Doctoral Thesis

Comparison of advanced tomographic neurofeedback with electromyographic biofeedback in attention-deficit/hyperactivity disorder

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COMPARISON OF ADVANCED TOMOGRAPHIC NEUROFEEDBACK WITH ELECTROMYOGRAPHIC BIOFEEDBACK IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A dissertation submitted to

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Presented by

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2013
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Summary

Attention-deficit/hyperactivity disorder (ADHD) is an early onset neurobehavioral disorder and one of the most frequently diagnosed psychiatric disorders in children. The cardinal symptoms are developmentally and persistent inappropriate levels of inattention, hyperactivity, and impulsivity, associated with distractibility, difficulties in sustained attention, restlessness, and impaired self-control. Other disorders (comorbidities), such as Developmental Coordination Disorder with impairment in fine motor ability, deficits in bimanual coordination and problems with force control, often concur with ADHD.

Multiple treatments are applied for the reduction of the core symptoms and for mitigation of associated problems. Pharmacological treatments are widely used and efficacious and are today regarded as the gold standard in the ADHD therapy. Nonetheless the Electroencephalographic (EEG) biofeedback, also called neurofeedback (NF), based on self-control of brain activity and cognitive states, is one of the non-pharmacological treatments enjoying increasing popularity as a complementary treatment. Two NF training protocols are typically used as treatment for children with ADHD: the regulation of theta/beta frequencies and the regulation of slow cortical potentials (SCP). The clinical effects of NF are still a matter of debate, as are also the demonstration and understanding of specific mechanisms of action of training protocols and their impact on the training outcomes.

Therefore the general goal of this thesis was to examine specific effects of a tomographic NF training through a comparison with a complex electromyographic biofeedback (EMG-BF) control condition permitting to control the various different unspecific treatment effects.

For this purpose an EMG-BF training was designed, which primarily matches the complex NF training protocols and serves for a satisfactory control of nonspecific effects. This training method feeds back activity from arm muscles involved in fine motor skills such as writing and grip force control. Tonic EMG-BF training involving bimanual motor tasks in activation and deactivation blocks matches the training of EEG frequency bands, while phasic EMG-BF training composed of short activation and deactivation trials was developed as an equivalent to the SCP training. The feasibility of this EMG-BF training method as well as the learning improvement of motor regulation in most task conditions and the clinically relevant reduction of behavioral ADHD symptoms were shown in a case study.

Afterwards in a group comparison evaluating the trainings as treatments for ADHD and investigating treatment specificity, thirteen children with ADHD trained their brain activity in the anterior cingulate cortex (ACC) whereas twelve ADHD children trained activity of their arm muscles. Despite medium effect sizes on primary outcomes favoring NF, both groups showed similar behavioral improvements. Specific effects were found only for the EMG-BF group in fine motor skills and bimanual coordination, whereas the NF group tended to present individual normalization of trained frequency bands in the ACC during rest throughout the training.

The results provide evidence that mostly unspecific effects common to both BF types appeared to underlie the behavioral improvement in this comparison between two active BF trainings for children with ADHD.
Zusammenfassung


Um anschliessend die zwei Trainingsarten als Formen der ADHS-Behandlung zu bewerten und um die Behandlungsspezifitäten zu untersuchen, trainierten dreizehn Kinder mit ADHS in einem Gruppenvergleich ihre Hirnaktivität in den Anterioren Cingulum (ACC), während zwölf Probanden die Aktivität der Armuskeln trainierten. Trotz mittlerer Effektgrössen für stärkere primäre Wirkungen in der NF Gruppe zeigten beide Gruppen ähnliche Verhaltensverbesserungen. Spezifische Effekte wurden nur bei der EMG-BF Gruppe in Form von verbesserter feinmotorischer Fertigkeiten und bimanualer Koordination festgestellt, während die NF Gruppe eine Tendenz aufwies,
Die trainierte Frequenzbänder im ACC während des Ruhe-EEG im Laufe des Training zu normalisieren.

Die Resultate dieser beiden aktiven Formen von Biofeedback Training für Kinder mit ADHS weisen darauf hin, dass vor allem unspezifische Effekte, die in beiden Biofeedback Arten vorkommen, die Verhaltensverbesserung bestimmen.
1. General Introduction

1.1. Attention-deficit/hyperactivity disorder

1.1.1. Disease pattern

Attention-deficit/hyperactivity disorder (ADHD) is an early onset neurobehavioral disorder and one of the most frequently diagnosed psychiatric disorders in children, with a worldwide prevalence of about 5% of school-aged children (Steinhausen 1994, Polanczyk 2007). The cardinal symptoms are developmental and persistent inappropriate levels of inattention, hyperactivity, and impulsivity, associated with distractibility, difficulties in sustained attention, restlessness, and impaired self-control. Other disorders (comorbidities), such as oppositional conduct defiant and internalising disorders or motor and reading disabilities, often concur with ADHD (Willcutt 1999, Christiansen et al 2008). One frequent comorbid disease in ADHD is Developmental Coordination Disorder (DCD). DCD co-occurs in one third (Fliers et al., 2008) up to half of children with ADHD (Gillberg, 1998; Wilson, 2005). For this reason impaired fine motor ability (Pitcher et al., 2003), deficits in bimanual coordination (Klimkeit et al., 2004) and problems with force control (Pereira et al., 2000; Pitcher et al., 2002; Steger et al., 2001) in ADHD have been reported by several studies.

In the context of neurobiological research on ADHD, neuroanatomical structural magnetic resonance imaging (MRI) studies indicate abnormalities in children’s brains with ADHD, for example difference in brain dimension (Castellanos et al., 2002). Significant reduced activity compared to controls in functional MRI studies related to executive function is reported in the frontal region, including anterior cingulate, dorsolateral prefrontal, and inferior prefrontal cortices as well as related regions (Dickstein et al., 2006). At the neurochemical level the dopaminergic system involved in the reward motivation and reinforcement learning, and noradrenergic systems involved in the arousal (entails alerting, phasic responding, and enhancing signal-to-noise ratio in attention), are assumed to present abnormalities (Nigg, 2005). Also based on this assumption, current ADHD drugs therapies aim to block the reuptake and/or promote the release of the involved neurotransmitter (Prince, 2008).

1.1.2. Clinical Assessment

The diagnostic criteria for the clinical examination of ADHD is based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, APA 2000), including predefined symptom categories, thresholds, criteria for persuasiveness, persistence of impairment and age onset. Three ADHD subtypes are distinguished according to DSM-IV criteria: predominantly inattentive, predominantly hyperactive-impulsive and a combined type. The ADHD diagnosis system is widely used for clinical and research purposes, but its validity and utility are criticized particularly regarding the subjectivity of informants and the influence by the clinician’s choice of instrumentations (interview, rating scales), informant (teacher or parent) as well as integration methods of information across informant and instrumentation (Valo et al., 2010).
For this reason objective measures such as biological markers for the purpose of diagnosis would be helpful add-ons. Neurophysiologic measures of brain functioning which are related to arousal, attention, and development could be promising ADHD markers.

**Brain Oscillatory Correlates**

In the resting state for ADHD research the frequency bands of most interest in electroencephalography (EEG) are theta, related to drowsiness or “cortical slowing”, and beta, related to mental activity and concentration. These frequency bands are reported separately or compared to each other (theta/beta ratio). However, the real functional significance of theta/beta ratio is unknown, through this calculation a single measure results including contributions of two relevant frequency bands in ADHD diagnosis and monitoring (Loo et al., 2012). An increased theta or theta/beta ratio compared to healthy individual throughout resting state is reported to be the most consistent marker of ADHD (Barry et al., 2003; Clarke et al., 1998; Koehler et al., 2009; Lansbergen, Arns, et al., 2011). General EEG slowing is reported to correspond to a maturational lag pattern in ADHD or to a cortical hypoarousal (Schneider et al., 1992). A decrease of beta activity, however, seems to be less pronounced in ADHD, particularly the reduction decline with increasing age (Bresnahan et al., 1999).

In the meta-analysis by Snyder et al. (2006) based on nine studies using increased theta and/or reduced beta for the discrimination of resting EEG of ADHD from controls, sizes of 1.31 for theta, -0.51 for beta power, and 3.08 for theta/beta ratio were identified. However, the meta-analyses by Magee et al. (2005), which reports only 40 % specificity to discriminate ADHD from healthy individuals, and other studies which revealed failures in replicating theta or theta/beta abnormalities (e.g. Liechti et al., 2013; Loo et al., 2009) relativize the reliability of EEG power analysis for diagnostic purposes.

**Event-Related Potential Correlates**

It is also common to assess neurophysiological dysfunctions in ADHD during task performance. The most robust markers of ADHD in EEG are reduced attentional, inhibitory, and preparatory event-related potential (ERP) components, such as the cue and NoGo P3, as well as the contingent negative variation (CNV) during preparation and activation (Johnstone et al., 2013). Basically the attenuated CNV seem to be a particularly stable ADHD marker, which continue into adulthood (Doehnert et al., 2010; Doehnert et al., 2013). However, according to the meta-analysis by Smith et al. (2003) a clinical application of ERP markers is not recommended for diagnosis considering the moderate discrimination of less than 80 % obtained.

1.1.3. Treatment

Multiple treatments are applied to the reduction of the core symptoms and for mitigation of associated problems. Pharmacological, behavioral therapies as well as educational, family and dietary interventions are identified. Pharmacological treatments are widely used and efficacious (Banaschewski et al., 2006) and are today regarded as the gold standard in the ADHD therapy. Medications used to treat ADHD include stimulants,
such as methylphenidate and amphetamine. But this treatment is also limited as only about 70% of the children with ADHD are responders (Barkley et al., 1991); side effects on appetite, sleep and growth are common (Graham et al., 2011) and long-term effectiveness is not established (van de Loo-Neus et al., 2011). A number of non-pharmacological treatments is available. The authors of a meta-analyse by Sonuga-Barke et al. (2013) investigate the efficacy of dietary and psychological treatments (including neurofeedback) concluding that although the clinical effects seem to be positive according to unblinded ratings, better evidence for efficacy from blinded studies is required. Multimodal treatment including medication is also a possible approach to an efficacious treatment of ADHD (Dopfner et al., 2004). Nevertheless, a good understanding of the mechanisms subordinate to the single treatment is important also for a better understanding of the positive interaction between them. EEG biofeedback, also called neurofeedback (NF), based on self-control of brain control and cognitive states, is one of the non-pharmacological treatments enjoying increasing popularity as a complementary treatment.

1.2. Biofeedback

Biofeedback (BF) aims to enable an individual to learn regulation or modification of physiological activity through instruments measuring physiological activity such as EEG, muscle activity, breathing, heart function, and skin temperature and immediate feedback of the measured information to the user. This process supports the change of the desired physiological activity often joint with changes in behavior, emotion or thinking, through operant conditioning. The goal is to improve health and performance of the trained person as much as possible without continued use of helping instruments. BF is reported as an effective treatment amongst others for headache, migraine, urinary incontinence, high blood pressure, and anxiety (Rief and Birbaumer 2010).

For the treatment of ADHD two types of BF are mainly reported, fewer the electromyographic BF (EMG-BF) aiming at motor control or relaxation and mostly reported is NF aiming at regulation of brain activity.

1.2.1. Electromyographic Biofeedback in Attention-deficit/hyperactivity disorder

In the eighties of the last century or earlier a large number of studies on EMG-BF training in ADHD have been carried out (see Lee (1991) for a review), with variable and often unsatisfying methodological standards as judged from a present point of view. These trainings most often aimed directly at muscle relaxation, sometimes in combination with visual imagery (e.g. Denkowski, Denkowski & Omizo (1983, 1984)), actometry (Hughes et al., 1980) or temperature feedback (Loux et al., 1980) in order to achieve a better control over hyperactive behavior through the improved ability to reduce movements, to relax muscle tension and to learn to calm down. Different kinds of relaxation training (e.g. Goldbeck et al., 2003) including yoga (Haffner et al., 2006; Jensen et al., 2004) have been used in ADHD therapy. Their usefulness has been proved, especially in combination with more comprehensive cognitive behavioral or multimodal treatments. A review of Arnold (2001) comparing alternative treatments for
patients with ADHD to medication expressed the need of further studies on EMG-BF training.
However, there is no study on EMG-BF training in ADHD so far that focuses directly on the improvement of fine motor skills rather than on general reduction of movements and relaxation.

1.2.2. Neurofeedback in Attention-deficit/hyperactivity disorder

The first studies which consider NF as possible treatment for ADHD were conducted by (Lubar et al., 1976; Shouse et al., 1979). As mentioned previously, EEG abnormalities of ADHD patients are reported and discussed in many studies. Assuming a direct relation of brain activity and behavior, the main attempt of NF is to correct or normalize these EEG abnormalities, resulting in an improvement of the regulation of attention, alertness, and behavior control in ADHD. Therefore two NF training protocols are typically used as treatment for children with ADHD. One protocol trains the regulation of theta/beta frequencies, whereas in the other protocol the regulation of slow cortical potentials (SCP) is practiced. In the theta/beta training children learn to increase the EEG activity of the theta frequency band (4-8 Hz) and to decrease the activity of the beta band (13-20 Hz) (Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Leins et al., 2007; Lubar et al., 1995; Thompson et al., 1998) based on the reporting results of increased theta activity and/or decreased alpha and beta activity in children with ADHD. In the SCP training slow DC-shift of the EEG activity is trained (Drechsler et al., 2007; Heinrich et al., 2004; Strehl, Leins, et al., 2006) based on the reported decrement of an SCP, the CNV.

The training of the self-regulation of neurophysiological parameters through NF using scalp EEG from a single channel (classical NF) is the most widespread approach, but an alternative approach targets at intracerebral activity in the specific brain regions affected by ADHD using on-line tomography EEG computed by multichannel scalp, which has been investigated by Liechti et al. (2012).

The clinical effects of NF are still a matter of debate. Based on their results of a meta-analysis Arns et al. (2009) recommend NF as an “efficacious and specific” ADHD treatment compared with a control group; whereas NF is considered only as “probably efficacious” in a review by Lofthouse, Arnold, Hersch, et al. (2012). In a recent meta-analysis (Sonuga-Barke et al., 2013) only a trend for probably blinded ratings of most teacher ratings were reported.

In addition, NF research aims to demonstrate and understand the specific mechanisms of action of training protocols and their impact on the training outcomes, and tries to clarify the nature of unspecific mechanisms. For this purpose two main approaches are applied to investigate specificity; the first examines the relation of the individual learning of neurophysiological regulation to the training outcome as proposed by Liechti et al. (2012). In this study the brain activity in the anterior cingulate cortex (ACC) was trained using theta-beta frequency and SCP protocols. The results indicate that clinical improvement was related mainly to unspecific effect or secondary NF effects. However, individual normalization of resting EEG activity and partial SCP control in the trained brain region indicate region specific effects.
The second approach is comparing NF effects to those of a control group. A waiting list control group is the simplest control condition to investigate whether a treatment is effective in contrast to the absence of treatment because it controls, which is particularly important for studies involving children and adolescents, for maturation and for the developmental course of the disorder. Due to this control condition a blinding of the children’s group assignment and of their parents is very difficult, unspecific treatment effects caused by the different exposure to a therapeutic environment such as motivation and expectation are hard to control (Loo et al., 2012). A placebo control group, during which the participant follows the same treatment protocol but receives a sham feedback, constitute the strictest test for a NF training group. In this case, differences in clinical outcome between regular and sham NF trainings, which are equivalent in all other setting aspects, can be attributed to the specific effects of learned regulation of brain activities. So far, sham-controlled NF studies (e.g. Lansbergen, van Dongen-Boomsma, et al., 2011; Logemann et al., 2010) were unable to show that NF group outperforms the sham group in terms of improvement of clinical ADHD symptoms, but the quality of NF may have been compromised and learning was not demonstrated. In addition, implementing a sham condition in clinical research with ADHD children is critical from an ethical point of view when standard treatment such as medication is available (La Vaque et al., 2001), and blinded ratings (Sonuga-Barke et al., 2013) plus evaluation scales (Gevensleben, Holl, Albrecht, Vogel, et al., 2009) may offer reasonable control for unspecific expectancies.

A comparison to another active group might be an alternative, such as a computerized attention training (Gevensleben, Holl, Albrecht, Vogel, et al., 2009), a cognitive-behavioral based group therapy (Drechsler et al., 2007) or an EMG-BF training (Bakhshayesh et al., 2011). They permit to control the different amount of unspecific treatment effects such as in a waiting list control group because these participants experience an active treatment. Despite some promising results of the reported studies with an active control condition, such as the significant improvement of parent-rated inattention compared to the control groups, none of these control conditions have received empirical support as a treatment for ADHD (Loo et al., 2012). For this reason a BF control condition with a possible therapeutic benefit could be a reasonable option. Moreover a real feedback of a BF treatment has additional possibility to control other unspecific effects. Using the same software and training procedure is possible to equalize type, timing and amount of feedback as well as the amount of training time spent with the therapist. Characteristic unspecific BF effects such as improved feeling of self-efficacy, improved self-awareness, and learning of behavioral contingencies should also be controlled. Similar training settings reduce effects of expectations generated by applying electrodes and being connected to a computer. Only one study (Bakhshayesh et al., 2011) with an EMG-BF as control condition is known to have applied a simple and unidirectional regulation dimension, which does not control sufficiently complex NF protocols with usually more regulatory dimensions and directions.
1.3. Aim of the Thesis

As reviewed in the last section, a reasonable control condition allowing the detection of NF specificity and the effects of learned cortical control on behavior is needed. As a result a BF training condition aiming to control the characteristic unspecific NF/BF-effects such as self-regulation, continuous learning to regulate a neurophysiological signal, improved feeling of self-efficacy, improved self-awareness, structured learning environment, and learning of behavioral contingencies seem to be meaningful. Especially when this control condition could induce positive effects on symptoms associated with a frequent and characteristic comorbid condition of ADHD.

