIRS vs. EMG: $U = 15.00$, $z = -2.26$, $p = 0.024$; EEG vs. EMG: $U = 26.50$, $z = -1.24$, $p = 0.222$). *Post hoc* analyses for the KID-KINDL showed significant higher quality of life scores in the NIRS-group in comparison to the EEG-group ($U = 0.00$, $z = -3.58$, $p = 0.000$) as well as in comparison to the EMG-group ($U = 0.00$, $z = -3.58$, $p = 0.000$), there was no difference between EEG- and EMG-group ($U = 26.50$, $z = -1.25$, $p = 0.222$).

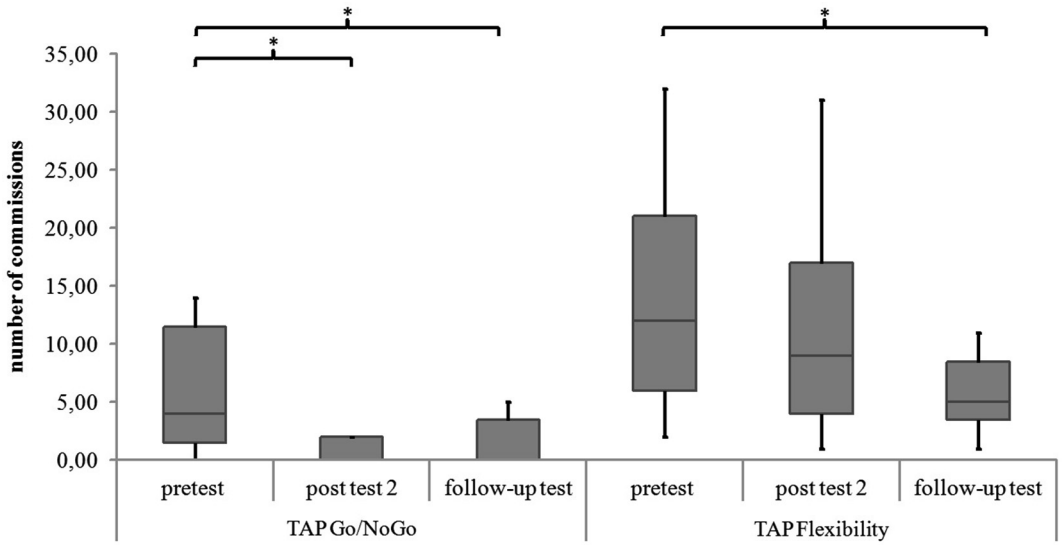

FIGURE 7 | Commissions in the TAP subtests Go/NoGo and Flexibility for all measurement points. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

Table 4 | Medians and interquartile ranges of FBB-ADHS, KID-KINDL and SDQ at pretest with group statistics.

		NIRS-group $n = 9$	EEG-group $n = 9$	EMG-group $n = 9$	Kruskal-Wallis
FBB-ADHS	*Mdn*	1.65	2.00	1.75	$H(2) = 2.66$
parents total score	*IQR*	1.33–2.15	1.75–2.23	1.60–1.90	$p = 0.264$
FBB-ADHS teachers	*Mdn*	1.10 ($n = 7$)	1.20 ($n = 8$)	1.95 ($n = 8$)	$H(2) = 1.73$
total score	*IQR*	0.80–2.15	0.61–1.45	0.56–2.45	$p = 0.421$
KID-KINDL	*Mdn*	4.13	2.88	3.08	$H(2) = 18.12$
total score	*IQR*	3.75–4.46	2.61–2.96	2.59–3.11	$\mathbf{p = 0.000}$
SDQ parents	*Mdn*	18.00	23.00	24.00	$H(2) = 6.33$
total score	*IQR*	16.50–23.00	19.50–28.50	21.00–32.00	$\mathbf{p = 0.042}$
SDQ teachers	*Mdn*	13.00 ($n = 7$)	17.00 ($n = 8$)	23.00 ($n = 8$)	$H(2) = 3.41$
total score	*IQR*	10.00–18.00	13.00–18.50	12.50–28.50	$p = 0.182$

Reaction times in milliseconds, Mdn = median, IQR = interquartile range, bold = significant at $\alpha \leq 0.05$, FBB-ADHS = Rating scale for ADHD, SDQ = Strengths and Difficulties Questionnaire, KID-KINDL = Questionnaire for health-related quality of life; if not reported otherwise: n = 9.

