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Evaluation of neurofeedback in ADHD: The long and winding road

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ABSTRACT

Among the clinical applications of neurofeedback, most research has been conducted in ADHD. As an introduction a short overview of the general history of neurofeedback will be given, while the main part of the paper deals with a review of the current state of neurofeedback in ADHD. A meta-analysis on neurofeedback from 2009 found large effect sizes for inattention and impulsivity and medium effects sizes for hyperactivity. Since 2009 several new studies, including 4 placebo-controlled studies, have been published. These latest studies are reviewed and discussed in more detail. The review focuses on studies employing (1) semi-active, (2) active, and (3) placebo-control groups. The assessment of specificity of neurofeedback treatment in ADHD is discussed and it is concluded that standard protocols such as theta/beta, SMR and slow cortical potentials neurofeedback are well investigated and have demonstrated specificity. The paper ends with an outlook on future questions and tasks. It is concluded that future controlled clinical trials should, in a next step, focus on such known protocols, and be designed along the lines of learning theory.

Attention-Deficit/Hyperactivity Disorder (ADHD) has become one of the most common neurodevelopmental and psychiatric disorders of childhood. The general rate of prevalence is reported between 3% and 7% of school age children (Cormier, 2008). In 40–60% of all cases ADHD persists into adolescence and adulthood (Faraone, Biederman, & Mick, 2006). Currently, the disorder is primarily diagnosed by referring to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or the International Statistical Classification of Mental Disorders (ICD-10). According to the DSM-IV, the disorder presents itself in three primary subtypes: predominantly inattentive type, predominantly hyperactive-impulsive type and the combined type. Therefore the core symptoms of ADHD consist of inattention, impulsivity and hyperactivity.

Currently, both stimulant medication and behaviour therapy are the most often applied and accepted treatments for ADHD. However, recent large-scale studies and meta-analyses have demonstrated limitations of these treatments. For example, limited long-term effects of stimulant medication (possibly the result of an up-regulation of the Dopamine Transporter (DAT) (Wang et al., 2013)) and behaviour therapy have been reported (Molina et al., 2009; Riddle et al., 2013). It hence becomes obvious there is a need for new treatments for ADHD with better long-term effects, which also explains the recent research interest in neurofeedback as a treatment for ADHD. In the following, neurofeedback as a treatment for ADHD will be reviewed in more detail, where we will briefly review the history of neurofeedback, followed by a more systematic overview of the current state of neurofeedback for the treatment of ADHD.

1. History of neurofeedback

Neurofeedback, which is a behaviour therapy technique to teach or improve self-regulation of brain activity, can already be traced back to the early 1930s. In these days the first observations were made that the EEG alpha-blocking response could be classically conditioned (Durup & Fessard, 1935; Loomis, Harvey, & Hobart, 1936), which was more systematically investigated and confirmed in the 1940s (Jasper & Shagass, 1941; Knott & Henry, 1941). These early studies clearly demonstrate that principles of classical conditioning can be applied to EEG parameters such as the alpha blocking response.

The first successful application of EEG conditioning with clinical effects, namely anticonvulsive, was reported in the early 1960s by Sterman. This work involved the training of the sensori-motor rhythm also called SMR, in the cat. This EEG rhythm was previously

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associated with stereotyped postures characterised by a complete cessation of spontaneous activity and immobile behaviour in the cat (Wyrwicka & Sterman, 1968). Furthermore, training of this EEG rhythm during wakefulness resulted in increased sleep spindle density during sleep (an EEG rhythm with the same frequency and topographical distribution as SMR) and improved sleep quality in cats (Sterman, Howe, & Macdonald, 1970), also replicated in humans (Hoedlmoser et al., 2008; Schabus et al., this issue). In a serendipitous finding the anticonvulsant effects of operant conditioning of this SMR rhythm in cats exposed to the pro-convulsant Monomethylhydrazine were demonstrated (Sterman, LoPresti, & Fairchild, 2010) followed by replications of these effects in humans (reviewed elsewhere: Tan et al., 2009).