The general goal of this thesis was to prove specific effects of a tomographic NF training on children with ADHD by a comparison with a complex EMG-BF control condition (study 2). For this purpose the EMG-BF training was designed primarily to match the complex NF training protocols, for a good control of unspecific effects. The validity and feasibility of this training method was proved on a child with ADHD (study 1).

The aim of study 1 was to develop an EMG-BF training protocol which matches a complex NF training described by Liechti et al. (2012) as closely as possible and which presents a comparable degree of difficulty. The hypotheses were that it should be feasible to carry out a control program with an ADHD child and thus to match a complex NF training program in structure and complexity. In addition, a continued improvement in the course of the training of motor control through EMG-BF and a decrease of ADHD cardinal symptoms severity after the training due to unspecific BF training effects which also contribute to NF were expected.

In study 2 we compared NF and EMG-BF in two groups of children with ADHD aiming to investigate specific differences between the two BF training on regulation performance and resting EEG changes in the course of the training and behavioral and neuropsychological changes between pre- and post-assessments. The hypotheses were that ADHD behavioral symptoms would be mitigated in both groups, although we expected larger effects for the NF group. Following the results of Liechti et al. (2012) providing more evidence for regional normalization at rest than for learning of regulation, the individual normalization of resting EEG activity in the ACC was expected to be specific to the tomographic NF treatment. Due to the complex EMG-BF training comprising different bimanual EMG protocols a stronger improvement on neuropsychological tasks related to fine motor skills and bimanual coordination was expected specifically for the EMG-BF group.
1.4. Electroencephalography

EEG was first described in the year 1929 by Hans Berger for the recording of brain activity under changing mental conditions in humans, such as rest, cognitive tasks, and sleep. EEG is a non-invasive neurophysiological technique with electrodes as sensors on the scalp measuring electrical activity. The EEG potentials are induced by a mass action of neighboring neurons with the same polarity aligned and propagated passively through the brain tissues and skull. This technique is mainly used clinically for the detection of dysfunctions or even for diagnosis of disorders in the central nervous system or for the research for the examination of normal brain function during the development or performance of different experimental tasks. In comparison to other neuroimaging techniques the EEG offers a high temporal resolution providing information in the millisecond range of spontaneous and event-related synchronous activity of neuronal networks. The potential differences between two electrodes over time of spontaneous oscillatory activity are in the range of 10-200 µV whereas the potential differences of event-related activity are in the range of 0.1-20 µV. Various oscillations of different amplitudes and frequencies compose the EEG waveforms. Using a multichannel recording from electrodes distributed uniformly over the scalp, quantitative analyses of EEG related to temporal, amplitude and spatial information are possible that allow a topographical visualization of EEG recordings (maps). Extracranial artifacts of technical or physiological nature, such as movement of eyes or body and muscle activity, have to be controlled and possibly corrected to allow a clear measurement of brain activity.

1.4.1. Spectral Content of Electroencephalographic Oscillations

One approach of EEG signal analyses is the quantification of EEG oscillations through a fast Fourier transformation (FFT), which is typically used for resting EEG analysis. The time domain of EEG epochs (usually of 1-5 seconds length) are decomposed into frequency domain with waves with different frequencies and amplitude, and finally averaged. The reproducibility within subjects of these analyses form is high, less across subjects, and it is employable for the characterization of the subject’s age (Ahn et al., 1980) or state of arousal (Borbely et al., 1999) as well as for the examination of systematic deviations from spectral power norm through the presence of psychiatric or neurological disorders (John et al., 1988). Distinct frequency bands, consisting of pooled value of the frequency band, are used for characterization of certain cognitive tasks (Michel et al., 2009). Slow and high amplitudes between 0.5 to 3.5 Hz characterize the Delta activity which is typical of slow wave sleep. A frequency band from 4 to 7 Hz is associated with focused attention and characterizes theta activity. Oscillations between 8 to 12 Hz characterize the alpha rhythm, typical during wakefulness and evoked by eye closure. Waves between 13 and 30 Hz characterize the beta activity, which are claimed to be typical during focused and active concentration during attention-demanding tasks or during active wakefulness. Most frequency bands show maturational changes throughout the development of children (Gasser et al., 1988).
1.4.2. Event-Related Potentials

A different approach of EEG signal analyses is to analyze the EEG potential changes that are time-locked to a defined event, called ERP. For the extraction of the small ERPs from the raw EEG a repetition of a defined event or the analysis of single trials by means of EEG/ERP analysis methods are used (Michel et al., 2009). Assuming stationarity of the stimulus response, the calculation of average of epochs containing the recurring event is the mostly used method for off-line analysis. In this way it is possible to maintain the activity which is temporally correlated to the event, while eliminating the activity which is not temporally correlated to the event. Time- and phase-locked to a stimulus presentation or motor response the resulting ERP curves consist of different components. ERP are composed of earlier and later components (>250ms): the first ones are dominated by the physical properties of the stimulus, however, the later components by the cognitive processes. The event, likewise the mental state and medical condition of the subjects, influence the amplitude, polarity, latency and scalp-topography of the ERPs.

1.4.3. Source Localization

For the localization of the activity’s source inside the brain extracted by the EEG information recorded on the scalp, the inverse problem has to be solved. The inverse problem is characterized by multiple possible source configurations in the brain for the generation of the same electrical potential on the scalp. An additional assumption of the number and/or the distribution of possible sources has to be taken for a unique source solution. The two main approaches to solve the inverse problem are the assumption of the number of point sources by the dipole modeling and the assumption of synchronous activity of neighboring neurons by the distributed source modeling. When it comes to the dipole strategy unknown numbers of sources or extensive distribution of sources appear to be problematic. Standardized Low-Resolution Electromagnetic Tomography (sLORETA) is a localization method based on the distributed source modelling. sLORETA calculates the three-dimensional current density of each 6239 voxel of the reference brain at every instant using realistic electrode coordinates. The smoothest of all possible three-dimensional current distributions is then calculated (Pascual-Marqui et al., 1999; Pascual-Marqui et al., 1994). The resulting tomography has a quite low spatial resolution caused by the constraint of smoothness, however, this approach is quite meaningful regarding the fact that EEG measurements only detect neuronal mass activity of extended regions.
1.5. Electromyography

Just as the EEG, electromyography (EMG) is a non-invasive neurophysiological technique with electrodes as sensor on the skin, but measuring electrical muscle rather than brain activity. These potentials are induced by a superposition of action potentials of motor units depending on their firing frequency and recruitment. A motor unit is defined as the smallest neural functional control unit of the muscular contraction process, composed by the cell body, dendrites and multiple axon branches of a motor neuron, and the muscle fibers that the motor neuron innervates. The range of the typically bipolar electrode measurement of a raw EMG can reach values between +/- 1000 microvolts, for athletes up to +/- 5000 microvolts with typically frequency contents ranges between 6 and 500 Hz, although most EMG activity is in the frequency range between ~ 20 and 150 Hz. The EMG signals are influenced by several external factors like tissue characteristics, physiological cross talk of neighboring muscles, geometry change between muscle belly and electrode size or external noise. This technique is used clinically for example for physiotherapy, rehabilitation, sports training and interactions of the human body with industrial products as well as for applied research purposes (Konrad, 2005).
2. Study / Publication Nr. 1: Differential EMG Biofeedback for Children with ADHD: A Control Method for Neurofeedback Training with a Case Illustration

Published in April 2013 in *Applied Psychophysiology and Biofeedback*. Authors: Stefano Maurizio, Martina Daniela Liechti, Daniel Brandeis, Lutz Jäncke, and Renate Drechsler

2.1. Abstract

The objective of the present paper was to develop a differential EMG-biofeedback training for children with Attention Deficit Hyperactivity Disorder (ADHD) matching multiple neurofeedback training protocols in order to serve as a valid control training. This differential EMG-biofeedback training method feeds back activity from arm muscles involved in fine motor skills such as writing and grip force control. Tonic EMG-biofeedback training (activation and deactivation blocks, involving bimanual motor tasks) matches the training of EEG frequency bands, while phasic EMG-biofeedback training (short activation and deactivation trials) was developed as an equivalent to the training of slow cortical potentials. A case description of a child who learned to improve motor regulation in most task conditions and showed a clinically relevant reduction of behavioral ADHD symptoms, illustrates the training course and outcome. Differential EMG-biofeedback training is feasible and provides well-matched control conditions for neurofeedback training in ADHD research. Future studies should investigate its value as a specific intervention for children diagnosed with ADHD and comorbid sensorimotor problems.

2.2. Introduction

Researchers have utilized different types of biofeedback (BF) for active treatment, or for control purposes in controlled Attention Deficit Hyperactivity Disorder (ADHD) intervention studies. ADHD is one of the most frequent disorders in child psychiatry, defined by the co-occurrence of symptoms of hyperactivity, impulsivity and inattention (American Psychiatric Association [APA] 1994). Many studies have shown that neurofeedback (NF) training based on self-regulation of neural EEG (electroencephalogram) activity is an effective treatment for children with ADHD in comparison to other interventions and control conditions (see meta-analysis by Arns et al., 2009; for reviews see e.g. Drechsler, 2011; Fox et al., 2005; Heinrich et al., 2007). The two common NF training protocols require tonic regulation of frequency bands, typically over minutes, or phasic regulation of slow cortical potentials (SCPs), typically over seconds. Sophisticated recent NF training studies (Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Liechti et al., 2012; Wangler et al., 2011) combine both these protocols, and often train regulation in both directions (i.e. increase of slow cortical negativity and positivity). Although the beneficial effects on clinical ADHD symptoms are

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1 Stefano Maurizio helped developing this EMG-BF methods, with the different training conditions which should be possible easy practicable, a good parallelization of the NF training and therapeutically meaningful. He helped to train the child and analyse the data. The manuscript was written by Stefano Maurizio and revised by the co-authors.
beyond doubt, the mechanisms leading to these improvements remain unclear. Several authors (Bakhshayesh et al., 2011; Drechsler, 2011; Lansbergen, van Dongen-Boomsma, et al., 2011; Loo et al., 2005; Monastra et al., 2002) have argued that NF training involves considerable unspecific effects and constitutes a sophisticated form of cognitive-behavioral training, whereby children learn to focus on attentional processes, improve feelings of self-efficacy, and are rewarded for sitting still. In addition, EEG frequency or polarity changes, which appear due to active cortical regulation, may instead be induced by respiration, eye movements or other muscle contraction. The specific contribution of cortical regulation to the physiological and clinical effects of NF must therefore be established using proper controls. “Sham” or “mock” NF utilizes the same setting and interface to feed-back unspecific or non-contingent signals which allows for (double-) blind placebo controlled designs, and probably presents the most powerful control condition in order to investigate the specificity of NF training effects. As “regular” and “sham” NF trainings are equivalent in all other aspects of setting, differences in clinical outcomes can be attributed to the specific effects of learned cortical regulation. Besides serious methodological difficulties associated with this approach (e.g. see Lansbergen, van Dongen-Boomsma, et al., 2011), researchers may be reluctant to provide sham feedback to children with ADHD over several months for study purposes due to ethical reasons. Another BF method with “correct” feedback signals may therefore represent the second best choice. From a theoretical and practical perspective, electromyographic biofeedback (EMG-BF) aiming at motor control rather than the regulation of cortical activity seems to be a suitable control method for investigating the specificity of NF and the effects of learned cortical control on behavior. The same training software programs may be used in very similar therapeutic settings. Type, timing and amount of feedback can be closely matched, and the same amount of training time is spent with the therapist. Characteristic unspecific BF-effects such as improved feeling of self-efficacy, improved self-awareness, and learning of behavioral contingencies should potentially result from both types of training.

To date, only one NF training study has used EMG-BF as a control condition with ADHD patients, using a simple tonic and unidirectional NF protocol. Bakhshayesh et al. (2011) compared NF training of the theta-beta frequency bands ratio with EMG-BF training of the frontal muscles. In their EMG-BF control condition, children were rewarded when muscle activity fell below baseline. Parents reported a significantly stronger reduction of inattention following NF than EMG-BF, although overall ADHD symptoms improved after both training types. However, there are several limitations of this simple type of EMG-BF. First, this unidirectional tonic EMG-BF can not control for the more complex NF protocols with bidirectional tonic and phasic regulation. Second, a simple BF of muscle relaxation may be easier and induce more rapid learning than complex NF training protocols in which learned activation and deactivation is contrasted, and different methods like SCP and frequency band training are combined (e.g. Gevensleben, Holl, Albrecht, Vogel, et al., 2009).

Our aim was therefore to develop an EMG-BF training protocol to match a complex NF training as in Liechti et al. (2012) (similar to those used by Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Wangler et al., 2011) as closely as possible.
2.3. Method Development

2.3.1. Reference NF training method

The reference NF contain protocols of the training of frequency bands and of SCPs (Table 2.1). In the “tonic” training protocol with training of theta-beta frequency bands, a decreased theta-beta ratio (activated state) or an increased theta-beta ratio (deactivated state) has to be maintained over several minutes. The time during which the trainee successfully maintains his cortical activation within the desired range is rewarded, indicated as continuous count.

In the SCP or “phasic” training protocol, shifts of central electrical brain potential on the scalp in the negative (=activation) or positive (=deactivation) direction are fed back to the participants during trials lasting for approximately 10s. Typically, each SCP trial consists of a short baseline phase, after which feedback regarding the direction of change is given. This is then followed by a change and feedback phase of a few seconds, during which the potential shift is supposed to occur. The activation is usually continuously fed back and a successful shift, i.e. when the child activates or deactivates above threshold, is rewarded by a bonus point.

The NF training software “SAM” used in this study was developed for children with ADHD by Heinrich (Gevensleben, Holl, Albrecht, Vogel, et al., 2009) and is constructed as a computer adventure game.

2.3.2. EMG-BF training procedures

For EMG muscle activity detection, two electrodes were placed on both arms on the muscle extensor digitorum, which is especially important for writing and pen grip (Figure 2.1). To allow concomitant EEG recording during the EMG-BF training and ensure artifact control, it was necessary to focus on isometric muscle contraction and on small scale movements such as regular circular pen movements. The EMG-BF training exercises thus aimed at improved force control, bimanual coordination, and smooth, automated writing or drawing movements. For this purpose, the following auxiliary material was used: a hand dynamometer (Bremshey BRSFU238 Accell Fitness, Almere, Netherlands), a writing tablet (Ituos 4 Wacom Co., Saitama, Japan), soft balls and hard rubber balls.

Tonic EMG-BF training. NF frequency training requires the simultaneous regulation of beta and theta band activity into opposite directions using separate feedback bars for each band. This “dual task” was translated into a bimanual motor task with different concurrent demands for the left and the right hand. Bars on the left and right side of the screen for the feedback of theta and beta activity were used here to indicate arm muscle activity of the left and right hand. To parallel the deactivation and activation trials of the NF frequency training, a tonic motor deactivation and a tonic motor activation task were created. The child was instructed to increase or decrease the height of the bars on the left and right side of the screen by controlling arm motor activity of both hands. In the tonic motor activation task (Figure 2.1b, Table 2.1), muscle activity in one arm had to be kept above a certain threshold while pulling a hand dynamometer. An upper limit was set at six times the baseline activity in order to avoid overexertion. At the same time, contralateral arm muscle activity had to be kept below baseline activity.
Table 2.1 Matched training procedures of EMG-BF and NF

<table>
<thead>
<tr>
<th></th>
<th>Tonic condition</th>
<th>Phasic condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deactivation</strong></td>
<td><strong>Activation</strong></td>
<td><strong>Deactivation</strong></td>
</tr>
<tr>
<td><strong>EMG biofeedback</strong></td>
<td>1. Dominant hand: Decrease of arm muscle tonus below threshold while performing circular drawing movement</td>
<td>1. One hand: Increase of arm muscle activity by pulling the hand-dynamometer (upper limit= 6 x baseline activity)</td>
</tr>
<tr>
<td></td>
<td>2. Other hand: Reduction of arm muscle tonus below threshold while balancing arm on soft ball</td>
<td>2. Other hand: Reduction of arm muscle activity while balancing arm on soft ball</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 blocks of 3 min</td>
<td>2x2 blocks of 3 min</td>
</tr>
<tr>
<td><strong>Neurofeedback analogue</strong></td>
<td>Training of frequency bands 1. Increase of theta activity 2. Decrease of beta activity</td>
<td>Training of frequency bands 1. Decrease of theta activity 2. Increase of beta activity</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 blocks of 4 min</td>
<td>2 blocks of 8 min</td>
</tr>
</tbody>
</table>
To this end, a starting position with some measurable tonus was required. This minimal
tonus was achieved by positioning the arm on two soft balls, while another ball had to
be held in the hand without exerting pressure. The participant was instructed to maintain
arm muscle activity for 3 min, by lightly pulling the dynamometer while relaxing the
muscles of the other arm. A baseline recording of 1 min with the same instructions
preceded the task. Compared to its NF analogue, the duration of the blocks was halved
and the number of blocks was doubled in order to avoid overexertion.

In the tonic deactivation task (Figure 2.1c, Table 2.1), a circular drawing movement was
performed by the writing hand for 3 min while ipsilateral arm muscle activity had to be
maintained below threshold. Movements were performed in a drawing template fixed on
a writing tablet. Thus, no visual control was needed. Movement velocity and precision
were recorded. The writing arm was positioned in a sling fixed on the ceiling in order to
reduce interference with irrelevant muscle activity.