Within-group comparisons to assess the pre-post effect of the twelve sessions separately for each group revealed a significant difference in the parents' rating of the FBB-ADHS only for the NIRS-group ($z = -2.25$, $p = 0.024$, $r = -0.531$, see **Table 5** and **Figure 8**). A trend for a lower FBB-ADHS score was observed for the EEG-group ($z = -1.90$, $p = 0.058$, $r = -0.447$) and the EMG-group ($z = -1.84$, $p = 0.066$, $r = -0.434$).

Comparing the three groups in the differences of parents' ratings of the FBB-ADHS (post test 1 values minus pretest values), there were no significant differences between the groups (NIRS: $Mdn = -0.65$, $IQR = -1.03 - -0.11$; EEG: $Mdn = -0.60$, $IQR = -1.06 - 0.03$; EMG: $Mdn = -0.20$, $IQR = -0.38$–0.04; $H(2) = 2.72$, $p = 0.256$).

DISCUSSION

In this pilot study NIRS-neurofeedback as a new method of neurofeedback training for children with ADHD was investigated. Hemodynamic brain activity in the dorsolateral prefrontal cortex was measured and fed back. Children should learn to gain control over their brain activity in 12 training sessions and 3 weeks of transfer exercises. Primary outcome was the effect on ADHD symptoms rated by parents. Teachers' ratings of symptoms as well as ratings of associated behavioral symptoms by parents and teachers, self-rated quality of life and performance in a computer based attention task were assessed. In addition, a comparison with two other feedback methods (EEG, EMG) was carried out.

NIRS -NEUROFEEDBACK—EFFECTS AND FEASIBILITY

As primary outcome, parents' ratings of ADHD symptoms in the NIRS-group were significantly reduced 4 weeks and 6 months after the training. Teachers' ratings of ADHD symptoms showed a significant reduction 4 weeks after the end of treatment. Attention and impulsivity in the computer based attention test TAP improved significantly (Go/NoGo: speed,

Table 5 | Parents' ratings of the FBB-ADHS at pretest and post test 1 for the three groups with test statistics.

		FBB-ADHS total score pretest	FBB-ADHS total score post test 1	Wilcoxon signed rank Test
NIRS-group	*Mdn*	1.65	1.25	$z = -2.25$
	IQR	1.33–2.15	0.83–1.44	$\mathbf{p = 0.024}$
				$r = -0.531$
EEG-group	*Mdn*	2.00	1.40	$z = -1.90$
	IQR	1.75–2.23	1.18–1.53	$p = 0.058$
				$r = -0.447$
EMG-group	*Mdn*	1.75	1.60	$z = -1.84$
	IQR	1.60–1.90	1.20–1.90	$p = 0.066$
				$r = -0.434$

Mdn = median, IQR = interquartile range, r = effect size, bold = significant at $\alpha \leq 0.05$, FBB-ADHS = Rating scale for ADHD.

variability, commissions; Flexibility: variability, commissions). According to these results, NIRS-neurofeedback might be as effective in reducing the main symptoms of ADHD, as it was shown before in randomized controlled studies for EEG-neurofeedback (e.g., Gevensleben et al., 2009; Meisel et al., 2013).