1.1. History of frequency band neurofeedback protocols in ADHD

In 1976, Lubar described the application of SMR neurofeedback in a child with hyperkinetic syndrome and found improvements in hyperactivity and distractibility (Lubar & Shouse, 1976). In this study Lubar employed an ABA design, and found that symptoms worsened when reversal training was employed. These findings were subsequently replicated several years later in a larger open label study (Shouse & Lubar, 1979). These studies can now be considered the earliest demonstration of clinical effects of neurofeedback in what is now called ADHD. Alpha enhancement neurofeedback (6–13 Hz) protocols have also been tested in these earlier years, but failed to find a specific effect on hyperkinetic behaviour (Nall, 1973).

In this same period Adey and his group at UCLA were the first group to collect a normative EEG database and using the first IBM computers applying techniques such as the Fast-Fourier Transform to EEG data, which we now refer to as quantitative EEG or QEEG (Arns & Lyle, 2011). This sparked a wealth of research, where groups of patients were analysed and compared against groups of healthy people. For ADHD this resulted in an often reported group average finding, namely that of excess theta and sometimes decreased beta (reviewed and summarised in Arns, Conners, & Kraemer, 2012). Based on these findings Lubar proposed the Theta/Beta EEG ratio (TBR; often defined as 4–8 Hz (Theta) over 13–21 Hz (Beta)) as a measure that could differentiate ADHD patients from healthy children (Lubar, 1991). This measure has also often been applied as a target for neurofeedback, where children are taught to decrease the excess theta and increase beta EEG activity at fronto-central locations.

The first randomised controlled trial (RCT) comparing neurofeedback to a waiting list control group in ADHD employing training of this TBR found improved cognitive measures (attention and IQ) (Linden, Habib, & Radojevic, 1996). Around the same time several non-randomised studies compared the effects of TBR neurofeedback to stimulant medication and in general found that the effects of neurofeedback were at least comparable to stimulant medication on measures of inattention and impulsivity (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Monastra, Monastra, & George, 2002; Rossiter, 2004; Rossiter & La Vaque, 1995), and these effects persisted after medication wash-out only for the group that also received neurofeedback (Monastra, Monastra, & George, 2002), discussed in more detail in section 2.2.

1.2. History of slow cortical potentials (SCP) protocols

The Contingent Negative Variation (CNV), first described by Walter (1964; Walter et al., 1964), is another well known EEG signature that can be used for self-regulation treatment. This very slow activity is characterised by a negative shift in the EEG, in anticipation of an expected event, e.g. waiting for the traffic light to turn green. The amplitude of this negative shift is a reflection of the resources allocated by the brain to prepare an adequate motor or cognitive response. Already in 1966, McAdam, Irwin, Rebert, and Knott (1966) described that subjects could exert 'voluntary control' over this EEG activity ('*. . .were able to control the amplitude of the contingent negative variation "at will"*.' (McAdam et al., 1966, p. 195)). Later, Elbert and Birbaumer pioneered the first studies on voluntary control of slow cortical potentials (SCP) employing a neurofeedback procedure, with the goal of investigating the functional relationship between SCP and performance during a signal detection task (Elbert, Rockstroh, Lutzenberger, & Birbaumer, 1980; Lutzenberger, Elbert, Rockstroh, & Birbaumer, 1979). Based on the observation that pro-convulsive procedures such as hyperventilation result in increased surface-negativity and anticonvulsants induce decreased surface-negativity, this SCP procedure was investigated in drug refractory epilepsy patients. As a part of preparatory work for this study, SCP neurofeedback was compared to alpha-enhancement neurofeedback, and only patients who received SCP neurofeedback demonstrated a significant reduction in seizure frequency (from: Rockstroh et al., 1993). Based on the observation of reduced CNV in ADHD (Banaschewski & Brandeis, 2007), probably reflecting deficient regulation of energetic resources, SCP was hypothesised to be beneficial for children with ADHD. In 2004, Heinrich and colleagues published the first application of SCP neurofeedback in the treatment of ADHD where reductions in the severity of ADHD were accompanied by an increase of the CNV (Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004).