**Figure 2.1** Training set-ups, devices and tasks of phasic and tonic EMG-BF training. In the phasic training (a) and tonic activation condition (b),
both arms were trained alternately. In the tonic deactivation condition (c),
only the dominant hand’s muscles had to be deactivated while performing
pen movements. Regarding the feedback signal, tasks are given by
arrows below the corresponding figures (↑ to increase and ↓ decrease
muscle activity).
The contralateral arm was balanced on two balls, while another ball had to be held in the hand. Muscle activity of the contralateral arm also had to be maintained below threshold. Time units with muscle activity of both arms below threshold were rewarded by bonus points. The participant was instructed to draw circles by performing slow, steady pen movements without pressure while keeping muscle activity low. At the same time, the other arm and hand also had to relax. A baseline recording of 1 min with the same instructions preceded the task.

Phasic EMG-BF training (Figure 2.1a, Table 2.1). A phasic motor deactivation and a phasic motor activation task were developed in order to match the SCP training. They consisted of short trials in which the child was instructed to find a strategy to move a ball, which provides continuous feedback, upwards on the screen. Each trial began with a 2s baseline phase, followed by a 4s feedback phase. The intertrial interval lasted for 4s (+/-1s). In both task conditions, a dynamometer was pulled by one hand while the other hand rested on the table. In the phasic deactivation task, arm motor activity of the hand pulling the dynamometer had to be decreased, whereas in the phasic activation task, it had to be increased, without exceeding an upper limit. In the phasic motor activation task, the child was instructed to briefly increase muscle activity, but not too much, while keeping the other hand relaxed. In the phasic motor deactivation task, the child was told to progressively relax the grip on the dynamometer, while keeping the other hand relaxed. After a learning phase, activation and deactivation trials were randomized within one training block. To avoid overexertion of the muscle, blocks with dynamometer trials for the left hand and the right hand were alternated.

2.4. First evaluation of the method – a case description of a child with ADHD trained by differential EMG-BF training

2.4.1. Feasibility of the method

In order to illustrate the feasibility, course and outcome of our EMG-BF training we present a case report of a 9 year 7 month old boy with ADHD, A.D., who completed this training program. A.D. received EMG-BF training in the context of a clinical study which compared effects of NF training to those of EMG-BF training in children with ADHD. Both training methods were introduced to the children and their parents as experimental BF treatments for ADHD, focusing either on motor or on brain wave activity. The participants agreed to be randomly assigned to one of the two training methods. The presented case was the first child of the EMG-BF training group with complete data and within the originally projected age range of the study and therefore was not selected according to training outcome. The diagnosis was confirmed by the PACS Interview (Parental Account of Children's Symptoms, Taylor et al., 1986) and the CTRS (Conners' Teacher Rating Scale, Conners et al., 1998b) according to a validated algorithm (see Valko et al., 2010). The child also fulfilled additional study selection criteria, such as IQ > 80, no severe ODD or other severe comorbidity, and no known neurological diseases. He was medication-naive. Parents gave written informed consent and the child assented to take part. The study was approved by the local ethics committee.

A large number of studies on EMG-BF training in ADHD were carried out in the 1980s or earlier most frequently aimed directly at muscle relaxation in order to achieve a better
control over hyperactive behavior through the improved ability to reduce movements, to relax muscle tension and to learn to calm down (for reviews, see Arnold, 2001; Cobb et al., 1981; Lee, 1991), but with varying and often unsatisfactory methodological standards from a present-day perspective. However, these early studies did neither focus on differential EMG control nor on comorbid motor coordination problems which frequently co-occur in children with ADHD (Fliers et al., 2008; Wilson, 2005). For a first evaluation of the EMG-BF training, we hypothesized that it should be feasible to carry out this control program with an ADHD child and thus to match a complex NF training program in structure and complexity. We expected motor control to improve continuously through EMG-BF in the course of the training and ADHD cardinal symptoms severity to decrease after the training, due to unspecific BF training effects which also contribute to NF. Further, we expected a more pronounced reduction of hyperactivity/impulsivity than of inattentiveness symptoms and improvements on tasks related to fine motor skills and bimanual coordination, as the training is directly aimed at motor control.

2.4.2. Assessment instruments

Pre- and post-training assessment included behavioral ratings by parents such as the FBB-HKS (Döpfner M., 2000), a German ADHD checklist based on DSM-IV serving as the primary clinical outcome in several NF studies (Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Liechti et al., 2012); the Conners’ Parents Rating Scale (CPRS), with a reliability of 0.67 for DSM Inattention and 0.81 for DSM Hyperactivity/Impulsivity (Conners et al., 1998a); the CTRS, with a reliability of 0.70 for DSM-Inattention and 0.47 for DSM-Hyperactivity/Impulsivity and the following neuropsychological tests:

Tests without a primary motor component. “Sustained attention”, a subtest of the computerized Test for Attentional Performance for Children (KITAP, Zimmermann et al., 2002), is a visual continuous performance test of 10 minutes duration, with a reliability of 0.90 for Errors and 0.88 for Omissions. The D2 Test of Attention is a paper-and-pencil cancellation task (Brickenkamp, 2002). The outcome measure reported here is the total number of items minus number of errors score (TN-E), with a reliability of 0.84.

Tests with a motor component. The visuomotor precision task is a subtest from the NEPSY (Korkman et al., 1998), designed to assess graphomotor skills. Children have to draw a line through two curved tracks while attempting to remain inside the track lines. The score reflects errors as well as time spent on task, with a reliability of 0.74.

In “Flexibility” (KITAP, Zimmermann et al., 2002), the participant has to alternate between two target stimuli. The two stimuli appear simultaneously on the screen, one on the right-hand side and one on the left. The child responds using two buttons, one for the left and the other for the right hand. In the first trial, the child is asked to press the button on the side where the first target is located, in the second trial where the second target is located, and so on. In approximately half of the trials, the target stimuli change the side. In this case, alternation of targets is not associated with the alternation of hands, and cognitive shifts and hand movements need to be coordinated under effortful control. The reliability of the median of response time is 0.55 and of the error 0.85. All measures are clinically validated tests and have been used previously in studies on ADHD (e.g. Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Maziade et al., 2009).

Subjective well-being during motor tasks. At the end of each lesson, the child was asked to rate how he had felt during the training tasks, separately for deactivation and
activation conditions, on a computerized visual analogue scale (18 cm) with the words “bad” and “good” as well as pictures as visual anchors at the ends of the scales.

2.4.3. Training protocol

The training consisted of 18 sessions held over a period of approximately 12 weeks. It began with an intensive phase of two to three sessions per week, and then continued with one to two training sessions weekly. Each session comprised two lessons. Additional sessions for pre- and post-training assessments were held before and after the training program. The duration of one session was approximately 3 hours, due to the complex experimental setting with concomitant 32-channel EEG recording. The two EMG-BF training lessons accounted for approximately 90 minutes, including a break. In the first two sessions, the four training conditions were introduced consecutively. At the beginning of the first three sessions, the child also performed a progressive muscle relaxation according to Jacobson (Speck, 2005). From the second session on, one of the two lessons was scheduled for phasic, and the other for tonic EMG-BF. The order alternated from one session to the next. Within each EMG-BF lesson, both hands (more specifically: arm muscle activity for hand grip) were trained in alternating order from one session to the next. In the tonic training, activation was trained with both hands consecutively, by alternating the order from one session to the next. Deactivation with drawing template was trained only with the dominant hand. In parallel to the NF protocol, transfer trials were introduced after some basic training, i.e. in the 6th session for phasic and in the 9th session for tonic training. In the transfer trials, participants received delayed or no feedback while EMG and EEG were being recorded.

2.4.4. Signal recording and processing

To parallel the NF protocol (Liechti et al., 2012), electrophysiological signals comprising 24 EEG-channels, were also recorded during the training using 32 active electrodes (AE1, Easy Cap, FMS, Munich), EEG recording reference Fz retrieved by average reference computation, ground at FC6, two EOG (electrooculogram) and one ECG (electrocardiogram) channels. For the EMG-BF training, six electrodes were used for the bipolar recording of EMG signals placed on the musculus digitorus of both arms and the musculus trapezius of the right shoulder according to the locations and orientations recommended by SENIAM (Hermens et al., 1999) (instead of being used for EEG - Afz, CPz, POz, Iz, FC1, FC2- in the NF protocol). All data were recorded at a rate of 500 Hz using a BrainAmp amplifier (Brain Products, Gilching, Germany) with a bandpass filter set at 0.016-250 Hz. In both protocols, a forward filter (Butterworth 2nd order) was used for signal processing, set at 0.1-30 Hz for EEG/ECG and 0.1-100 Hz for EMG signals, which were additionally filtered (55-95 Hz) using Butterworth bandpass filters (48 DB / octave). For the feedback of the phasic training, the bipolar EMG signal was finally rectified. An online eye-artifact correction excluded artifactual ICA components calculated from a resting EEG at the beginning of each training session. Artifacts and muscle tonus above defined thresholds were fed back to the children as a sad face. After initial individual adaptation, artifact thresholds were typically kept constant through the course of training. For offline analysis, the same procedures were used, with the exception of zero phase filters, which were used to avoid unnecessary distortions potentially caused by forward filters.
2.4.5. Analyses of motor learning across training sessions

For the analysis of improved motor regulation, the following indices were calculated for all animations with contingent feedback from sessions 2 to 18 (Table 2.2, Figure 2.2). 

**Tonic EMG-BF:** For the tonic EMG-BF, the relative time spent in the desired state of regulation was calculated for each lesson, separately for the activation and deactivation conditions (time score activation, time score deactivation). These two time scores were defined as the percentage of the training time spent within the desired activation range relative to the total training time free of artifacts. As the threshold for successful regulation was set at each training lesson according to baseline, improved regulation could be expressed by increased time scores as well as by changes in absolute baseline. Therefore, the absolute baseline muscle activity was also included in the analysis. Baseline measures were analyzed separately for the resting arm positioned on soft balls (baseline resting arm) and the arm performing the motor activity (baseline motor arm). In the tonic deactivation condition, in which decrease of muscle activity should be achieved while performing a circular pen movement on a tablet, speed (revolutions per second [r/s]) and imprecision (degree of coverage) of movement were both recorded and analyzed with a custom-written program in LabVIEW (National Instruments, Austin, TX, U.S.A.) and in MATLAB (Math-Works, Inc., Natick, MA. Version 2008b), respectively.

**Table 2.2** Slope of EMG-BF training parameters by lesson number, indicating changes during the course of the training

<table>
<thead>
<tr>
<th>Tonic condition</th>
<th>[measure]</th>
<th>slope by lesson number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time score</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation</td>
<td>0.800</td>
</tr>
<tr>
<td></td>
<td>Deactivation</td>
<td>1.240 *</td>
</tr>
<tr>
<td>Baseline resting arm</td>
<td>µV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Deactivation</td>
<td>0.174 °</td>
</tr>
<tr>
<td>Baseline motor arm</td>
<td>µV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation</td>
<td>-0.335 **</td>
</tr>
<tr>
<td></td>
<td>Deactivation</td>
<td>-0.023</td>
</tr>
<tr>
<td>Tablet (deactivation only)</td>
<td>Speed [r/s]</td>
<td>-0.002</td>
</tr>
<tr>
<td></td>
<td>Imprecision [doc]</td>
<td>-3.519 *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phasic condition</th>
<th>[measure]</th>
<th>slope by lesson number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time score</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>Deactivation</td>
<td>1.725 ***</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.965 ***</td>
</tr>
<tr>
<td>Muscle activity change from baseline [µV]</td>
<td>Activation</td>
<td>-0.124</td>
</tr>
<tr>
<td></td>
<td>Deactivation</td>
<td>-0.565 *</td>
</tr>
<tr>
<td>Differentiation (activation – deactivation) [µV]</td>
<td>Total</td>
<td>0.441 *</td>
</tr>
</tbody>
</table>

[r/s]=revolutions per second, [doc]=degree of coverage  *0.1 > p > .05, * p<.05, ** p<.01, *** p<.001
Phasic EMG-BF. In analogy to the SCP training, the mean muscle activity changes were calculated for activation and deactivation trials separately. Likewise, in parallel to the SCP training “differentiation”, the mean difference between the muscle activity during activation and deactivation trials was calculated for each phasic training lesson (differentiation). The percentage of time spent in the desired range of regulation was calculated for activation and deactivation separately (time score activation; time score deactivation). In the phasic training protocol, activation and deactivation trials were presented at random and trained within the same block. As activation and deactivation both depend on baseline activity, a total time score, the percentage of total time spent within the desired state of muscle activity was also calculated (Table 2.2). In addition, the mean EMG trajectories were calculated for phasic deactivation and activation trials of each block across all training blocks and lessons for the right and left arm separately (Figure 2.3).

Changes over time
To show training effects on muscle regulation over time, linear regressions of EMG-BF scores over lessons were calculated with slopes representing changes over the course of the training (Figure 2.2). All the reported single-case statistics only test for linear changes over time, and do not allow for generalization across subjects. P values are estimated based on the assumption of heteroskedasticity and independence of error terms. Therefore, we also report R² values as effect size estimators. Time score analyses provided the main outcome measure for the learning of muscular regulation. As the other training parameters served as exploratory measures, we did not correct for multiple comparisons.

Pre-post-training changes on behavioral ratings and neuropsychological tests were analyzed descriptively. Pre-post differences are expressed in standard deviations of the corresponding scale. The interpretation of results is based on the clinical relevance of pre-post differences. In many neuropsychological tests T-scores below 40 (percentiles (PR) < 16) and for scaled scores values below two standard deviations under the mean indicate impaired performance (Strauss et al., 2006). In most clinical scales, T-scores above 64 (PR ≥ 95) indicate clinical impairment, T-scores between 64 and 60 (≈ PR 85 - 94) subclinical impairment, and T-scores below 60 (≈PR<85) no impairment. While this matches the common clinical interpretations of the well validated scales, we caution again that our single case results do not allow for generalization.

![Figure 2.2](image-url) Course of motor control in phasic and tonic training conditions from sessions 2 to 18. Time scores relate to the percentage of time spent within the desired range of activity (for corresponding slopes, see Table 2.2).
2.5. Results and first evaluation

2.5.1. Improvements in learned motor regulation

Learning of motor regulation over the course of the training is presented in Table 2.2 and Figure 2.2. A.D. showed improved motor control (time score) during tonic feedback in the deactivation condition, with circular pen movements also becoming more precise (imprecision). In the activation condition, baseline activity of the hand pulling the dynamometer decreased over time.

In the phasic training, the child increased time scores in the deactivation but not in the activation condition over time. For the deactivation condition, the muscle activity decreased from baseline and the differentiation between activation and deactivation increased over time. As indicated in Figure 2.2, the total time score started at about 60 % and increased progressively until it reached 90 % at the end of the training.

As illustrated in Figure 2.3, deactivation and activation during phasic motor training clearly differed physiologically. Figure 2.3 also shows that A.D. tended to already increase muscle activity during baseline.

![Figure 2.3](image)

**Figure 2.3** Means of all phasic trials (including transfer) from sessions 2 to 18. Means of rectified EMG activity trajectories for the right and left hand during activation (gray) and deactivation (black).

2.5.2. Changes on behavioral scales

Parents’ ratings on the ADHD checklist FBB-HKS showed a reduction in ADHD symptoms of 26 % (Table 2.3). On the Conners’ scales, parents’ ratings were in the normal range after training for both hyperactivity/impulsivity and inattention, which indicates substantial clinical improvement (Table 2.3). In contrast, teacher ratings remained within the clinical range.
Table 2.3 Pre- and post-results and pre-/post differences of behavioral ratings by parents and teacher and neuropsychological tests

<table>
<thead>
<tr>
<th>Behavioral scales</th>
<th>Pre</th>
<th>Post</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBB-HKS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score (R)</td>
<td>1.35</td>
<td>1.00</td>
<td>-26 %</td>
</tr>
<tr>
<td><strong>Conners Parents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM Inattention (T)</td>
<td>63</td>
<td>53</td>
<td>- 1.0 SD</td>
</tr>
<tr>
<td>DSM Hyperactivity/Impulsivity (T)</td>
<td>68&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58</td>
<td>- 1.0 SD</td>
</tr>
<tr>
<td><strong>Conners Teacher</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM Inattention (T)</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- 0.4 SD</td>
</tr>
<tr>
<td>DSM Hyperactivity/Impulsivity (T)</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- 0.5 SD</td>
</tr>
<tr>
<td><strong>Neuropsychological tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuomotor precision Total Score (SS)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>3.6 SD</td>
</tr>
<tr>
<td>Flexibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (T)</td>
<td>71</td>
<td>75</td>
<td>0.4 SD</td>
</tr>
<tr>
<td>Error (T)</td>
<td>57</td>
<td>&gt;68</td>
<td>&gt; 1.1 SD</td>
</tr>
<tr>
<td>Sustained attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error (T)</td>
<td>58</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>Omission (T)</td>
<td>39&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47</td>
<td>0.8 SD</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN-E (PR)</td>
<td>16&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>54</td>
<td>1.1 SD</td>
</tr>
</tbody>
</table>

Pre= pre-training test score; post= post training test score; Diff= difference post minus pre transformed in SD. SD=standard deviation, T=T-scores, PR=percentiles, R=raw scores, SS=scaled scores (mean=10; SD=3). MD=median response time, SD-RT standard deviation of response time. Diffs ≥ 1 SD are indicated in bold. Behavioral scales: Low scores indicate low impairment; negative SD Diffs indicate improvement. Neuropsychological tests: low scores indicate low performance; positive SD Diffs indicate improvement. Clinical impairments or impaired performances are indicated with <sup>a</sup>; <sup>(a)</sup> indicates borderline impairment.