The effect size for the parents' ratings of ADHD symptoms in the NIRS-group was high for pre-post comparison ($r = -0.587$). This is comparable to effect-sizes of EEG-neurofeedback as reported in the meta-analysis of Arns et al. (2009). Here, high effect sizes for inattention and impulsivity and medium effect sizes for hyperactivity in pre-post designs of EEG-neurofeedback-studies were observed. With larger sample sizes in NIRS-neurofeedback, a differentiated analysis of effects on symptom groups (inattention, impulsivity, hyperactivity) could be conducted, allowing detailed comparisons with effect sizes of EEG-neurofeedback.

The general question of feasibility of NIRS-neurofeedback for children with ADHD can be answered by taking into account different variables. On the one hand, the technical implementation was possible; on the other hand, children and parents accepted the procedure. All nine children took part in all twelve sessions. At the beginning of each training session, motivation was rated on a 4-point smiley scale (1 = totally motivated, 2 = quite motivated, 3 = not much motivated, 4 = not motivated at all). The mean motivation over all sessions and children was high ($M = 1.51$; $sd = 0.89$). Parents rated their satisfaction with the training on a six-item scale 4 weeks and 6 months after the training. They were asked to rate satisfaction with the training, satisfaction with the trainer, empathy of the trainer, trust in the training, trust in the competence of the trainer and recommendation of the training on a 7-point scale (endpoints: 0 = not at all, 7 totally). The mean of parent satisfaction 4 weeks and 6 months after training was high (post test 2: $M = 5.48$, $sd = 0.58$, follow-up test: $M = 5.57$, $sd = 0.57$). Additionally, parents were asked for adverse side effects in relation to measurement and training at all measurement points. No serious adverse events were documented. Two children reported to have had transient headaches directly after some of the training sessions, possibly caused by the fixation of the probe set. In conclusion, NIRS-neurofeedback seems to be a feasible and accepted intervention for children with ADHD.

COMPARISON WITH EEG-NEUROFEEDBACK AND EMG-FEEDBACK AND FUTURE DIRECTIONS

The NIRS-group showed a significant reduction of ADHD symptoms in parents' ratings after twelve training sessions. A trend towards decreased ADHD symptoms was observed for

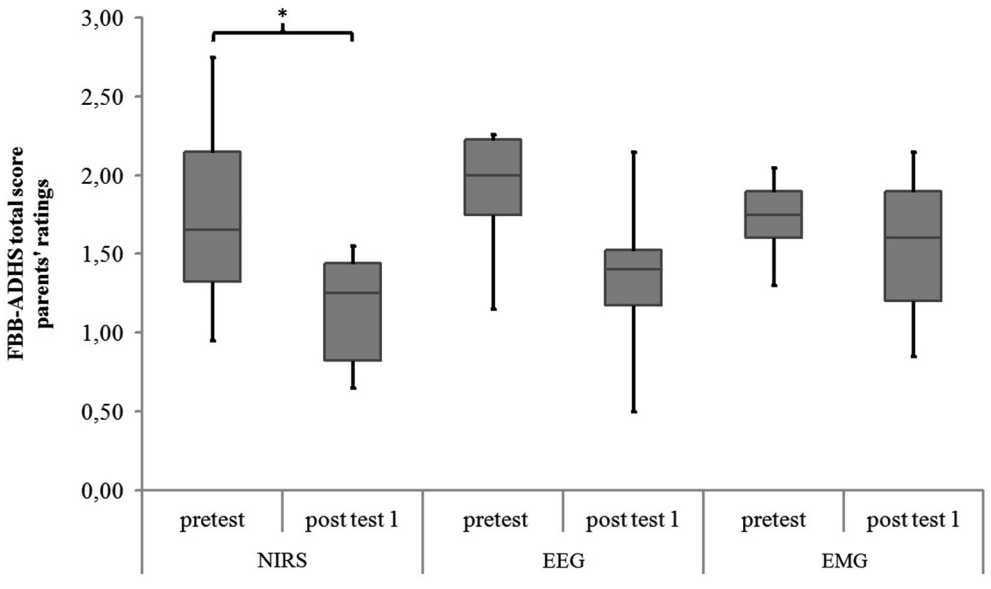

FIGURE 8 | FBB-ADHS total score of parents' ratings for NIRS-, EEG- and EMG-group at pretest and post test 1. Middle line of boxes = median, box = interquartile range, error bars = minimum respectively maximum, * = significant.

the EEG- and the EMG-group. In the between group comparison there were no significant differences in symptom reduction. Despite the matching, the three groups differed significantly in some of the initial values of clinical impairment (quality of life and associated behavioral problems).