2. Current state of neurofeedback in ADHD: outcome and specificity

In recent years, an increasing number of well-controlled studies have been conducted to evaluate the effects of neurofeedback in the treatment of ADHD (also see: Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Gevensleben, Rothenberger, Moll, & Heinrich, 2012). Most studies have applied TBR, SMR and/or SCP protocols in the treatment of ADHD.

Previous reviews have criticised the older neurofeedback research of methodological limitations (such as a lack of randomisation) and lack of an adequate control group. Since neurofeedback requires many treatment sessions (30–40 session) and thus implicates a substantial amount of client-therapist interaction, non-specific effects as in any other therapeutic relation occurs, and planned control groups should control for such non-specific factors. Non-specific effects could consist of cognitive training by having a child focus on a computer screen for 30–40 sessions, a child improving as a result of the many occurences of positive feedback shown on the screen as well as the verbal reinforcements provided by the therapist, etc. In recent studies, several different designs have been employed for investigating the efficacy of neurofeedback and controlling for these non-specific effects. Conceptually we will divide these into the following control conditions:

- Semi-active control conditions (section 2.1): These studies have employed a control condition aiming at controlling for non-specific effects of neurofeedback such as the amount of client-therapist interaction, time committed, etc. For example a cognitive training task that requires the same amount of time interacting with a computer, or muscle-training biofeedback, which is identical to the neurofeedback condition except for the origin of the trained parameter (muscle vs. brain). These control conditions thus aim to control for the non-specific effect, but are not expected to have a clinically meaningful effect in ADHD. The hypothesis behind these studies is that neurofeedback has a significantly larger effect on inattention, impulsivity and hyperactivity as compared to this semi-active control group.

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- Active control conditions (section 2.2): These studies have employed a control condition known to have clinical effects on ADHD. For example a comparison of two different neurofeedback protocols, or a comparison of neurofeedback with medication. Issues regarding specificity of neurofeedback will be discussed further in section 2.3.
- Placebo control conditions (section 2.4): These designs are often regarded as the gold standard in intervention research, and consist of a control condition where everything is identical, except that in this case the feedback is not related to the brain activity of the subject. Using this control condition will also allow blinding the treatments thereby controlling for unspecific expectancy effects. As will be discussed in more detail in section 2.4 such designs have methodological problems in the application of neurofeedback.

Finally, in section 2.5 comparisons of effect sizes from meta-analyses for neurofeedback and medication will be presented. In the following we will only focus on randomised studies.

2.1. Outcome of semi-active control conditions

Though there are different ways of applying neurofeedback, partly depending on the neurofeedback protocol and electrode site used but also concerning the way the training is introduced to the participants, addressing transfer into daily life, etc., the results of studies conducted up to 2009 are rather coherent, as confirmed in a meta-analysis by Arns et al. (2009). This meta-analysis incorporated 15 studies (of which six RCTs: Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Holtmann et al., 2009; Leins et al., 2007; Lévesque, Beauregard, & Mensour, 2006; Strehl et al., 2006) and found that neurofeedback resulted in large and clinically relevant effect sizes for inattention and impulsivity and a medium effect size for hyperactivity. For RCTs that also performed follow-up to 6 months or 2 years it was demonstrated that the effects did not disappear with time, and a tendency for further improvement across time for hyperactivity/impulsivity (Gani, Birbaumer & Strehl, 2008; Gevensleben et al., 2010; Leins et al., 2007; Strehl et al., 2006, also see: Arns & Kenemans, 2012, figure 2 for a summary). Recently, Sonuga-Barke et al. (2013) published a systematic review and meta-analysis on randomised controlled trials in the treatment of ADHD that also included neurofeedback. For so-called most-proximal ratings (typically from parents) they demonstrated comparable ES to the meta-analysis by Arns et al. (2009), whereas for 'probably blinded' ratings (primarily teacher ratings, there was a tendency ($p = .07$). Arns and Strehl (2013) reflected critically on the procedure and criteria of this meta-analysis (e.g., change of medication status not taken into account, selection of control condition, not focussing on standard training protocols). If only RCTs are considered where TBR or SCP training was applied and attention training or EMG biofeedback training used as control conditions, a significant effect is also obtained for teacher ratings (Arns & Strehl, 2013). Therefore, it may be concluded that meta-analyses substantiate at least medium effects for the TBR and SCP neurofeedback protocols on ADHD symptoms.