2.5.3. Changes in neuropsychological test performance

In three out of four neuropsychological tests (visuomotor precision, D2, Sustained attention omissions) A.D. showed clinically impaired performances at the beginning. He obtained results within the normal range on all tests after training.
2.5.4. Subjective well-being during motor regulation tasks and clinical observation

Ratings of well-being during tonic activation and deactivation were in the positive range on average (mean deactivation rating = 32 (±23) and mean activation rating =17 (±19) on a scale from -100 (=very bad) to plus 100 (=very good)). In the phasic training, ratings of subjective well-being were also positive on average, with a mean deactivation rating = 16 (±34) and a mean activation rating = 42 (±28). According to clinical observation, compliance and motivation was good throughout the training.

2.6. Discussion

The goal of the present study was to develop an EMG-BF program that parallels complex NF training, comprising both training of the frequency bands and training of SCPs. We created phasic and tonic EMG-BF training tasks that closely matched the NF training conditions and allowed us to use NF software and matched training protocols. As indicated by the total time score and illustrated by Figure 2.2, A.D. showed increased motor control in the course of the phasic training, whereas in the tonic conditions, learning was less consistent. In the tonic activation condition, learning effects were probably masked by the fact that baseline activity of the hand pulling the dynamometer decreased over time. The reduction of the baseline lowered also the upper threshold, decreasing the range of regulation which consequently made regulation probably more difficult. In the tonic deactivation condition, the child had also to improve pen movement precision, what he successfully did, but possibly this additional challenge reduced improvements in the fed back regulation of muscle activity. All in all, in the main outcome measure for the training success (percentage of time spent in the desired state), the child showed a tendency for improvement over time which indicates that our motor control program is feasible with the different protocol conditions. In addition, positive ratings of well-being indicated that holding or changing muscle activity over several minutes was not associated with unpleasant or painful feelings. The course of the achieved motor regulation across the training (Figure 2.2) demonstrates that taken together, A.D. continuously increased his performance over the training sessions. The fact that no ceiling seemed to be reached early on indicates that the method is sufficiently challenging to match a corresponding NF training protocol.

Our first analyses of the EMG data also identified a strategy used by A.D. during EMG-BF phasic training: He tended to increase muscle activity already during the short baseline phase. Thus, during activation trials he could not increase muscle activity any further when the feedback phase began, but during deactivation trials he started from a high activation level and therefore could reduce muscle activity more easily. Consequently, A.D. showed increased time scores in the deactivation but not in the activation condition. This strategy is also reflected by increasing reduction of muscle activity from baseline in deactivation over time. As activation and deactivation trials appeared randomized on the screen, this strategy had a chance to be effective in half of the trials.

Besides its valuable contribution as NF control training, our EMG-BF training proved to be a clinically effective treatment of some ADHD behaviors in this single case. A.D. demonstrated substantial clinical improvement of ADHD symptoms according to parents’ ratings (26 % symptom score reduction on FBB-HKS, which meets the criterion for responders by Gevensleben, Holl, Albrecht, Vogel, et al. (2009) of 25 % symptom
reduction), and CPRS scores fell below the clinical cut-off after training. Teacher ratings did not indicate comparable improvements. Discrepancies between parents’ and teacher ratings concerning the magnitude of change are a common finding in NF studies (Arns et al., 2009), with teachers usually reporting smaller improvements, if any. In contrast to our hypothesis, we did not find a differential effect of EMG-BF on hyperactivity/impulsivity compared to inattention symptoms. One possible explanation for this is that unlike previous EMG-BF with ADHD, this EMG-BF was not aimed at motor relaxation, but rather at fine motor skills, placing much higher demands on focused and sustained attention and on executive control. The attentional improvements may indicate that EMG-BF training targeting motor skills to a certain degree also partly constitutes an attention training, which is a “unspecific” aspect of any demanding BF training. Besides that, there should still be room for specific effects expected for NF training, which hopefully in future studies can be separated from unspecific effects by using our EMG-BF as a suitable control condition. Likewise, positive trends in neuropsychological performances were not confined to tests with motor components, although practice effects have to be taken into account. Neuropsychological performances were clinically impaired in three out of four tests before and within the normal range after training. Closer inspection of the visuomotor precision task showed that the improvement was mostly due to an increase in speed, therefore the result was obviously in part related to a change of strategy and to familiarity with the test rather than to an improvement of motor precision. Nevertheless, the two neuropsychological tests with motor component showed the most sizable improvements, which probably may be assigned to a specific effect of the EMG-BF training.

The presented results are based on a single subject allowing only a restricted interpretation. For this reason group analyses are needed for further evaluation of the program, particularly with regard to its potential as a treatment for motor coordination deficits.

2.7. Conclusion

A differential EMG-BF training procedure could be successfully designed and adapted to closely match the complex training protocols currently used for NF training in clinical practice and research, and effectively tested for feasibility on a child with ADHD. In addition, it was possible to show that differential motor skill learning resulted from this EMG-BF training in a child with ADHD. Future studies will have to examine its possible value as a specific intervention for children with ADHD and comorbid motor skill problems.

2.8. Acknowledgments

The authors wish to thank the children and their families for their participation. We express our gratitude to Hartmut Heinrich for providing the BF software and Yamilée Schwitter for her support in the development of the EMG-BF method. We are thankful to Antonia Bak, Guylaine Thalman, Lea Meier, Markus Mächler, Matthias Hartmann, Melanie Achermann, Nadia Mock, and Stefanie Hossmann for their valuable support during the training period. We are also thankful to Robert Riener, Roland Müller, Peter Wolf and Andreas Brunschweiler for providing technical support. The study was supported by the SBF COST B27 ENOC and by a grant to the GD of the Canton of Zurich.
3. Study / Publication Nr. 2: Comparing Tomographic EEG Neurofeedback and EMG Biofeedback in Children with Attention-Deficit/Hyperactivity Disorder

Accepted for publication in October 2013 in Biological Psychology.
Authors: Stefano Maurizio, Martina Daniela Liechti, Hartmut Heinrich, Lutz Jäncke, Hans-Christoph Steinhausen, Susanne Walitza, Daniel Brandeis, and Renate Drechsler

3.1. Abstract

Two types of biofeedback (BF), tomographic electroencephalogram (EEG) neurofeedback (NF) and electromyographic biofeedback (EMG-BF), both with phasic and tonic protocols were evaluated as treatments for attention-deficit/hyperactivity disorder (ADHD), and compared to investigate treatment specificity. Thirteen children with ADHD trained their brain activity in the anterior cingulate cortex (ACC), and twelve trained activity of arm muscles involved in fine motor skills. In each training session, resting state 24-channel EEG, training performances, well-being and training strategies were recorded. Pre-/post behavioral changes were assessed by questionnaires and neuropsychological tests. Both groups showed similar behavioral improvements and artifact reduction in selected conditions, with no significant advantages despite medium effect sizes on primary outcomes for NF. Only the EMG-BF group, however, showed clear improvement in training regulation performance. Specific effects were found for the EMG-BF group for fine motor skills and bimanual coordination. The NF group tended to present individual normalization of trained frequency bands in the ACC during rest across training. The results provide evidence for some specific effects in our small sample, albeit only to a small extent. Still, unspecific effects common to both BF types appeared to underlie more of the behavioral improvement in this comparison of two active BF trainings for children with ADHD despite some specific changes of EEG tomography and artifact regulation over training sessions.

3.2. Introduction

Attention-deficit/hyperactivity disorder (ADHD), with a worldwide prevalence of approximately 5.2 %, is one of the most frequent disorders in psychiatry (Polanczyk et al., 2007; Steinhausen et al., 1998). The core symptoms of ADHD are inappropriate levels of inattention, impulsiveness, and hyperactivity (Barkley, 1997). In addition, children with ADHD often have comorbid motor coordination problems (Fliers et al., 2008; Kadesjo et al., 2001; Rommelse et al., 2007; Slaats-Willemse et al., 2005; Steger et al., 2001).

With regard to the core symptoms of ADHD, several treatments are typically used. Although the use of stimulant medication is widespread, only about 70 % (Barkley et al.,

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2 Stefano Maurizio helped implementing the study, assisted to adapt the software SAM (self-regulation and attention management) for multichannel recording, conducting the measurement (as recruitment, scheduling appointments, training of children), developed novel analysis approaches, and analysed the data. The manuscript was written by Stefano Maurizio and revised by the co-authors.
Comparison tomographic Neurofeedback and EMG-Biofeedback

1991) of children with ADHD respond to pharmacological treatment. In addition, side effects, reluctance to take medication, and the lack of clear positive long-term effects are serious limitations of this treatment (Banaschewski et al., 2006). Consequently, there is a strong demand for alternative behavioral treatments such as neurofeedback (NF), which, based on learning of regulation or operant conditioning of brain activity, is considered an alternative or additional treatment (Heinrich et al., 2007). NF is geared towards building the self-control of neurophysiological functions which are altered in ADHD (Doehnert et al., 2013; Monastra et al., 2001) and to normalize them, but may also support compensatory regulation strategies (Gevensleben et al., 2012). The regulation of theta (4-8 Hz) and beta (13-20 Hz) frequencies as well as the training of slow cortical potentials (SCP) are typical NF training protocols used for the treatment of children with ADHD (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Heinrich et al., 2004; Leins et al., 2007; Lubar et al., 1995; Strehl, Leins, et al., 2006; Thompson et al., 1998), which have been used in an adapted and tomographic variant in the study presented here (see also Liechti et al., 2012).

There is increasing evidence that training the self-regulation of neurophysiological parameters through NF, using scalp electroencephalogram (EEG) from a single channel (conventional NF), improves ADHD symptoms (Doehnert et al., 2008; Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Heinrich et al., 2004; Kropotov et al., 2005; Leins et al., 2007; Strehl, Trevorrow, et al., 2006). Correspondingly, a meta-analysis (Arns et al., 2009) reporting large effect sizes for inattention and impulsivity and a medium effect size for hyperactivity, even when compared to control groups, recommended NF as an "efficacious and specific" ADHD treatment. In contrast, a review by Lofthouse et al. (2012) considered it only as "probably efficacious", and a recent meta-analysis (Sonuga-Barke et al., 2013) reported only a trend for probably blinded ratings (mostly teacher ratings). As discussed in our previous publication (Liechti et al., 2012), a more efficient approach than conventional NF might be the training of intracerebral activity in specific brain regions affected in ADHD such as the anterior cingulate cortex (ACC). This brain region has consistently been implicated both in EEG-based (Albrecht et al., 2010; Fallgatter et al., 2004) and other imaging studies (metaanalyses, Cortese et al., 2012).

An important aim in NF research is to demonstrate and understand the specific mechanisms of action of training protocols and their impact on the training outcomes, and to clarify the nature of unspecific mechanisms. One approach to investigate specificity, which was pursued in our previous paper (Liechti et al., 2012), is to examine the relation of the individual learning of neurophysiological regulation to the training outcome. Another approach is to compare NF effects to those of a control training or group, which is pursued in this paper comparing the same NF group with an electromyographic biofeedback (EMG-BF) control group. An active control condition, which consists of a comparable amount and intensity of cognitive demands and patient-therapist interaction, allows to disentangle the specific and unspecific effects of NF treatment. This approach controls for unspecific effects induced by the NF setting, such as patient-therapist interaction, immediate feedback, reward, systematic training to sit still, attentional aspects of the training, expectations generated by applying electrodes, and being connected to a computer (Arns et al., 2009; Brandeis, 2011). This is contrasted with a waiting list group, which is a passive control condition eliminating only those unspecific confounds due to elapsed time and test repetition.
Some studies also reported protocol-specific neurophysiological changes (Brandeis, 2011), particularly for SCP training (Heinrich et al. (2004); Wangler et al. (2011); Doehnert et al. (2008)). Some specific results have also been reported for frequency band training protocols. For example, Gevensleben et al. (2009) found that behavioral outcome after theta/beta training correlated with theta decrease. Only few studies have examined associations between the training regulation performance during the training and behavioral improvement, but most of them provided at least some evidence for significant relations (most recently Gevensleben et al. (2013), for reviews see (Drechsler, 2011; Moriyama et al., 2012)). In our previous publication (Liechti et al., 2012), improved clinical ADHD symptoms and differential ACC modulation were also found after NF, but there was no or little training regulation success and consequently no relationship between the training success and the training outcome. For these reasons, we concluded that unspecific or secondary NF effects such as artifact control account for much of the clinical improvement, but in order to clarify the remaining specific treatment effects, a comparison with an active control group is essential.

Control conditions are critical to determine specific effects of NF in randomized controlled trials. The choice of the appropriate control condition for NF remains a matter of debate (Gevensleben et al., 2012; Lofthouse, Arnold, & Hurt, 2012; Loo et al., 2012). A sham NF group with placebo feedback utilizing the same setting and interface for training represents the most powerful control group in some respects (Lansbergen, van Dongen-Boomsma, et al., 2011; Logemann et al., 2010). Differences in clinical outcome between regular and sham NF training which are equivalent in all other aspects of the setting, can be attributed to the specific effects of learned regulation of the targeted brain activity. However, sham NF training may induce higher drop-out rates (Arns et al., 2009) and reduce the active effort. In addition, implementing a sham condition in clinical research with ADHD children is critical from an ethical point of view. Another biofeedback (BF) method with genuine feedback and a possible therapeutic benefit, such as the feedback of motor activity, seems to be a preferable alternative. In addition, blinded ratings (Sonuga-Barke et al., 2013) plus evaluation of blinding (Gevensleben, Holl, Albrecht, Vogel, et al., 2009) may offer reasonable control for unspecific expectancies. EMG-BF has been used in several studies to improve muscle relaxation and reduce hyperactivity in children with ADHD (for reviews see Arnold et al., 2011; Cobb et al., 1981; Lee, 1991). In the present study, EMG-BF focuses directly on the improvement of fine motor skills and motor regulation, which is often impaired in children with ADHD (Pitcher et al., 2002; Pitcher et al., 2003) and may therefore represent a meaningful treatment for this group. In addition, this EMG-BF training provides well-matched control conditions for NF training (for a more detailed description of the method, please refer to the case description of this control condition by Maurizio et al. (2013) and to the Supplementary material).

So far, only one study has used EMG-BF as a control condition for NF (Bakhshayesh et al., 2011). In this study, the participants had to reduce the EMG amplitude of the feedback signals of the forehead musculature. Significant improvement of ADHD symptoms was reported after both training conditions; there was more improvement after NF for inattention symptoms on parent rating scales and reaction times in neuropsychological tests, but no significant differences were found on teacher ratings or other measures, suggesting that NF may only have limited specific behavioral effects when unspecific factors are controlled for. The specific mediators of response of NF and
Comparison tomographic Neurofeedback and EMG-Biofeedback

EMG-BF, however, are still unknown and need to be investigated further. For this reason, in the present study, we compare NF and EMG-BF in two groups of children with ADHD and investigate training regulation performance, artifact control, and resting EEG changes in the course of the training and behavioral and neuropsychological changes between pre- and post-assessments.

We hypothesized that ADHD behavioral symptoms would be mitigated in both groups, although we expected larger effects for the NF. Through this new training technique, we had expected that children would learn to specifically regulate their EEG in a brain region most affected in ADHD and thereby show stronger improvement on behavioral rating scales and neuropsychological tests tapping into attention compared to the EMG-BF treatment. However, due to unspecific effects, some ameliorations in the EMG-BF group were also expected, in accordance with Bakhshayesh et al. (2011). Following our previous results providing more evidence for regional normalization at rest than for learning of regulation (Liechti et al., 2012), we expected the individual normalization of resting EEG activity in the ACC to be specific to the tomographic NF treatment. For the EMG-BF group, changes in the resting EEG and a stronger improvement on neuropsychological tasks related to fine motor skills and bimanual coordination were expected.

3.3. Methods

In a randomized controlled clinical trial (ISRCTN 82524080) we planned to investigate three different BF treatments of ADHD using tomographic NF, conventional NF (not completed due to time constraints), and EMG-BF in a blinded parallel group pre-post design, with randomization constrained by group balancing requirements. The trial conformed to the standards of the Declaration of Helsinki and was approved by the local ethics committee.

3.3.1. Subjects

The participants had to meet diagnostic criteria for ADHD combined subtype (DSM-IV, 2004). For a few participants (NF: n=1, EMG-BF: n=3) the ADHD DSM-V age-of-onset criterion was used (see also Liechti et al., 2012), and one (NF) subject’s symptoms were not fully met at school. The diagnostic procedure included a semi-structured clinical diagnostic interview PACS (Parental Account of Children’s Symptoms; (Taylor et al., 1986)) and the Conners’ Teacher Rating Scale Revised (CTRS; (Conners et al., 1998b)), according to a validated algorithm (Valko et al., 2010). Further inclusion criteria were age between 8.5-13 years, IQ≥80, no known neurological disorder, and no severe comorbid conduct disorders, depression or anxiety disorders. Stimulant medication was permitted if the dosage was kept constant throughout the training period. For pre- and post-training assessments, medication had to be suspended at least 48 hours previously. Twenty-eight subjects were randomly assigned to one of the two (originally three) completed BF training programs, which were all introduced as experimental treatments for ADHD. The children and their parents gave written consent to participate in the study and agreed to be informed about the training assignment only after post-
assessments were completed. Thus, both parents and teacher were blinded with regard to treatment assignment.

Two subjects dropped out of the EMG-BF group (insufficient compliance due to oppositional behavior, after the eighth training session, depressive occurrence caused by the medication after pre-testing) and one child from the NF group had to be excluded from the analyses due to a change of medication. Group characteristics for the remaining children (NF: n=13, EMG-BF: n=12) are listed in Table 3.1. Before the training, there were no significant differences between the groups regarding demographic, psychological and clinical variables.