NIRS-neurofeedback was effective in the reduction of the main symptoms of ADHD and possibly more time-effective in comparison to EEG-neurofeedback. However, this interpretation has to be confirmed, due to the fact that differences in improvement after the 12 sessions did not reach significance, and that the initial values in quality of life and associated behavioral symptoms of the groups differed. Moreover, a completed intervention was compared with two uncompleted interventions, based on the assumption of a more rapid improvement with NIRS neurofeedback, and the sample sizes were small. For future studies, sample sizes have to be enlarged and a randomized controlled design is mandatory. NIRS-neurofeedback could enlarge the treatment options for ADHD, with the possible advantage of being a shorter intervention in comparison to EEG-neurofeedback. The analysis of NIRS-data throughout the training will hopefully allow conclusions as regards to the learning of self-regulation and number of sessions needed. Birbaumer et al. (2013) assume that faster learning of self-regulation of blood oxygenation in comparison to neuroelectricity is associated with the sensoric input processed for the vascular system allowing a faster development of an adequate response. Future studies should analyze the differences in the protocols and learning curves of NIRS- and EEG-neurofeedback to gain more insights into the underlying mechanisms of self-regulation. As regards to the different velocity of the feedback signals one might speculate that a slower signal facilitates learning. In the absence of any study investigating this issue it should be noted for future research.

As a limitation it has to be taken into account, that medication could have a distorting effect on the results: seven of nine children in each group received a medication with methylphenidate during the training. The effects of medication were not assessable in this study. It might be possible, that symptom reduction only occurs in less impaired children or because medication allows a better training. Larger sample sizes, subgroups with medicated and unmedicated children are necessary to control for effects of medication. As an example, results of the multicenter study (comparison of EEG- and EMG-feedback), show that effects of neurofeedback were independent of medication (Holtmann et al., 2014c) and the relationship between symptom severity and outcome is inverse.

Whether NIRS-neurofeedback can be implemented as a stand-alone or part of a multimodal treatment of ADHD will only be answered after studies with a corresponding design. A combination of different interventions according to individual forming of problems is another field of future research in the treatment of ADHD. A multi-center stepped care study dealing with severity-adapted combined interventions including SCP-neurofeedback will be conducted in Germany from February 2015 (ESCAlife: Evidence-based, Stepped Care of ADHS along the life-span)[1]. Results could give a hint on additional effects of neurofeedback and medication.

NIRS-neurofeedback is a promising intervention for children with ADHD and can enlarge the range of options for a treatment of ADHD. Future studies should focus on randomized controlled designs. Especially the comparison with EEG-neurofeedback, and with its final rather than its intermediate outcome, is necessary to further support the assumption that NIRS-neurofeedback needs fewer sessions for comparable symptom reduction. It would also be important to clarify whether longer NIRS-neurofeedback training (i.e., with more than 12 sessions) yields further clinical improvement. For further development of NIRS-neurofeedback the identification of other possible feedback regions based on the growing number of NIRS-studies with children with ADHD is required. The prefrontal cortex plays a central role in ADHD. However, involving a greater database and identifying target regions according to symptomatology could lead to an evidence-based adaption of feedback protocols for individualized treatment of ADHD.

[1]Project description: http://akip.uk-koeln.de/forschung-publikation/forschungsprojekte/fg_esca_06_2014_weg.pdf [14.09.2014]

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