Up to now, four RCTs have been published either using a computerised attention skills training (Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Holtmann et al., 2009; Steiner, Sheldrick, Gotthelf, & Perrin, 2011) or an electromyogram (EMG)-based biofeedback training (Bakhshayesh et al., 2011) as a control condition. In all studies, except Holtmann et al. (2009), neurofeedback training effects were greater than for the control condition with respect to ADHD symptoms (typically medium ES) according to parent and also largely teacher ratings. Note that these control groups are considered semi-active control groups, and thus the reported medium ES are rather conservative, due to the control groups also having clinical effects with a small ES. In Holtmann et al. (2009), where an inhibition-related effect of reduced impulsivity errors for neurofeedback was obtained, the neurofeedback training consisted of 20 training sessions, which is generally considered a low number of sessions, known to have smaller effects (Arns et al., 2009). In the largest RCT to date, superiority of neurofeedback training (compared to attention skills training) was confirmed at six-month follow-up (Gevensleben et al., 2010) and changes of EEG and ERP measures in the expected direction (Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Wangler et al., 2011).

2.2. Outcome of active control conditions

Comparisons of TBR neurofeedback to SCP neurofeedback revealed (on average) comparable effects at the behavioural level in ADHD, with no differential effects on inattention, impulsivity and hyperactivity (Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Leins et al., 2007). Recently, Gevensleben et al. (2013) demonstrated an advantage of SCP training in reducing associated ADHD behaviour in children with tic disorders over a theta/low-beta (12–15 Hz) training, mainly for the hyperactive/impulsive symptom domain as transfer into daily life targeted inhibition of behaviour. This may hint to evidence for specific effects at the behavioural level from comparing different neurofeedback protocols, but this requires further research.

Several studies directly compared the efficacy of neurofeedback to stimulant medication. The earlier studies already mentioned under 1.1, which had also been considered in the meta-analysis (Arns et al., 2009; Fuchs et al., 2003; Monastra et al., 2002; Rossiter, 2004; Rossiter & La Vaque, 1995), mostly found comparable effects of neurofeedback and methylphenidate for measures of inattention, impulsivity and hyperactivity. However, none of these studies used randomised group assignment, and families self-selected their preferred treatment. According to typical design requirements this may limit the conclusions from these studies but it has to be considered that such a strategy may be a viable alternative because it maximises expectancy effects in both groups. Recently, two RCTs have been published where neurofeedback was compared to methylphenidate (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). In both studies, methylphenidate was not superior to neurofeedback training, confirming the findings from the above non-randomised studies. In Meisel et al. (2013), significant pre-post academic performance improvements were obtained only in the neurofeedback group. The low sample sizes from these studies do not allow any conclusions about the equivalence of medication with neurofeedback. However, the consistency of results of these six studies comparing methylphenidate to neurofeedback is promising and awaits further confirmation from new studies and meta-analyses.

2.3. Evidence of specificity based on neurophysiological effects

Outcomes of neurofeedback have also been observed at the neurophysiological level and may underline the specificity of neurofeedback treatment. Protocol-specific effects on event-related potential (ERP) components in attention tasks have been reported. For example, the contingent negative variation (CNV) increased after SCP training (Heinrich et al., 2004; Wangler et al., 2011). Mayer, Wyckoff, and Strehl (2012) observed an approximation of CNV to levels of a healthy comparison group after 15 sessions of SCP neurofeedback in adults with ADHD. Effects on ERPs, which reflect neuropsychological processes and often