<table>
<thead>
<tr>
<th></th>
<th>NF n = 13</th>
<th>EMG-BF n = 12</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys/girls</td>
<td>11 / 2</td>
<td>11 / 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age [years]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>10.6 ± 1.3</td>
<td>10.0 ± 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Range</td>
<td>8.9 - 12.9</td>
<td>8.5 - 12.0</td>
<td></td>
</tr>
<tr>
<td>Handadness (left/right)</td>
<td>0 / 13</td>
<td>1 / 11</td>
<td></td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>111.1 ± 10.0</td>
<td>118.1 ± 12.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stimulant medication</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CPRS [T-scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global index</td>
<td>69.8 ± 10.1</td>
<td>65.4 ± 7.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inattention (DSM-IV)</td>
<td>73.5 ± 10.0</td>
<td>68.4 ± 7.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity (DSM-IV)</td>
<td>74.3 ± 10.1</td>
<td>71.7 ± 8.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total score (DSM-IV)</td>
<td>75.3 ± 9.6</td>
<td>71.4 ± 7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>CTRS [T-scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global index</td>
<td>63.2 ± 9.7</td>
<td>68.8 ± 8.5</td>
<td>n.s.</td>
</tr>
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<td>Inattention (DSM-IV)</td>
<td>61.2 ± 6.7</td>
<td>65.3 ± 8.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity (DSM-IV)</td>
<td>62.2 ± 12.6</td>
<td>69.3 ± 8.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total score (DSM-IV)</td>
<td>62.7 ± 9.7</td>
<td>68.5 ± 8.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>CBCL [T-scores]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Social withdrawal</td>
<td>54.0 ± 10.5</td>
<td>52.9 ± 10.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>61.9 ± 12.1</td>
<td>55.7 ± 7.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anxiety/Depression</td>
<td>52.9 ± 8.7</td>
<td>55.7 ± 8.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Social problems</td>
<td>59.3 ± 8.4</td>
<td>62.7 ± 9.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Thought problems</td>
<td>51.8 ± 7.7</td>
<td>55.3 ± 11.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Attention problems</td>
<td>64.5 ± 3.8</td>
<td>66.6 ± 5.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>60.1 ± 10.5</td>
<td>57.8 ± 10.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>62.1 ± 10.8</td>
<td>61.3 ± 6.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Internalising problems</td>
<td>56.4 ± 10.9</td>
<td>55.5 ± 9.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Externalising problems</td>
<td>62.0 ± 10.9</td>
<td>61.0 ± 5.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total problem score</td>
<td>61.7 ± 9.2</td>
<td>62.5 ± 7.8</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

CPRS= Conners’ Parent Rating Scale; CTRS= Conners’ Teacher Rating Scale. ADHD primary symptoms are quantified by CPRS and CTRS DSM-IV T-scores, and general psychopathology by parent-rated CBCL T-scores; estimated IQ is based on four subtests of the German version of the Wechsler Intelligence Scale for Children IV

Table 3.1 Group characteristics (NF group already reported in Liechti et al. (2012))
3.3.2. Study design

The training consisted of 36 training units held as double lessons two to three times per week over a period of approximately 12 weeks. Before and after the training program, pre- and post- training assessments took place. In addition to EEG, ERPs in cognitive tasks, and a battery of neuropsychological tests, these assessments included behavioral ratings by parents, teachers, and participants.

The training program of both groups consisted of a tonic and a phasic protocol. While in the tonic training, participants had to maintain the same state (activation/deactivation) over several minutes, in the phasic training, they constantly had to switch between states of activation and deactivation, according to the short (10 s) randomized trials. The first session of the training program started with tonic training only, followed by sessions including both protocols arranged in alternating order from one session to the next (Supplementary Figure 3.1). In the course of the training, transfer blocks were introduced successively, enabling the subjects to practice their strategies with reduced feedback from the computer.

At the beginning of each training session, an eyes-open resting EEG was recorded for 2 minutes, followed by epochs of systematic eye movements to calculate artifactual ICA components for online eye-artifact correction during the training. All lessons of both training groups consisted of four training blocks of 3-8 minutes each, followed by self-ratings of current mental states and feeling of feedback control. The duration of an entire training session was about 3 hours, including preparation and the placement of 32 electrodes, EEG-baseline recording, instructions, break, and hair washing.

Figure 3.1 Training setting and electrodes of the two training methods. The body signals are recorded by the electrodes, amplified and processed by the computer system and fed back to the participant on the computer screen. Only the “recording + feedback” electrodes (●) signal is used for the processing of the feedback. The “only recording” electrodes (●) signal is used for offset analysis, whereas sham electrodes (○) are not used for signal recording, but applied on the arm of the NF group to facilitate blindness of the study. In both treatments, all recording electrodes flowed into the artifact control and were fed back through a sad face appearing on the screen and interrupting the regulation feedback.
3.3.3. Training procedures

In preparation for NF and EMG training sessions, 24 electrodes were placed at the scalp according to an extended 10-20 montage with reference at Fz and ground at FC6 (Figure 3.1). Two additional electrodes were used for electrooculography (EOG) and another one for electrocardiography (ECG) recording. In addition, pairs of electrodes (at a centre-to-centre distance of 20 mm) were placed on the *musculus digitorum* of the right and left forearm and for the EMG-BF group also on the right *musculus trapezius* in accordance with the locations and orientations recommended by SENIAM (Hermens et al., 1999). In the NF group, the EMG electrodes were only mock, allowing the topographic EEG to be expanded by six scalp electrodes (Afz, CPz, POz, Iz, FC1, FC2; see also Figure 3.1).

During the training, signals were continuously recorded from 33 active electrodes (AE1, Easy Cap, FMS, Munich) in both groups. The signal was amplified through a BrainAmp amplifier (Brain Products, Gilching, Germany), analogue filtered between 0.016 and 250 Hz, and digitized at a sampling frequency of 500 Hz. To avoid EEG distortion, artifacts at 16.66 Hz from a nearby railway track was compensated by an active shielding. For signal processing, a forward bandpass filter (Butterworth 2nd order) set at 0.1-30 Hz was used for EEG/ECG and at 0.1-100 Hz for EMG signals.

The software SAM (“Self-regulation and Attention Management”) (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009), which had been adapted for multichannel recordings, advanced artifact handling, and estimation of intracerebral activity using standardised low resolution electromagnetic tomography (sLORETA, Pascual-Marqui, 2002) was used for online feedback calculation and presentation (Liechti et al., 2012). While the activity of the ACC with the Montreal Neurological Institute (MNI) coordinates (X, Y, Z)=(5, 10, 30) was fed back for the NF group, the EMG activity of the forearms was used for feedback in the EMG-BF group. The influence of artifact was controlled through a sad face appearing on the screen and interrupting the feedback any time EEG or EOG signals exceeded ±100-250 µV or ±15-25 µV for the 25-35 Hz band and through the monitoring of the quality on a separate surveillance station. The artifact thresholds were typically kept constant throughout the training course after initial individual adjustment for the individual base level, and was readjusted only rarely for major changes on specific days... In the EMG-BF group, except for the tonic deactivation condition, an additional upper EMG threshold was defined for EMG channels and flowed in as artifact, which was also fed back using the sad face. Otherwise, both the NF and EMG-BF were parallelized regarding training settings and protocols, as illustrated in Figure 3.1 and described below.

3.3.4. Tonic protocol

The tonic protocol consisted of blocks of 120 s to 480 s. Children were requested to simultaneously regulate two separate dimensions, represented by separate bars on the left and right side of the screen. The task of the children was to regulate the heights of the bars below or above a desired threshold, which represented the frequency content of the feedback parameters. Positive feedback was received as long as the criteria of both dimensions were met. The frequency content was calculated using a Butterworth bandpass filter (48 dB/octave). Every 100 milliseconds, feedback was given using a moving time window of 2 s length. The activation condition lasted for twice as long as the deactivation condition, and except for the first session, both conditions were trained
in each tonic lesson. Individual thresholds were determined according to recorded daily baseline values.

Neurofeedback
In NF tonic training, theta (4-7.5 Hz) and beta (14-20 Hz) band activity in the ACC voxel (length of vector (ACC-l) representing the amplitude of this source vector irrespective of its orientation; see Figure 2 in Liechti et al., 2012) were trained. The participant had to enhance beta and simultaneously reduce theta activity in the activation condition, whereas a reduction of beta and an enhancement of theta was required in the deactivation condition. Theta and beta activity were fed back by the bars on the left and on the right of the screen. As baseline, a 3-minute resting EEG with eyes open was measured at the beginning of the tonic lesson.

EMG-biofeedback
In the EMG-BF tonic training, muscle activity (55-95 Hz) of both arms was trained simultaneously with different demands for each hand. Muscle activity of the right arm was fed back by the bar on the right side, muscle activity of the left arm by the bar on the left side. In the activation condition, muscle activity of one arm had to be increased by pulling a hand dynamometer, but without exceeding an upper muscle activity threshold. At the same time, the muscle activity of the other arm had to be reduced. In order to maintain some measurable muscle activity in this arm, it was balanced on two soft balls while holding a small ball in the hand. Compared to the NF training, the duration of the blocks was shorter, the number of blocks was doubled, and the training program alternated between both hands in order to avoid overexertion. The baseline recording lasted for 60 s preceding each training condition, during which the participant pulled the dynamometer (1.5 kg) while the contralateral arm balanced on two balls with a third ball in the hand (see Figure 1b in Maurizio et al., 2013).
In the deactivation condition, muscle activity of both hands had to be reduced while the writing hand was performing a circular drawing movement in a drawing template. Meanwhile, the contralateral arm was resting on two softballs, with another ball in the hand (see Figure 1c in Maurizio et al., 2013). The participants were instructed to perform steady pen movements without pressure. Baseline lasted for 60 s with the same instructions as in the feedback phase.

3.3.5. Phasic protocol
The phasic protocol consisted of blocks with 20-40 trials each. Each trial presented a 2 s baseline followed by a 4 s-feedback phase. The trials were separated by an inter-stimulus interval of 4 ± 1 s. Every 100 ms, the position and color of a flying ball was given as feedback, using a 500 ms-length moving time window on the fed-back signal. Except for a learning phase of two sessions, during which the conditions were trained separately, activation and deactivation trials were presented with equal frequency (1:1) in a random order in the same block. A red or blue colored bar appearing at the beginning of each feedback phase indicated whether an increase or decrease of activation was required, relative to the calculated threshold of the last 1.5 s of the baseline. A “+” was indicated at the end of successful trials, whereas a “-” appeared on the screen for unsuccessful trials. A trial was successful when the ball stayed in the correct part of the screen for most of the feedback time. The participant was told that he should find appropriate strategies in order to move the ball on the screen up or down.
**Neurofeedback**

In the NF phasic protocol, the regulation of slow potential shifts in the vertical z-direction of the ACC activity (ACC-z; see Figure 2 in Liechti et al., 2012) was trained. In the activation condition, an increase of ACC-z activity inducing negative potential shift in the central region on the scalp was requested, whereas during deactivation trials, opposite polarities should occur.

**EMG-biofeedback**

In the EMG-BF phasic protocol, in both conditions, a dynamometer was pulled by one hand while the other hand/arm rested on the table (see Figure 1a in Maurizio et al., 2013). The EMG activity of the hand pulling the dynamometer had to be increased in the activation condition and decreased in the deactivation condition. In the activation condition, the participant had to accurately dose his force in order not to exceed an upper EMG limit. For feedback in the phasic blocks, the EMG signal was filtered with a Butterworth bandpass filter (55-95 Hz, 48 dB/octave) and rectified. To avoid overexertion, dynamometer training alternated between the left and right hand.

### 3.3.6. Data processing and analyses

To evaluate the training regulation performance of all blocks except transfer blocks, for the NF and EMG-BF training in both phasic/tonic protocols and activation/deactivation conditions, the percentage (score) of time spent in the desired state of regulation was calculated and related to the total trial duration without time-comprising artifacts. The percentage of time with artifact feedback (sad face) was determined using the same procedure. For the phasic condition, an additional total score summed over deactivation and activation was calculated per block.

For all offline analyses, the program Brain Vision Analyzer (Version 1.05.0005, Brain Products, Gilching, Germany) was used. The EEG was filtered off-line using a bandpass filter set at 0.1-70 Hz and a 50 Hz notch filter. Large technical and movement artifacts were rejected automatically. For ocular correction, an ICA was used. An average reference was calculated, including the Fz recording reference. Through visual appraisal, remaining artifacts were rejected semi-automatically. For analyses of the activity in the ACC, additional channels were calculated using sLORETA-based linear combinations of 24 scalp channels. For fast Fourier transformation (FFT), resting EEG data were segmented into 2.048 s epochs using power density computation (0.488 Hz resolution, 10 % Hanning windowing, full spectrum). The absolute power of theta (4–7.5 Hz), beta (14–20 Hz) activity, alpha (7.5–12.5 Hz in supplementary material), whole spectrum (total, 1.5-25 Hz) and theta/beta ratio was calculated. In addition, averaged power of the pool across all scalp channels (all) used in the EMG-BF training and the three sagittal regions (frontal, central, posterior) were calculated.

### 3.3.7. Questionnaires and behavioral assessments

For the screening of clinical conditions and comorbidities, the parents completed the Child Behavior Checklist (CBCL, (Achenbach et al., 1991)). To estimate the IQ, a short form of the German version of the Wechsler Intelligence Scale for Children IV (HAWIK-
Comparison tomographic Neurofeedback and EMG-Biofeedback

IV, (Waldmann, 2008)) with the following subtests was used: “Vocabulary”, “Block Design”, “Letter-Number Sequencing”, and “Symbol Search”. Pre- and post-training assessments included the German standardized DSM IV questionnaire for ADHD (FBB-HKS (Döpfner M., 2000)), the Conners’ Parent Rating Scale-Revised (CPRS, (Conners et al., 1998a), the Behavior Rating Inventory of Executive Function (BRIEF; (Gioia et al., 2000)) and the German version of the Strengths and Difficulties Questionnaire (SDQ, (Goodman, 1997)), rated by the parents. In addition, a questionnaire assessed parents’ assumption about their child’s group assignment as well as their expectations regarding efficacy of the different treatments. The teacher assessment included the CTRS (Conners et al., 1998b) and the teachers’ version of the BRIEF (Gioia et al., 2000). The subscores for inattention and hyperactivity/impulsivity of the FBB-HKS constituted the primary outcome measures of the study.

A comprehensive battery of neuropsychological tests included the subtests “sustained attention” and “flexibility” from the computerized Test for Attentional Performance for Children (KITAP, (Zimmermann et al., 2002)), the subtest “Alertness” from the computerized Test for Attentional Performance (TAP, (Zimmermann et al., 2007)), the D2 Test of Attention (Brickenkamp, 2002); the Test of Visuomotor Precision from the NEPSY (Korkman et al., 1998), and the pegboard task from the Zurich Neuromotor Assessment Battery (Largo et al., 2002). At the beginning and end of every training lesson, participants were asked to rate their current well-being, and after the lesson how they had felt and which strategies they had applied during the training. These ratings were completed on computerized visual analogue scales with the opposite attributes and symbolic pictures as visual anchors at both ends of the scales.

3.3.8. Statistical analyses

For statistical analyses, the Statistical Package for the Social Sciences version 18.0 (SPSS) was used. Pre to post changes were analyzed with univariate analyses of variance (ANOVA) with repeated measures (time: pre, post) and two groups (NF, EMG-BF). Post hoc t-tests were conducted to separately analyze time effects per group. In the case of multiple dependent variables, multivariate analyses of variance (MANOVA) were calculated.

To analyze performance, mean values and linear regression of training performance were calculated across sessions for each participant. Group means and standard deviations (SD) were used.

As common for neuroimaging data, t-test were used for descriptive and topographic (t-maps) scalp EEG group comparisons. Our main hypothesis based on the literature and our previous paper was for changes at electrode Cz for NF, and over motor regions (C3 and C4) for EMG-BF. For the other electrodes, p-levels around 0.01 typically correct adequately for multiple testing with this number of electrodes for the smooth EEG topographies (Maurer et al., 2005). A Bonferroni correction (requiring p = 0.00213 with 24 electrodes) would be too strict for topographic EEG analysis because the tests are not independent across electrodes.

To analyze performance, mean values and linear regression of training performance were calculated across sessions for each participant. Group means were calculated...
from the individual slopes, intercepts of the linear regressions and means over lessons, and then compared.

The effect size (ES) of change was computed as the difference between the means (post – pre) divided by the corresponding pooled SD (Cohen’s d, (Cohen, 1988)) for each measure and group separately. For the ANOVAs, partial eta squared is reported instead. For statistical analysis, only significant results (p<0.05) or trends (p<0.10) of specific interest are reported.
3.4. Results

3.4.1. Behavioral outcome

Both groups showed a similar significant improvement after training in the primary outcome measure (Table 3.2). Significant but not group-specific improvements after training were also found according to most other questionnaires. No GROUP by TIME interaction was found for the primary outcomes although some parent ratings reached medium effect sizes in favor of NF. The repeated measures MANOVA with group as independent factor and nine composite scores of parent-rated scales (FBB-HKS: inattention, hyperactivity/impulsivity; CPRS: global index, inattention, hyperactivity/impulsivity; SDQ: hyperactivity, total problem score; BRIEF: behavioral regulation index, metacognition index) revealed a significant improvement for TIME (F[9,15]=4.04, p=0.008), but no GROUP (F[9,15]=1.54, p=0.220) or GROUP by TIME interaction (F[9,15]=0.52, p=0.837). A corresponding repeated measures MANOVA including five teacher-rated composite scores (CTRS: global index, inattention, hyperactivity/impulsivity; BRIEF: behavioral regulation index, metacognition index) also yielded a significant improvement over TIME (F[5,19]=5.43, p=0.003), but no GROUP (F[5,19]=1.45, p=0.252) or GROUP by TIME interaction (F[5,19]=1.45, p=0.253).