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deviate in ADHD (Banaschewski & Brandeis, 2007; Barry, Johnstone, & Clarke, 2003), have also been observed after neurofeedback (Arns, Drinkenburg, & Kenemans, 2012; Holtmann et al., 2009; Kropotov et al., 2005). Changes in resting EEG power have been described (e.g., decreased theta (4–8 Hz) after TBR neurofeedback: Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Monastra et al., 2002) and increase of alpha activity after SCP training (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008), although changes in resting EEG do not necessarily correspond to the neurofeedback protocol applied (Arns, Conners, & Kraemer, 2012; Arns, Drinkenburg, & Kenemans, 2012; Egner, Zech, & Gruzelier, 2004; Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009). Furthermore, effects of neurofeedback on neural substrates of selective attention imaged with fMRI have been reported in ADHD (Lévesque et al., 2006).

Neurophysiological measures such as ERP and EEG measures have been associated with clinical outcome to neurofeedback. For example, pre-treatment alpha and CNV predicted about 30% of the variance of the success of SCP neurofeedback (Wangler et al., 2011) and pre-treatment theta explained about 20% of the outcome to TBR neurofeedback (Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009), further evidenced by the fact that pre-selection on this TBR measure substantially improves clinical outcome to TBR neurofeedback (Arns, Drinkenburg, & Kenemans, 2012; Monastra et al., 2002).

In spite of these promising results, strictly speaking, none of the above studies used a design that would be able to control for all unspecific aspects of neurofeedback. Unspecific effects contribute to *any* outcome in *any* treatment (be it medication, surgery or psychotherapy; see Oken, 2008) in both positive and negative ways. Therefore, the aim should not be *'to rule out'* but *'to control for'* those variables that have an impact on the outcome and are not related to the specific part of the treatment delivered to the patient. According to Benedetti et al. (2005, p. 10390) the placebo effect is *"...a psychobiological phenomenon that can be attributable to different mechanisms, including expectation of clinical improvement and Pavlovian conditioning..."*. In order to control for these mechanisms the setting has to be as identical as possible, expectations and satisfaction of patients (and their relevant others) should be assessed. In addition, the relation between the independent and dependent variables should be under closer investigation: In controlled neurofeedback trials, indices of self-regulation skills should correlate with behavioural outcome. An important prerequisite is the operationalisation of "success of training" or "self-regulation skill". Up to now most studies reporting such data are from studies with healthy subjects (Gruzelier & Egner, 2005; Keizer, Verment, & Hommel, 2009; Keizer, Verschoor, Verment, & Hommel, 2009; Raymond, Varney, Parkinson, & Gruzelier, 2005; Ros et al., 2009; Ros, Munneke, Ruge, Gruzelier, & Rothwell, 2010). For ADHD, Drechsler et al. (2007), Strehl et al. (2006) and Gevensleben et al. (2013) analysed self-regulation skills related to outcome after SCP neurofeedback. The two former studies used a median split-half method to separate "good" from "poor" performers. While Drechsler et al. (2007) assessed the difference between negative and positive potential shifts during transfer trials, Strehl et al. (2006) chose the negativity of amplitudes as the criterion during transfer trials (transfer trials in neurofeedback are trials without feedback). Gevensleben et al. (2013) considered potential shifts in the course of the training. In all three studies good performance was significantly correlated with reduction of symptoms. While one double-blind placebo controlled study failed to find an effect of neurofeedback on ADHD symptoms at the group level (deBeus, personal communication), there were significant effects of neurofeedback on teacher ratings and a CPT test when comparing 'learners' (74% of the sample) vs. 'non-learners' in their study (DeBeus & Kaiser, 2011), further demonstrating the importance of learning associated with clinical outcome.

Liechti et al. (2012) reported clinical improvement in ADHD after tomographic neurofeedback (sLORETA, standardised low-resolution electromagnetic tomography, neurofeedback), although there was no substantial learning to control activity of the anterior cingulate (only partial learning of anterior cingulate activity was found, though unrelated to clinical outcome). This result may be attributed to nonspecific or secondary effects of neurofeedback. On the other hand, a medium ES was obtained for the primary outcome measure when comparing sLORETA neurofeedback to EMG biofeedback training (Maurizio et al., 2013), which argues against merely unspecific effects. The mechanisms of action may thus be more complex than expected.