3.4.2. Training performance

Unless otherwise stated, the results for performance during the actual training include only blocks with contingent feedback across all animations (Figure 3.2). The NF group showed no significant change in the score. The EMG-BF group showed a significant improvement in the phasic deactivation as well as in the tonic activation condition. Similar results were found for the total score in the phasic training, which showed no significant improvement for the NF group (t=-0.35, p=0.735) but did demonstrate a significant improvement for the EMG-BF group (t=4.56, p<0.01). The differences in improvement between the groups were significant for the tonic activation/deactivation conditions and the phasic deactivation condition scores, as well as for the phasic total score (t=-4.54 p<0.001). The starting points (intercept) of the score of the two groups differed significantly for all four conditions. For the EMG-BF group, all starting points were significantly higher than the expected chance level (phasic 50%, tonic 25%), whereas for the NF group, the starting points were around or even lower than the expected chance level (significant for tonic activation).

A reduction of the artifacts was observed in all conditions for the NF group, but only in the phasic deactivation condition in the EMG-BF group. The phasic deactivation condition did not show a significantly higher reduction of artifacts for the NF compared to the EMG-BF group as was found for the phasic activation and the two tonic conditions. Generally, the EMG-BF group started the training with a higher rate of artifacts than the NF group (see results for intercept in Figure 3.2). This was significant for the two activation conditions, whereas a trend was shown for the phasic deactivation condition.
Figure 3.2 Training performance of NF and EMG-BF groups for all trials with contingent feedback of the phasic and tonic protocols. A) For the activation (filled circles) and deactivation condition (open circles), group means of training regulation success (score) and artifacts during phasic and tonic protocol are represented. The linear regression line across the lessons represents the changes (learning) in the course of the training. The levels of chance for the phasic protocol (50%) and for the tonic protocol (25% for the logical two dimensions conjunction) are represented by thin solid lines. For activation/deactivation conditions standard deviations per lesson are indicated by solid/dashed lines separately (NF group already reported in Liechti et al. (2012)) B) For learning curve statistics the mean and standard deviation of the slopes and intercepts of the individual scores (training regulation success) and artifact regressions are represented for the two conditions activation (act) and deactivation (deact) separately. Significant deviations of the individual groups from chance (usually 0, otherwise indicated by a dotted line) are indicated inside the graphs, whereas the significant deviations between the groups are indicated outside at the margin of the graphs by: ° p<0.1, * p<0.05, ** p<0.01, *** p<0.001.
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Table 3.2 Behavioral data pre- and post-training (NF group already reported in Liechti et al. (2012))

<table>
<thead>
<tr>
<th></th>
<th>NF n = 13</th>
<th>EMG-BF n = 12</th>
<th>Repeated measures ANOVAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre training</td>
<td>Post training</td>
<td>ES</td>
</tr>
<tr>
<td>Parents ratings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBB-HKS [severity]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>2.28 ± 0.44</td>
<td>1.62 ± 0.59</td>
<td>-1.26</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity</td>
<td>1.55 ± 0.67</td>
<td>1.10 ± 0.71</td>
<td>-0.65</td>
</tr>
<tr>
<td>Total score</td>
<td>1.88 ± 0.47</td>
<td>1.34 ± 0.56</td>
<td>-1.05</td>
</tr>
<tr>
<td>CPRS [raw scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global index</td>
<td>16.2 ± 4.7</td>
<td>12.5 ± 4.7</td>
<td>-0.80</td>
</tr>
<tr>
<td>Inattention (DSM-IV)</td>
<td>20.5 ± 4.8</td>
<td>15.1 ± 5.6</td>
<td>-1.04</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity (DSM-IV)</td>
<td>15.0 ± 3.7</td>
<td>10.5 ± 4.8</td>
<td>-1.05</td>
</tr>
<tr>
<td>Total score (DSM-IV)</td>
<td>35.5 ± 7.3</td>
<td>25.5 ± 9.4</td>
<td>-1.18</td>
</tr>
<tr>
<td>SDQ parents [raw scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>7.62 ± 1.76</td>
<td>6.54 ± 1.71</td>
<td>-0.62</td>
</tr>
<tr>
<td>Total problem score</td>
<td>17.38 ± 5.35</td>
<td>14.77 ± 5.42</td>
<td>-0.49</td>
</tr>
<tr>
<td>BRIEF parents [raw scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural regulation</td>
<td>57.7 ± 10.4</td>
<td>51.2 ± 7.8</td>
<td>-0.71</td>
</tr>
<tr>
<td>Metacognition</td>
<td>99.8 ± 14.6</td>
<td>92.1 ± 14.4</td>
<td>-0.54</td>
</tr>
<tr>
<td>Teacher ratings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRS [raw scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global index</td>
<td>11.9 ± 5.2</td>
<td>9.7 ± 4.0</td>
<td>-0.48</td>
</tr>
<tr>
<td>Inattention (DSM-IV)</td>
<td>14.2 ± 4.6</td>
<td>14.3 ± 5.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity (DSM-IV)</td>
<td>10.8 ± 6.3</td>
<td>9.2 ± 4.7</td>
<td>-0.30</td>
</tr>
<tr>
<td>Total score (DSM-IV)</td>
<td>25.1 ± 10.2</td>
<td>23.5 ± 8.2</td>
<td>-0.17</td>
</tr>
<tr>
<td>BRIEF teacher [raw scores]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural regulation</td>
<td>50.9 ± 12.4</td>
<td>44.2 ± 8.7</td>
<td>-0.63</td>
</tr>
<tr>
<td>Metacognition</td>
<td>92.2 ± 17.0</td>
<td>82.8 ± 16.3</td>
<td>-0.56</td>
</tr>
</tbody>
</table>

FBB-HKS: Parent-rated DSM-IV checklist (severity scores); CPRS: Conners Parents Rating Scale; CTRS: Conners Teacher Rating Scale; SDQ: Parents’ Strengths and Difficulties Questionnaire; BRIEF: Behavior Rating Inventory of Executive Function. Repeated-measures analyses of variance with factors group, time and group x time interaction were calculated for group comparison and paired t-tests as post-hoc (representing separate time effects per group) test with significance levels *p<0.1, *p<0.05, **p<0.01, ***p<0.001; ES: effect size as Cohen’s d; ηp²: effect size as partial eta-squared
3.4.3. Course of resting EEG

The analysis of systematic changes in the resting EEG over all training sessions is illustrated in Figures 3.3 and 3.4. Statistics for the mean regression slopes of the EEG parameters across all subjects for theta and beta activity, theta/beta ratio and whole spectrum activity during the eyes-open resting condition in the course of the training are shown in Figure 3.3. There was no systematic change for theta, beta, full band, or theta/beta ratio in the region of training for the NF group. In the EMG-BF group, an increase of beta in the ACC-I and a decrease of the theta/beta ratio in the ACC-I and ACC-z were observed. However, there was no significant difference between the groups in the ACC. On the scalp, a significant increase of beta activity was found for the EMG-BF group for the total scalp activity, supported by the increase over frontal and posterior regions. These results were also reflected in the group comparison, which showed significantly less increase of beta activity in the NF group in this region (only a trend in the posterior region) than in the EMG-BF group. The NF group also showed less increase of full band power in the frontal region than the EMG-BF group.

![Figure 3.3](image-url)

Figure 3.3 Course of topographic resting EEG changes across all training sessions (regression statistics for mean linear regression slopes) across all subjects for theta (4–7.5 Hz) and beta (14–20 Hz) activity, theta/beta ratio and whole spectrum (total, 1.5-25 Hz) activity during eyes-open resting condition across all training sessions. Pictured are the scalp electrodes, the three sagittal regions (f: frontal, c: central, p: posterior), the pool across all channels (all), and the ACC voxel (vector length: ACC-I, z-component of vector: ACC-z) for the NF and EMG-BF groups, and the comparison between the groups (NF vs EMG-BF). The blue/red colors indicate declining/increasing group mean slopes, and the color levels indicate the significance levels of the corresponding statistic. For Bonferroni correction accounting for multiple independent testing for 24 electrodes (which is actually not fully given and thus too strict for EEG analysis), a p level of p = 0.00213 would apply.
The analysis of the dependence of the topographic and tomographic resting EEG changes on the initial values is shown in Figure 3.4. The children’s individual time courses revealed that particularly for the NF training, the resting EEG trajectories converged from their different initial values at the beginning of the treatment towards the group mean ("normalization", quantified by the intercept/slope ratio (Liechti et al., 2012)). For NF, particularly the two trained parameters (theta and beta) and the total frequency band normalized significantly, whereas for EMG-BF, the only significance was found for the theta/beta ratio. Compared to the EMG-BF group, the NF group showed a significantly greater normalization in the ACC-I for the total band spectrum and a trend in the theta and the beta band. In addition, in the beta band, the ACC-z also showed a significantly greater normalization in the NF group. For the NF group, this normalization was also significant on the scalp, for all sagittal regions and the total scalp activities. For the theta/beta ratio, the effects were smaller (frontal region and total scalp showed only a trend and the central region no normalization).

**Figure 3.4** Baseline dependence of topographic resting EEG changes across training, illustrated by the partial correlation statistics between individual slopes and intercepts for theta (4–7.5 Hz) and beta (14–20 Hz) activity, theta/beta ratio and whole spectrum (total, 1.5-25 Hz) activity during eyes-open resting condition in the course of the training, corrected for age. Pictured are the scalp electrodes (maps), the three sagittal regions (f: frontal, c: central, p: posterior), the pool across all channels (all), and the ACC voxel (vector length: ACC-I, z-component of vector: ACC-z ) for the NF and EMG-BF group, and the comparison between the groups (NF vs EMG-BF). The blue/red colors indicate converging/diverging of the individual regression, and the color levels indicate the significance levels of the corresponding statistic. For Bonferroni correction accounting for multiple independent testing for 24 electrodes (which is actually not fully given and thus too strict for EEG analysis), a p level of $p = 0.00213$ would apply.
The EMG-BF group only showed normalization in the theta/beta band, for the central and the posterior region. However, this group showed an opposite course in the central region for the beta and the total band spectrum: In the beta band, the time course diverged significantly. In the group comparison, the NF group showed greater normalization mostly in the beta band, but also in some of the theta and total band, whereas in theta/beta ratio, the EMG-BF group showed significantly greater normalization in the central region, and a trend in the posterior region. For the EMG-BF group, all starting points were significantly higher than the expected chance level (phasic 50 %, tonic 25 %), whereas for the NF group, the starting points were around or even lower than the expected chance level (significant for tonic activation).

A reduction of the artifacts was observed in all conditions for the NF group, but only in the phasic deactivation condition in the EMG-BF group. The phasic deactivation condition did not show a significantly higher reduction of artifacts for the NF compared to the EMG-BF group as was found for the phasic activation and the two tonic conditions. Generally, the EMG-BF group started the training with a higher rate of artifacts than the NF group (see results for intercept in Figure 3.4). This was significant for the two activation conditions, whereas a trend was shown for the phasic deactivation condition.

3.4.4. Test performance in pre- and post-assessments in neuropsychology

In most of the neuropsychological tests listed in Table 3.3, significant TIME effects were found, but GROUP by TIME interactions were significant only for KITAP flexibility and Visuomotor Precision. The interaction resulted from larger improvements in the EMG-BF group.

3.4.5. Subjective ratings by the participants

As indicated in Figure 3.5, all subjective ratings on the current state before the training sessions (“alertness”, “mood”, “tension”, “restlessness”, “stress” and “motivated for the training” did not differentiate between the groups. However, the groups showed differences in the feeling of control and the strategy adopted during the training. The EMG-BF group showed a better feeling of control in the phasic condition, although this was still high on average in the NF group. A significant group difference was found for the strategy (relaxed vs. concentrated) used in the two tonic conditions, with the NF group appearing to have used more differentiated strategies for activation and deactivation than the EMG-BF group (Figure 3.5). Nevertheless, both groups agreed on the use of different strategies for activation and deactivation in the tonic (NF: t=9.72, p<0.001; EMG-BF: t=2.42, p<0.05) as well as in the phasic protocol (NF: t=8.32, p<0.001; EMG-BF: t=2.90, p<0.05). They also showed no group differences in ratings on well-being or on how much they had liked the training.
Table 3.3 Neuropsychological test results pre- and post-training (D2 concentration performance of NF group already reported in Liechti et al. (2012))

<table>
<thead>
<tr>
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<th>NF n = 13</th>
<th>EMG-BF n = 12</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre training</td>
<td>Post training</td>
<td>ES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP, alertness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-median without warning [ms]</td>
<td>279.0 ± 32.0</td>
<td>263.0 ± 32.0</td>
<td>-0.50</td>
</tr>
<tr>
<td>RT-SD without warning [ms]</td>
<td>48.5 ± 20.7</td>
<td>54.2 ± 29.5</td>
<td>0.22</td>
</tr>
<tr>
<td>RT-median with warning [ms]</td>
<td>269.5 ± 33.4</td>
<td>247.9 ± 30.4</td>
<td>-0.68</td>
</tr>
<tr>
<td>RT-SD with warning [ms]</td>
<td>48.5 ± 16.9</td>
<td>41.9 ± 23.5</td>
<td>-0.32</td>
</tr>
<tr>
<td>KITAP, flexibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-mean [ms]</td>
<td>943.0 ± 203.2</td>
<td>869.8 ± 190</td>
<td>-0.37</td>
</tr>
<tr>
<td>RT-median [ms]</td>
<td>891.6 ± 202.7</td>
<td>845.4 ± 189</td>
<td>-0.24</td>
</tr>
<tr>
<td>RT-SD [ms]</td>
<td>274.9 ± 88.1</td>
<td>231.9 ± 65.4</td>
<td>-0.55</td>
</tr>
<tr>
<td>Hits</td>
<td>42.3 ± 6.4</td>
<td>44.2 ± 4.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Errors</td>
<td>2.9 ± 3.2</td>
<td>1.9 ± 2.1</td>
<td>-0.37</td>
</tr>
<tr>
<td>KITAP, sustained attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-median total [ms]</td>
<td>833.3 ± 95.7</td>
<td>791.3 ± 88.5</td>
<td>-0.46</td>
</tr>
<tr>
<td>RT-SD total [ms]</td>
<td>232.6 ± 55.0</td>
<td>188.4 ± 43.0</td>
<td>-0.90</td>
</tr>
<tr>
<td>Hits</td>
<td>41.5 ± 3.6</td>
<td>43.9 ± 4.4</td>
<td>0.60</td>
</tr>
<tr>
<td>Errors</td>
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<td>4.5 ± 4.2</td>
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</tr>
<tr>
<td>Omissions</td>
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<td>6.1 ± 4.4</td>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Time [s]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>22.3 ± 2.8</td>
<td>21.3 ± 2.3</td>
<td>-0.37</td>
</tr>
<tr>
<td>Non-dominant</td>
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<td>23.8 ± 4.8</td>
<td>-0.13</td>
</tr>
<tr>
<td>Visuomotor Precision</td>
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<tr>
<td>Raw Score</td>
<td>27.9 ± 9.2</td>
<td>25.8 ± 7.7</td>
<td>-0.24</td>
</tr>
<tr>
<td>D2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>269.3 ± 62.4</td>
<td>307.9 ± 50.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Concentration performance</td>
<td>104.6 ± 24.0</td>
<td>121.9 ± 23.0</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Test for Attentional Performance (TAP), Test for Attentional Performance for Children (KITAP), D2 Test of Attention (D2), reaction time (RT), standard deviation (SD). Repeated-measures analysis of variance with factors group, time and group x time interaction was calculated for group comparison and paired t-tests as post-hoc test (representing separate time effects per group) with significance levels *p<0.1, *p<0.05, ** p<0.01, *** p<0.001; ES: effect size; np2: partial eta-squared
### 3.4.6. Parent’s blinding - assumptions and expectations

All but one parent completed the questionnaire, and 16 of them indicated assumptions regarding group assignment (the remaining parents were undecided). In the NF group, 7 out of 9 assumed NF and 2 out of 9 EMG-BF training (chance 6/9 vs. 3/9 for two NF vs one BF training types: \( \chi^2=0.5, p=0.480 \)). In the EMG group, 3 out of 7 parents assumed NF and 4 out of 7 EMG training (\( \chi^2 =1.8, p=0.181 \), over both groups \( \chi^2=2.3, p=0.515 \)). All parents expected all treatments forms offered to be effective, except for one parent in the NF group who expected even lower efficacy for tomographic NF training.