2.4. Placebo-controlled studies

Some recent neurofeedback studies (mainly pilot and feasibility studies) have employed a placebo-controlled design and failed to provide clear evidence for the superiority of 'real' neurofeedback compared to sham-neurofeedback (Arnold et al., 2012; DeBeus & Kaiser, 2011; Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013).

The recent van Dongen-Boomsma et al. study (2013) included all subjects from the Lansbergen et al. (2011) study. In this study, at least some advantage for the neurofeedback group was found for example regarding hyperactivity/impulsivity and the number of responders which did not turn out significant due to the small sample size. In addition, pooling of data after changing the research design midway may be considered problematic.

Some methodological aspects of these studies have to be reflected upon critically:

- Since operant conditioning principles play an important role in neurofeedback, it is crucial that the active treatment and control condition are in line with principles of learning theory and conditioning principles (also see: Sherlin et al., 2011) for review).
  An often-used method to ensure neurofeedback studies remain 'double-blind' is by using automatic-thresholding, to ensure the clinician applying the neurofeedback is also blind to the treatment (in: Lansbergen et al. (2011) and Arnold et al. (2012)). Using such a procedure results in rewarding the child irrespective of its actual achievement in self-regulation, and prevents 'shaping' or 'scaffolding'. Therefore this automatic-thresholding is clearly not in accordance with principles of learning theory. Furthermore, in the Lansbergen et al. study (2011) and van Dongen-Boomsma et al. study (2013) reinforcement was provided 80% of the time, which might have been too high and have prevented learning to take place. Therefore the validity of the training protocol has to be questioned. In other words: If the treatment is not a real treatment a double blind study does not make sense.
- Apart from the pilot study of Perreau-Linck et al. (2010), non-standard neurofeedback protocols have been used such as 'QEEG-based' protocols with 2-channel training where often the SMR was trained over the frontal cortex instead of over the motor cortex (Lansbergen et al., 2011) or training of the so-called 'engagement index' at Fz (decreasing theta and alpha and increasing SMR and beta) (DeBeus & Kaiser, 2011; Arnold et al., 2012). Results and efficacy of these protocols in the treatment of ADHD have not been published before, and none of such studies were incorporated in the 2009 meta-analysis. Therefore, in line with the earlier lack of clinical effects of alpha-neurofeedback in ADHD (Nall, 1973), these results do not contribute to the question of

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efficacy of well-investigated neurofeedback protocols such as TBR, SMR and SCP neurofeedback protocols.
- The way feedback was provided also substantially differed from previous studies. Previous studies mainly employed discrete auditory and visual feedback or in general 'uncomplicated feedback', whereas for the studies of DeBeus and Kaiser (2011) and Arnold et al. (2012) feedback was provided with a Sony PlayStation® game controller (exciting games) and the feedback in the Lansbergen et al. (2011) study consisted of movies. Such feedback may have impeded the outcome of the training, making it too difficult to extract the signal on which feedback was provided ('entertainment' vs. 'treatment').
- None of the studies reported whether learning actually took place, except the already mentioned DeBeus and Kaiser study (2011) that reported significant effects of neurofeedback on teacher ratings and a CPT test when comparing 'learners' (74% of the sample) vs. 'non-learners'. This further strongly emphasises the importance of focusing on learning, similar to the findings discussed in section 2.3.
- Finally, none of the studies implemented techniques to promote 'generalisation' into daily life such as transfer trials, which seem to play a role in the correlation between learning and outcome (see Gani et al., 2008; Strehl et al., 2006).

Irrespective of these methodological issues and the more general issue whether a placebo-controlled trial is appropriate in the evaluation of neurofeedback, it has to be noted that the placebo conditions partly provide large ES (albeit calculated on small sample sizes). One could speculate which of the possible unspecific factors (expectation, amount of positive feedback and reinforcement, effort, treatment setting) have contributed to these results. An attempt to overcome these methodological shortcomings is the proposal of the Collaborative Neurofeedback Group (Arnold et al., 2013), which has included ADHD researchers and neurofeedback experts (Arnold, Arns, Conners, deBeus, Hirshberg, Kerson, Kraemer, Lofthouse, Lubar, McBurnett & Monastra). The details of this design can be found in more detail in Arnold et al. (2013).

Concluding, if double-blind placebo controlled designs are considered, it is important that such designs are in line with the above principles of learning theory and use a well-investigated neurofeedback protocol. Interpretation of trials must be restricted to the protocol applied and do not hold for neurofeedback in general.

2.5. Comparison of effect sizes for different treatments

ES are scale free statistics allowing comparison of clinical effects among treatments. They can be calculated for within- or between-group comparisons. The ES for neurofeedback on symptoms of inattention appear to be comparable to the ES[1] reported for methylphenidate (ES NF = 0.81 vs. ES methylphenidate = 0.84), whereas for hyperactivity and impulsivity the ES for methylphenidate is higher (ES NF = 0.4/0.69 vs. ES methylphenidate = 1.01; Faraone & Buitelaar, 2009; Sherlin, Arns, Lubar, & Sokhadze, 2010). These results tend to be in line with the above referenced studies (see 2.2) that compared neurofeedback to stimulant medication and suggest that at least for inattention the effects could be similar. However the studies referenced in 2.2 were of insufficient statistical power to support that conclusion statistically. Therefore, larger randomised controlled trials assessing effects of both neurofeedback and medication treatment are required. In addition, it also has to be noted that clinical guidelines recommend a multimodal treatment approach. In this respect, research should not only focus on comparing neurofeedback and medication but also address how (and when) to combine different treatments in such a multimodal approach. An even more interesting and promising development would be to predict which individual patients respond best to which treatment, also called personalised medicine (for review see: Arns, 2012).

3. Future directions

As a rationale for TBR neurofeedback in ADHD, the findings of QEEG studies that children with ADHD are characterised by increased theta and/or reduced beta activity has typically been used as a justification. However, recent studies challenge the TBR as a marker present in a majority of ADHD patients (e.g. Arns, Conners, & Kraemer, 2012; Arns, Drinkenburg, & Kenemans, 2012; Liechti et al., 2013) but rather suggest an increased TBR in only 20–30% of ADHD patients (see Arns, Conners, & Kraemer, 2012; Arns, Drinkenburg, & Kenemans, 2012 for a meta-analysis), also reflected by the notion that, ADHD is considered a heterogeneous disorder (Banaschewski et al., 2005). In line with current developments such as NIMH's adoption of Research Domain Criteria (RDoC) and 'precision medicine'[2], future research should try to investigate in more detail the relations between ADHD subtypes (e.g. established by QEEG, CNV or ERP's) and individually tailored neurofeedback protocols. Converging evidence suggests that excess theta could predict treatment outcome to stimulant medication (Arns, Gunkelman, Breteler, & Spronk, 2008; Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002; Satterfield, Cantwell, Saul, Lesser, & Podosin, 1973; Suffin & Emory, 1995). Regarding neurofeedback, several studies suggest a personalised approach could improve clinical outcomes (Arns, Conners, & Kraemer, 2012; Arns, Drinkenburg, & Kenemans, 2012; Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Monastra et al., 2002), however more controlled studies with larger sample sizes are required to investigate this in more detail.

However, how does this relate to studies applying TBR neurofeedback to all patients, and thus a majority of whom have no deviating TBR? An explanation of the positive results after TBR neurofeedback could be that *not* a neural dysfunction is addressed, but a compensatory mechanisms is actually trained. In this respect, children could learn an attentive (focused and attentive but relaxed) state, thereby strengthening underlying neural networks.

Two important aspects may be derived from this discussion about the rationale of TBR neurofeedback in ADHD. First, knowledge about the mechanisms of action appears to be rather limited. So, future studies have to contribute to unravel these mechanisms in more detail. And second, neurophysiological subtypes may exist in ADHD and it may be questioned whether and under which circumstances one specific neurofeedback protocol fits for all patients with ADHD (Mayer, Wyckoff, & Strehl, 2012).