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**Figure 3.5** Subjective ratings of the training programs by the NF(▲) and EMG-BF(▲) groups. Mean values and standard deviation of the ratings are represented compiled on a visual analogue scale before and after each training session. Each category has two opposite attributes at the end of the scale (in italics). Group differences are indicated by: ° p<0.1, * p<0.05, ** p<0.01, *** p<0.001
3.5. Discussion

Comparing two types of BF training, NF and EMG-BF, we identified both common and differential neuropsychological and neurophysiological changes in children with ADHD. As expected, ADHD symptoms were significantly reduced after both types of training. Improvement after training was found on all parental ratings and the BRIEF teacher rating scale. Although the number of responders who showed an improvement of at least 25% in the FBB-HKS total score was slightly higher in the NF group (53.8%) compared to the EMG-BF group (41.7%), which is in line with previous studies (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Leins et al., 2007), the NF training did not show the expected specific and stronger improvements. The medium to large effect sizes for pre-/post-changes of both groups according to parental ratings and only minor effects according to teacher ratings are roughly in line with the meta-analysis of conventional NF training reported by Sonuga-Barke et al. (2013). Although most effect sizes appeared to be slightly larger for NF than EMG-BF, the differences were not significant, even though the higher impairment scores in the NF group also left more room for improvement. Still, effect size differences computed as in Sonuga-Barke et al. (2013) reached 0.52 for total score, 0.72 for inattention, and 0.36 for hyperactivity/impulsivity on parental FBB-HKS ratings (primary outcome), reflecting some medium effect sizes in favor of NF like the corresponding ANOVA interactions, but requiring much larger sample sizes to reach statistical significance. The similarity of control and experimental protocols was a landmark feature of our study. We not only controlled for the unspecific effects due to time, attentional demands, and high-tech setting, but also for expectations, the specific BF setting, and frequent rapid feedback. The sizeable clinical improvement in both of our groups without a significant advantage for NF over EMG-BF is in line with meta-analytic evidence for smaller effects in better controlled studies, particularly those with semi-active control (Arns et al., 2009), and underlines the clinical importance of unspecific effects. The results also indicate that superior BF-based learning as in the EMG-BF control group is not sufficient for superior clinical outcomes, and clarifies that reliable BF based learning need not correlate directly with behavioral improvement. This suggests that learning success and its relation to clinical outcome depends on the trained BF modality and its specific implementation.

Considering the electrophysiological data, except for a significant reduction of theta/beta ratio in the posterior region, there were no systematic changes in the analyzed bands of the resting EEG (Figure 3.3) in the NF group means across the training. However, the course of the individual regressions converged significantly to the group mean during the course of the training in these bands (Figure 3.4; see also Liechti et al. (2012)), which may be interpreted as a “normalization”. These effects tended to be stronger during the NF training process compared to the EMG-BF training. The NF group showed a stronger normalization of the trained theta and beta bands in the ACC-I, although the difference to the EMG-BF only reached the trend level. No such normalization was found for the theta/beta ratio in ACC-I in group comparison, which may be explained by the fact that the two bands were trained separately with an “and”-relation reducing normalization effects in the NF group. The finding of a trend towards resting EEG “normalization” in a previously heterogeneous group may be explained by the fact that a complex training protocol with an alternating up- and down-regulation was
Comparison tomographic Neurofeedback and EMG-Biofeedback

used instead of a simple unidirectional theta/beta training protocol. It also suggests that a personalization of NF training by selecting protocols on individual EEG biomarkers, as proposed for example by Arns et al. (2012), could be a valuable approach. The EMG-BF group, in contrast, showed a significant increase of the beta value in the course of the training. Studies investigating visuomotor learning on the neurophysiologic level (Kranczioch et al., 2008; Studer et al., 2010) reported that tracking movements were accompanied by power decrease in the beta band during the task and increase after the task, which corresponds to our findings for the resting condition. The beta increase was found in the resting EEG in the course of the EMG-BF training and could be related to an improved functional connectivity and structural changes induced by the muscular motor training (Taubert et al., 2011). This change together with the corresponding changes for the total frequency band seem to be specific for the EMG training, given that a significant difference was found between the groups. Moreover, the significant divergence of the individual regression lines in the central region for beta and the total frequency band in the EMG group could be interpreted as changes in the motor cortex, which however seem not to be homogeneous in the EMG-BF group. The supplementary analysis of the alpha band (Supplementary Figure 3.3) also indicated prominent EMG-BF-specific changes, particularly for the mu activity over central regions specifically associated with motor processing. These changes resembled those seen for the total band, suggesting that mu activity dominated the total band effects. The baseline dependent divergence of mu activity with EMG-BF was particularly pronounced and focal over lateral and motor regions (C3, C4 and Cz) and opposite to the changes seen with NF, further supporting their specificity to motor aspects of the EMG-BF training. The complex results thus indicate that the two training programs influenced the resting EEG differentially. Changes in pre-/post-resting EEG in NF with ADHD have been reported in previous studies (e.g. Doehnert et al., 2008), but this is the first study to report the course of the resting EEG measured in each training session over the training period, thus permitting a closer monitoring of changes.

As reported by Liechti et al. (2012), learning to control artifacts might have had an influence on behavioral improvement. ADHD symptom reduction after NF was related to artifact reduction, as children obviously learned through EEG-artifact feedback how to avoid artifacts by producing less movement and sitting still. Therefore, NF indirectly included an additional motor feedback component, which might have served as an efficacious treatment factor, albeit an unspecific one, as the NF was primarily aimed at the control of brain activity. This possible confound applies not only to our complex NF training, but potentially to any type of NF or BF training with additional artifact feedback, particularly in multichannel applications, although this has never been systematically investigated. In EMG-BF, in addition, artifacts and artifact control were directly associated with the trained domain, i.e. muscle activity and fine motor control. In fact, in addition to the general artifact feedback for EEG channels, which was active in NF and EMG-BF training, the participants of the EMG-BF also received artifact feedback when a defined muscle tonus threshold was exceeded in one of the EMG channels. Improved motor skill, however, was not automatically expressed by a reduction of motor artifacts. On the contrary, depending on the trained condition, coming closer to the artifact threshold and maintaining increased motor activity just below threshold (i.e. during activation conditions) might have been a sign of improved motor control and of an effective strategy, which was accompanied by an enhanced risk of producing EMG artifacts. In consequence, in EMG-BF, significant artifact reduction was found only in the phasic deactivation condition. Given these results and the different implications of learned artifact control in both training programs, for the time being, we are unable to
establish whether the learning of artifact control is a causally mediating or an associated factor of positive behavioral effects of NF training. One limitation of our protocol was the susceptibility to artifacts which was mainly due to the large number of channels needed for source localization. However, this might have resulted in treating some behavioral aspects of the disorder in an unspecific manner by training discipline and frustration tolerance of the children. Overall, our results were dominated by the consistent artifact reduction and a general lack of substantial learning in the target region. This points out that a good artifact correction is mandatory for NF training. In our study, independent component analysis (ICA)-based eye-artifact correction combined with amplitude criteria proved to be successful; otherwise the systematic changes in artifacts would have affected at least some of the trained parameters. Further studies are needed to optimize artifact handling also with regard to frequency band and threshold settings.

On the neuropsychological level, the two groups showed similar improvements on several tests. This is in line with previous findings based on different control conditions (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009) and to a certain degree confounded with practice effects. However, the EMG-BF group showed a significantly stronger improvement in the Flexibility and the Visuomotor Precision tasks. These two tasks have a motor coordination or a motor skill component, respectively; therefore, these improvements in children who trained fine motor skills and coordination seem to reflect a specific effect of the EMG-BF training.

This finding of specific effects for EMG-BF suggests that the small sample sizes are not necessarily the reason for the poor NF-specific effects. Our results rather indicate that the clear improvement of training regulation performance in the EMG-BF but not in the NF group (Liechti et al., 2012) is likely the main reason for the absence of the expected stronger and specific effects in the NF group. This highlights the importance of including training regulation performance analyses in order to gain more solid evidence of specific effects of NF training. The most influential multicentre study, by Gevensleben et al. (2009), did not include learned regulation among its outcome measures. However, in a recent review, Gevensleben et al. (2012) discuss, among other factors, the importance of successful cortical regulation, which may account for behavioral changes, but also point out the problem of how to quantify neuroregulation. So far, only a small number of studies have reported learning of EEG regulation as a relevant objective measure for training regulation success in the course of the NF training (i.e. Drechsler et al., 2007; Gevensleben et al., 2013; Kropotov et al., 2005; Leins et al., 2007). These studies and our own findings (2012), show that it is possible to quantify the regulation performance of a BF treatment.

There are several possible explanations for the lack of learning in the NF group, such as an enhanced difficulty for children with ADHD to gain control over the activation of the ACC, or methodological and technical reasons (2012). We assume that a less demanding training protocol for the ACC training with fewer protocol alternations (activation/deactivation, tonic/phasic) might possibly result in better learning of regulation of ACC activity. Targeting a single voxel of a brain region known from literature to be clearly affected in ADHD should also be considered very critically. As suggested by its name, the sLORETA approach provides rather low spatial resolution (Pascual-Marqui et al., 1999; Pascual-Marqui et al., 1994), which for example can not clearly distinguish between activities from different ACC sub regions. This blurring, which is more pronounced for deeper sources, also implies that we trained a more extended region than our target voxel. Despite a possible localization inaccuracy and the fact that multiple nearby sources cannot be resolved, the sLORETA approach has
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Proven plausible and concordant with fMRI activations for a variety of cortical localizations including frontal ones at some depth such as the ACC (Müller et al., 2004). Consistent ACC localizations have also been reported in inhibition tasks (Fallgatter et al., 2004). sLORETA might fail, however, for more artifact-prone cortical or deeper subcortical regions. Future studies could systematically investigate training of more extended ACC regions, and of other brain regions or networks implicated in ADHD.

Variables such as self-efficacy, locus of control, achievement motivation or social reinforcement may have contributed to the acquisition of cortical regulation and might thus have influenced the outcome of NF treatment ((Drechsler et al., 2007; Monastra et al., 2002), reviews (Drechsler, 2011; Gevensleben et al., 2012; Moriyama et al., 2012)). In our study, we found no difference in the self-rated attitude towards the training between the two groups, as indicated by the children’s ratings before each training session, despite clear differences found between the groups in training regulation success.

As reported in more detail in the supplementary material, the EMG-BF, with its tonic and phasic protocols, was developed to match the NF training in terms of complexity and difficulty. In addition, parents were kept blind and did not reliably find out or assume to which treatment their child was assigned. This allowed us to control for effects generated by different expectations towards the treatment. Parents also reported very similar and positive expectations for all BF treatment protocols, indicating that an influence of negative or differential expectations on training outcomes in our study can be excluded. Also other critical factors reported to influence the results (Arns et al., 2009; Loo et al., 2005) were fully controlled, such as similar patient-therapist interaction, similar levels of cognitive training and demands on attentional processes, expectations generated by applying electrodes and being connected to a computer, additional support given to the family, and motivation and investment needed to complete the training. The EEG montage also allowed us to analyze brain processes before and during the training (see also Liechti et al., 2012). Both groups received genuine feedback and were rewarded for successful regulation, meaning that the impact of BF-generated learning was also fully controlled. However, these were not the only aspects which made this EMG-BF training interesting as a control condition for NF studies. The fact that the EMG-BF showed a specific improvement in motor coordination or motor skill tasks made it a meaningful treatment for children with ADHD, who often have deficits in these domains. This clearly puts it at advantage compared to a mere “placebo” EMG-BF training such as that used in the study by Bakhshayesh et al. (2011). It might be worthwhile to test the value of this training as a specific intervention for motor skill problems in a purely ADHD group of children diagnosed with comorbid development coordination disorder or other motor coordination problems.
3.6. Conclusion

The fact that both our NF and EMG-BF training induced similar behavioral improvements suggests that mostly unspecific effects common to both types of complex BF underlie the behavioral improvement despite some specific neurophysiological and neuropsychological effects. However, it cannot be ruled out that the training may have different specific effects resulting in a similar clinical impact. Finally, some evidence was found that the NF and EMG-BF both induce continuous systematic, but training-specific changes to the resting state.

The lack of learning to control ACC activity in the NF group and our small sample size limit the value of this study about specific effects of this training. Further studies with larger sample sizes are needed to find out more about the learning process underlying BF training with respect to different EEG, but also artifact measures. However, the EMG-BF represented a valuable control training with meaningful motor coordination and skills training for children with ADHD, which can be adopted for further NF studies, offering the possibility to avoid the use of a sham group. Finally, these results underline the importance of training regulation performance analyses and artifact control analyses in order to gain more well-founded evidence about specific effects of NF training.

3.7. Acknowledgments

Part of an SBF-funded project in the European COST B27 Action “Electric Neuronal Oscillations and Cognition (ENOC)”, this study was additionally supported by a grant from the Health Department of the Canton of Zurich. The authors are grateful to Antonia Bak, Guyslaine Thalmann, Lea Meier, Matthias Hartmann, Melanie Achermann, Nadia Mock, Silvia Brem, Stefanie Hossmann, Urs Maurer, and Yamilée Schwitter for their assistance with testing, training and data processing, and to Markus Mächler for assistance in data analysis. We also thank Robert Riener, Roland Müller, Peter Wolf and Andreas Brunschweiler for providing technical support and the editor and the anonymous reviewers for their helpful suggestions. Our gratitude also goes to the children and their families for their participation. All authors have no biomedical financial interests or potential conflicts of interest with the present project.
3.8. Supplement

This supplementary material contains additional information about the design of the EMG-BF training as an NF control condition. For more information about tomographic NF or EMG-BF training methods, please refer to Liechti et al. (2012), or Maurizio et al. (2013) respectively. In addition, supplementary analyses of the mu rhythm (alpha band 7.5 – 12.5 Hz) were done for the course of topographic resting EEG changes across all training sessions (Figure 3.3), and for baseline dependence of topographic resting EEG changes across training (Figure 3.4).

**Goal of the EMG-BF training**

- matches tomographic NF training program with tonic and phasic protocol and serves as valid control training
- specific training for children with ADHD with comorbid motor coordination problem

### Supplement Figure 3.1

Matched training programs of the two BF methods. During tonic and phasic lessons, activation and deactivation conditions were trained. According to baseline (b) values individual thresholds were determined. At the beginning of every session, a resting EEG was recorded in an eyes-open condition (eo). At the beginning of the first three sessions, the children of the EMG-BF group performed a progressive muscle relaxation (MR) without computer feedback.
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<table>
<thead>
<tr>
<th>phasic</th>
<th>Neurofeedback training: brain activity in the anterior cingulate cortex (ACC)</th>
<th>EMG-Biofeedback training: arm muscle activity of the musculus digitorum</th>
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<tr>
<td>activation</td>
<td>negative shift of slow potential</td>
<td>increase of muscle activity of one arm</td>
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<tr>
<td>deactivation</td>
<td>positive shift of slow potential</td>
<td>decrease of muscle activity of one arm</td>
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<tr>
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<td></td>
<td>- increase of beta activity (14-20Hz)</td>
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<tr>
<td></td>
<td>- increase of theta activity (4-7.5Hz)</td>
<td>- reduction of muscle activity while drawing mandalas</td>
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<tr>
<td></td>
<td>- reduction of beta activity (14-20Hz)</td>
<td>- reduction of muscle activity of one arm at rest</td>
</tr>
</tbody>
</table>

Supplement Figure 3.2 Matched training procedure of EMG-BF and tomographic NF

A) Course of topographic resting EEG changes across all training sessions

- NF
- EMG-BF
- NF vs EMG-BF

Supplement Figure 3.3 Course of topographic resting EEG changes across all training sessions (Figure 3.3) and baseline dependence of topographic resting EEG changes across training (Figure 3.4) in the mu or alpha band (7.5 – 12.5 Hz) during eyes-open resting condition.

Pictured are the scalp electrodes (maps), the three sagittal regions (f: frontal, c: central, p: posterior), the pool across all channels (all), and the ACC voxel (vector length: ACC-I, z-component of vector: ACC-z) for the NF and EMG-BF group, and the comparison between the groups (NF vs EMG-BF). A) The blue/red colors indicate declining/increasing group mean slopes, and the color levels indicate the significance levels of the corresponding statistic. B) The blue/red colors indicate converging/diverging of the individual regression, and the color levels indicate the significance levels of the corresponding statistic. For Bonferroni correction accounting for multiple independent testing for 24 electrodes (which is actually not fully given and thus too strict for EEG analysis), a p level of p = 0.00213 would apply.
4. General Discussion

The main goal of the present thesis was to examine specific effects of a tomographic neurofeedback (NF) training. For this purpose an electromyographic biofeedback (EMG-BF) program that parallels a complex NF training comprising both NF training protocols, the tonic frequency bands training and the phasic slow cortical potentials (SCP) training, was developed.

4.1. Specific Effects of Biofeedback Training

The comparison between the NF and EMG-BF showed common and differential neuropsychological and neurophysiological changes in children with Attention-deficit/hyperactivity disorder (ADHD) (Figure 4.1). Looking at the reduction of ADHD symptoms according mainly to the parents rating scales, both groups showed similar ameliorations. These ameliorations could be related to the reduction of the artifact in the course of the training, which was more evident in the NF as in the EMG-BF.

<table>
<thead>
<tr>
<th>pre</th>
<th>post</th>
<th>Neurofeedback</th>
<th>g x t</th>
<th>EMG-Biofeedback</th>
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<td>FBB-HKS Hyperactivity/Impulsivity</td>
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<tr>
<td>FBB-HKS Total score</td>
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<tr>
<td>KITAP: Test for Attentional Performance for Children. Significant pre- and post-training improvements are indicated at the margin of the graphs and group by time interaction in the columns indicated with “g x t” by: ° p&lt;0.1, * p&lt;0.05, ** p&lt;0.01</td>
<td></td>
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</tbody>
</table>

Figure 4.1 Graphic representation of the main results from table 3.2 and 3.3. The primary outcome measure FBB-HKS (top) represents a parent-rated DSM-IV checklist (severity scores). The selected neuropsychological test (bottom) contains a motor skills or coordination component. KITAP: Test for Attentional Performance for Children. Significant pre- and post-training improvements are indicated at the margin of the graphs and group by time interaction in the columns indicated with “g x t” by: ° p<0.1, * p<0.05, ** p<0.01
As discussed in more detail in study 2 for the EMG-BF group artifacts feedback was given additionally when defined muscle tonus threshold was exceeded in one of the EMG channels, which probably confound the artifact reduction in this group. Finally all biofeedback (BF) trainings including an artifacts control for promoting sitting still and less movement have an additional motor feedback component, which may act as an efficacious unspecific treatment factor. That is why it had to be considered in the analyses of BF treatments. Although not significant, most effect sizes appeared to be slightly larger for NF than for EMG-BF, which would probably reach a statistical significance with larger sample sizes. This might indicate that a directed training of an ADHD affected brain region would achieve more stronger and specific ameliorations of the related ADHD symptoms.