In a recent review, Arns and Kenemans (Arns & Kenemans, 2012) postulated that ADHD symptoms in a larger subgroup of ADHD patients might actually be caused by sleep problems, more specifically sleep onset insomnia and reduced sleep duration. Part of this model was recently supported by the finding of a lower prevalence of ADHD in geographical areas with a high solar intensity, probably due to improvements in circadian clock disturbances (Arns, van der Heijden, Arnold, & Kenemans, 2013) and/or interactions with the dopamine receptor type 4 (DRD4) which is circadian in nature and under photoneural control (Arns, van der Heijden, Eugene Arnold,

[1] It has to be taken into account that effect sizes for methylphenidate are related to placebo. The ES for neurofeedback are the between group ES compared to semi-active control groups.

[2] http://www.nimh.nih.gov/about/director/2011/improving-diagnosis-through-precision-medicine.shtml.

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Swanson, & Leon Kenemans, 2013). They postulated that SMR and maybe SCP neurofeedback achieve their clinical effects by training the sleep-spindle circuitry, and thereby normalise sleep, resulting in vigilance stabilisation and associated improvements in ADHD symptoms. Future research has to further substantiate if this model can be confirmed, but at least this provides a testable model wherefrom hypotheses can be generated. Furthermore, it shifts the focus to also incorporate sleep data in future studies.

Another promising future development, is that of increasing the specificity of the feedback signal. For example the use of EEG-based tomographic neurofeedback training (using sLORETA) has been demonstrated to be feasible, albeit with lower spatial resolution as compared to fMRI. Recently, a first EEG-based tomographic neurofeedback training (using a LORETA) was applied in children with ADHD, who had to modulate acitivity (SCP, TBR) in the Anterior Cingulate (ACC). This region has often been implicated in functional imaging studies. Children in this study only partially learned self-regulation of brain activity in the anterior cingulate cortex (Liechti et al., 2012), indicating further studies to develop this approach further. Furthermore, the application of fMRI neurofeedback could also be a method to further improve the specificity. The group of Rubia has initiated a first controlled study where children with ADHD have to increase activation in the right frontal cortex and the nucleus caudate voluntarily using fMRI-neurofeedback. It is expected that neuroregulation of these structures is associated with reductions in symptom severity of inattention, hyperactivity and impulsiveness (ISRCTN12800253: www.controlled-trials.com/ISRCTN12800253/).

4. Conclusions

Based on the studies available and presented in this review, it may be concluded that TBR, SMR and SCP neurofeedback are clinically effective treatment (modules) for children with ADHD and several clinical, neurophysiological and neuroimaging findings support its specificity. The effects of neurofeedback appear to be lasting judging from the limited data available. Further studies are on their way that will hopefully further substantiate this. For example, Holtmann and Strehl are finalizing a large multicenter RCT comparing SCP neurofeedback to an EMG biofeedback training and including a relapse-prevention arm (www.controlled-trials.com/ISRCTN76187185/). One important feature of this study is the control of unspecific mechanisms of effect like expectations, satisfaction and subject-trainer-relation by specific placebo questionnaires.

Though there are open questions to be answered concerning the exact mechanisms of action of neurofeedback and moderators and mediators of neurofeedback training in ADHD, there is increasing evidence for the specificity of effects for 'standard' protocols such as TBR, SMR and SCP neurofeedback. These protocols have been under investigation for about 40 years. Whether the efficacy of these protocols can be further improved by individualising training, along the lines of precision medicine, has to be assessed by future studies. In any case, principles of learning theory have to be taken into account in designing valid treatment and control groups. As regards to the placebo issue, specific as well as unspecific mechanisms of effect have to be controlled for. This can be done by treatments that resemble the experimental condition in all unspecific aspects, by relating clinical outcome to progress in self-regulation and by assessing expectations of patients. With clinical trials being underway these questions are already being addressed. Based on these studies, neurofeedback may be interpreted as an evidence-based treatment for ADHD and thus may lead us further on the long and winding road. . ..

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