The neurophysiological results indicate that the two training programs influenced the resting electroencephalogram (EEG) differentially. The trained theta and beta bands in the anterior cingulate cortex (ACC) of the NF group show a stronger convergence of the initial heterogeneous individual value to a common value. The alteration between regulation of activation and deactivation conditions presented in this NF tonic protocol, instead of a simple unidirectional theta/beta training protocol, could be the reason for this homogenization of theta and beta power throughout the training. The EMG-BF group, in contrast, showed a significant increase of the beta power during rest in the course of the training, which could be related to an improved functional connectivity and structural changes induced by the muscular motor training (Taubert et al., 2011). In addition, in accordance with the hypotheses, this group showed a significantly stronger improvement in neuropsychological performance tests comprising motor coordination or motor skill components. This result reflects a specific effect of the EMG-BF training aiming to train these motor components.

4.2. Significance of Electromyographic Biofeedback as Control Condition for Neurofeedback

The phasic and tonic EMG-training tasks closely match the NF training conditions and allow to use NF software and parallelized training protocols. The fact that isometric force and small scale movements were used for EMG-BF tasks, minimized movement artifacts and allowed a concomitant EEG recording. This permitted to monitor EEG parameters during EMG-BF at all phases of the training and to compare this neurophysiological measurement to the tomographic NF data. In addition, the use of an EEG montage in the EMG-BF group and of sham electrodes placed at the arm of the NF group participants facilitates blinding in the study. As reported earlier, parents did not find out accurately or assume to which treatment their child was assigned.

The training performance of motor control improved during the EMG-BF training, although training success differed between task conditions. The course of the motor control throughout the training demonstrates that for three of four conditions the children continuously increased their performance from the beginning to the end of the training. In the original dissertation by Bakhshayesh (2007), the EMG-BF group underwent training using only one protocol condition by relaxing the forehead muscles. This training design did not show continuous learning after the initial successful sessions. For this reason, the fact that no ceiling seemed to be reached early in our results
indicates that the method is challenging enough to allow continuous learning, suitable to match a corresponding NF training. This EMG-BF training allows to control many critical unspecific factors associated with NF training (Arns et al., 2009; Loo et al., 2005), such as patient-therapist interaction, level of attentional demands, learning, expectations generated by applying electrodes and being connected to a computer, additional support given to family, and motivation and effort needed to complete the training. In addition, the setup of this control training facilitates blindness of participants and parents, which allows to control effects generated by different expectations towards the BF treatments. Finally, the reported medium to large effect sizes for pre-/post-changes of ADHD symptoms according to parental ratings are similar to the corresponding (uncontrolled and not blinded) effects as reported for NF in recent meta-analyses. Similarly, the improvement in motor coordination or motor skill tasks makes this complex EMG-BF a more meaningful control condition rather than a sham control group and supports the feedback of muscle activity instead of other possible physiological parameters such as skin conduction or heart rate variability. For these physiological parameters deviance due to ADHD is less established, making them less suitable for the creation of clinically meaningful regulation training. In addition to these parameters a good parallelization of a complex NF design with phasic and tonic protocol would be difficult.

4.3. Motivation and compliance of the patients during the training

Variables such as self-efficacy, locus of control, motivation or social reinforcement contribute to the acquisition of regulation skills and might thus influence the outcome of the BF treatments (Drechsler et al., 2007; Monasta et al., 2002), reviews (Drechsler, 2011; Gevensleben et al., 2012; Moriyama et al., 2012)). As reported for study 2 (Figure 3.5), no group difference was found in the self-rated attitude towards the training and all ratings were in the positive range, as indicated by the children’s ratings before or after each training session. Motivation ratings decreased significantly throughout both types of training (Figure 4.2), which is probably related to a decreased interest and increased monotony towards the end of the training, but the ratings remained in the positive range also in the final phase of the training. Probably this phenomenon was reduced by the use of different training animations (Figure 4.3) and a reward system for the individual rewards the children received after each session (Figure 4.4). Some of the animations were linked to a child’s adventure story combined with specific duties the participant had to master throughout the training in order to get ahead in the writing

Figure 4.2 Subjective motivation’s rating of the training programs by the NF and EMG-BF groups throughout the training session. NF: $R^2 = 0.371$, $p = 0.007$  
EMG-BF: $R^2 = 0.430$, $p = 0.003$
process of the story. On the other hand, all visual displays used in these studies were based on purpose on the same principle, namely bars that had to be regulated on the left and right side of the animations for the tonic condition, and a flying ball that had to be moved upwards below the animations in the phasic condition. Correct regulation in the required directions was rewarded by getting points and was fed back by the positive outcome of various animations regarding the child’s story or by the enhanced quality of the picture on the screen while watching a film (Figure 4.3 B). This basic continuity of the animations was maintained throughout the training because as reported by Liechti et al. (2012) learning process and measure of self-regulation could be compromised by high variation within animations or actions presented on the screen (e.g. films).

The reward system was illustrated as a castle with rooms representing the training lessons. For each lesson the children received colored sticker points that were to be stuck on the reward system, with different colors representing good training performance and compliant participation. After a maximum of five colored sticker points gained throughout lessons they received one sticker representing the main character of the story. In the end a defined number of obtained stickers could be converted to little gifts. This surely contributed substantially to maintain the children’s motivation throughout the training.

Figure 4.3 Visual display of the feedback training animation. A) Example of scenes of a child’s adventure story presented to the children. B) Example of tonic and phasic feedback in the biofeedback software SAM for activation (red frame for tonic, red bar for phasic) and deactivation (blue frame for tonic, blue bar for phasic) condition. Usually points are presented in the upper right corner of the feedback screen. Beside the illustrated example of the different animations used in the training, all displays were based on purpose on the same principle. In the tonic protocol the vertical position of the ball represented the deflection of the SCP in NF and muscle activity in EMG-BF. Baseline values (mean value across 0.5-2s of the trial) are indicated by white horizontal lines. In the phasic protocol the vertical position of the ball represented the deflection of the SCP in NF and muscle activity in EMG-BF. Baseline values (mean value across 0.5-2s of the trial) are indicated by white horizontal lines. The desired directions of change in activity for the respective physiological parameter are indicated by arrows (presented are the two NF conditions).
The fact that only two subjects dropped out, one of them before starting the training, shows that this training design is feasible for children with ADHD and that the compliance of the patients was good. The child who dropped out during the training could be indicative of the fact that one exclusion criteria for these trainings could be oppositional behavior of the children, which could induce to insufficient compliance.

From our results indicating that also unspecific effects such as artifacts control seem to contribute to the clinical improvement for both trainings, we can conclude that further studies are needed for the detection of the specific mechanism of NF to allow a meaningful implementation of the treatment for clinical purpose. The presented design is technically complex. It proved suitable for our research purpose, but for clinical use it should be clearly simplified.

4.4. Limitations

The small sample size of the two groups is one of the major limitations of this study caused by the time-consuming and demanding setup of these two BF trainings. These small sample sizes reduced the statistical power of the group comparisons, particularly regarding assumed group-specific effects. However, the significant specific effect of EMG-BF on the neuropsychological performances tests with motor component suggests that this fact is not necessarily the only reason for the poor NF-specific effects. Probably the absence of improvement of training regulation performance in the NF group, but not in the EMG-BF group, is the main reason for the absence of the expected stronger and specific effects in the NF group. In order to express possible explanations for this failure of learning in the NF group, several reasons should be taken into consideration. Children with ADHD could present particularly enhanced difficulty to gain control over the activation of the ACC. In addition, the versatile protocols (activation/deactivation, tonic/phasic) could essentially complicate the learning success of the children.
Technical problems may also have contributed, such as low signal-to-noise ratio for Standardized Low-Resolution Electromagnetic Tomography (sLORETA) in single case analyses (Gevensleben et al., 2013). Regarding the SCP protocol, the use of a high-pass filter of 0.1 Hz instead of 0.01 Hz typically used in other studies for removing slow wave artifacts could have compromised the SCP components and thus unnecessarily may have complicated the learning of SCP control (for a detailed discussion, see Liechti et al. (2012)).

4.5. Outlook

For further studies it is important that continuous learning of regulation of brain activity can be achieved and shown for different NF types and protocols throughout the training. This would enhance the explanatory power of the present study and exhaust the possible analyses of specific and unspecific effects in this complex study design. The sophisticated study design with a comparison of two different BF trainings was well chosen. Using multichannel recordings for both NF and EMG-BF allowed to examine and to compare training-specific regulation mechanisms also in terms of brain topographies during the training and changes of the resting EEG throughout the training lessons.

A first approach to enhance the learning improvement in the NF group could be a simplification of the training protocol with fewer conditions. Based on our resting EEG results, showing a normalization of the trained theta and beta bands in the ACC for the NF group to an mean value, a personalization of NF training in the tonic protocol by selecting only one condition based on the individual initial value, as proposed for example also by Arns et al. (2012), could make sense. This reduction to one condition in the tonic protocol could also contribute to simplify the whole training procedure for the participant.

In addition, aiming at a higher positive reward rate of 60-70 % in the training as proposed by Heinrich et al. (2007), instead of the 50 % for phasic and 25 % for tonic in the NF group, could enhance the motivation for the training of the participants and thereby have a positive impact also on the learning process. However, since the participants of the two groups did not indicate motivational difference respective to the subjective rating scale of the training, although the positive reward rate was significantly higher in the EMG-BF group, the higher positive rate does not seem to have a major influence.

A different approach could be the training of a different brain region or EEG parameter which may lead to higher regulation learning: for example, a different brain region also assumed to be involved in ADHD, such as the dorsolateral prefrontal cortex, which could be easier to regulate for children with ADHD than the ACC. Also reasonable could be the evaluation of standard Cz NF, as initially planned, compared to EMG-BF, but recording from multiple channels for analysis purposes. Some studies showed that children with ADHD could learn cortical regulation based on the feedback of the Cz electrode. In case of substantial learning of cortical regulation, it would be interesting to use the extra channels for topographical maps and consequently for source localization as presented by Gevensleben et al. (2013) for the SCP training. The identified activations of fronto-parietal areas through the SCP training of the Cz-electrodes in Gevensleben et al. (2013) should be compared to the brain activation during the phasic training of the EMG-BF to prove if this findings are really involved in the networks.
contributing to the generation of SCPs or if unspecific brain network, for example which are involved in the signal processing of the feedback signal, are responsible for these findings. Similar analyses would be also interesting for the tonic protocol.

Further approaches based on different brain signal processing could be also interesting. Instead of the feedback of a single channel as characterizes the classical NF or of an estimate activity at some brain voxel through distributed inverse solution as in the tomographic NF, different or additional EEG methods could be taken into consideration for EEG feedback signal processing, such as spatial factor analysis, cluster or filters (Michel et al., 2009). As proposed by Congedo (2006), for instance, a methodical adaptation of tomographic NF training involving spatial filter or principal component analysis could be meaningful for a better spatial resolution and/or an enhanced signal-to-noise ratio.

Also other neuroimaging techniques with more directed and reliable training of brain region than EEG could be considerable, such as near infrared spectroscopy (NIRS) or real-time functional magnetic resonance imaging (fMRI), both relaying on the blood oxygenation level dependent (BOLD). NIRS has the benefit to be available and more cost effective as real-time fMRI, but is restricted to effect only in the cortical areas. Most NIRS studies in ADHD patients reported an attenuated oxygen metabolism during different experimental paradigms within the frontal lobe (Ehlis et al., 2013). This dysfunction could possibly be alleviated by a NIRS NF training in this brain region for ADHD. A recent study on healthy adults showed that a NF could train the left motor area more specifically and focused than did the sham control group over eight training sessions (Kober et al., 2013). This demonstrates the feasibility of this NF technique, which could also be applied as an alternative or additional intervention in ADHD patients. Compared to the EEG the advantages are that the montage of the NIRS optodes is very fast and that the sensitivity to motion-artifacts is lower allowing measurements with higher degree of movement (Kober et al., 2013). Real-time fMRI, on the other hand, has high spatial resolution and whole-brain coverage overcoming the limitation of EEG. However, the temporal delay of the hemodynamic response as by the NIRS, which is the delay between onset of neuroelectric activity and delivery of blood to active neuronal tissues, amount up to 6s. Based on operant conditioning learning an increase of the delay between the activity and the feedback/stimulus diminishes the speed of learning, which should be temporally closer in order to be more effective (Sherlin et al., 2011). Nonetheless, several studies showed learning of self-regulation of local BOLD response in different brain areas and progress in the related behavioral effects such as modulation of pain, reaction time, linguistic or emotional processing in healthy and/or patient (for a review see Weiskopf, 2012). Also, a combination of the two neuroimaging methods is supposable. Studies analyzing EEG SCP regulation in the fMRI showed the involvement of cortical and subcortical structures (Hinterberger et al., 2003; Hinterberger et al., 2005; Strehl, Trevorrow, et al., 2006). A simultaneous on-line recording and feed back of the high spatial resolute real-time fMRI signal and of the high temporal resolute EEG signal would be complementary and could be exploited in the training process.

In addition, using such BF training data could pave the way to analyze and gain further evidence about learning processes related to the feedback related negativity (FRN). FRN is an ERP modulation which follows the display of negative feedback and is assumed to be involved in the learning process. As reviewed by Sherlin et al. (2011) NF, but also all other BF techniques, is based on the operant learning principle. A
distinct behavior can be influenced as consequence of rewards or punishments; the question of how such learning occurs is formalized by reinforcement learning theories. A relationship between strength of the FRN and learning success was found by Santesso et al. (2008) through a smaller (more positive) FRN by learners compared to non-learners. Other factors such as reward probability and behavior change through experience also seem to be related to FRN (Walsh et al., 2012). Due to our different feedback forms (continuous feedback, transfer), feedback animations, feedback conditions, feedback parameters as well as different training success within and between the subjects during prolonged training periods a lot of information regarding these topic could be analyzed and gathered.

For the EMG-BF training it could be worthwhile to test the value of this training as a specific intervention for motor skill problems in a purely ADHD group of children diagnosed with comorbid development coordination disorder or other motor coordination problems. Despite the high scientific value of the sophisticated BF designs presented here, for clinical applications or as independent treatment and home use the BF setups need to be adapted and simplified regarding the equipment and complexity of the protocols.

4.6. Conclusion

With the EMG-BF training a differential procedure could successfully be designed and adapted. Without compromising the potential for successful and specific learning, this training condition closely matches the complex training protocols used for NF training in our research and thus serve as near-optimal control condition. The comparison of a tomographic NF training with this EMG-BF training showed similar behavioral improvements suggesting that principally these unspecific effects, common to both types of complex BF and for which the presented control condition had to control, underlie the behavioral improvement. However, it cannot be excluded that similar clinical impact results from different specific effects. The training-specific, continuous and systematical changes in the resting state and some specific neurophysiological and neuropsychological effects found could support this presumption.

The absence of improvement in regulation learning of the ACC activity in the NF group and the small sample size of the two groups limit the value of this study about specific effects. Further studies with larger sample sizes and adapted NF methods are recommended to find out more about the learning process underlying different BF training. However, the EMG-BF seems to offer a possibility to avoid the use of sham control condition for further NF studies because it not only represents a satisfying control condition for unspecific effects but also a meaningful motor coordination and skills training for children with ADHD.
5. References


References


References


APPENDIX

List of Abbreviations

ACC  anterior cingulate cortex
ACC-I vector length of the activity in the ACC voxel
ACC-z amplitude of the z-component of the activity in the ACC voxel
ADHD attention-deficit/hyperactivity disorder
ANOVA analysis of variance
BF biofeedback
BOLD blood oxygenation level dependent
BRIEF behavior rating Inventory of executive function
BRIEF behavior rating inventory for executive functions
CBCL child behavior checklist
CNV contingent negative variation
CPRS Conners’ parent rating scale—revised
CTRS Conners’ teacher rating scale—revised
DCD developmental coordination disorder
DSM-IV diagnostic and statistical manual of mental disorders IV
ECG electrocardiogram
EEG electroencephalogram
EMG electromyogram
EMG-BF electromyographic biofeedback
EOG electrooculogram
ERP event-related potential
ES effect size
FBB-HKS German standardised DSM IV (parent) questionnaire for ADHD
FFT fast Fourier transformation
fMRI functional magnetic resonance imaging
FREQ (theta-beta) frequency
FRN feedback related negativity
HAWIK-IV wechsler intelligence scale for children IV
Hz hertz (cycles per second)
ICA independent component analysis
IQ intelligence quotient
KITAP computerized test for attentional performance for children
LORETA low resolution electromagnetic tomography
MANOVA multivariate analysis of variance
MNI Montreal neurological institute
MRI magnetic resonance imaging
NF neurofeedback
NIRS near infrared spectroscopy
PACS parental account of children’s symptoms (semistructured clinical interview)
SAM self-regulation and attention management
<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>SCP</td>
<td>slow cortical potential</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>SDQ</td>
<td>strength and difficulties questionnaire</td>
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<tr>
<td>sLORETA</td>
<td>standardized low resolution electromagnetic tomography</td>
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<tr>
<td>TAP</td>
<td>test for attentional performance</td>
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Publications


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