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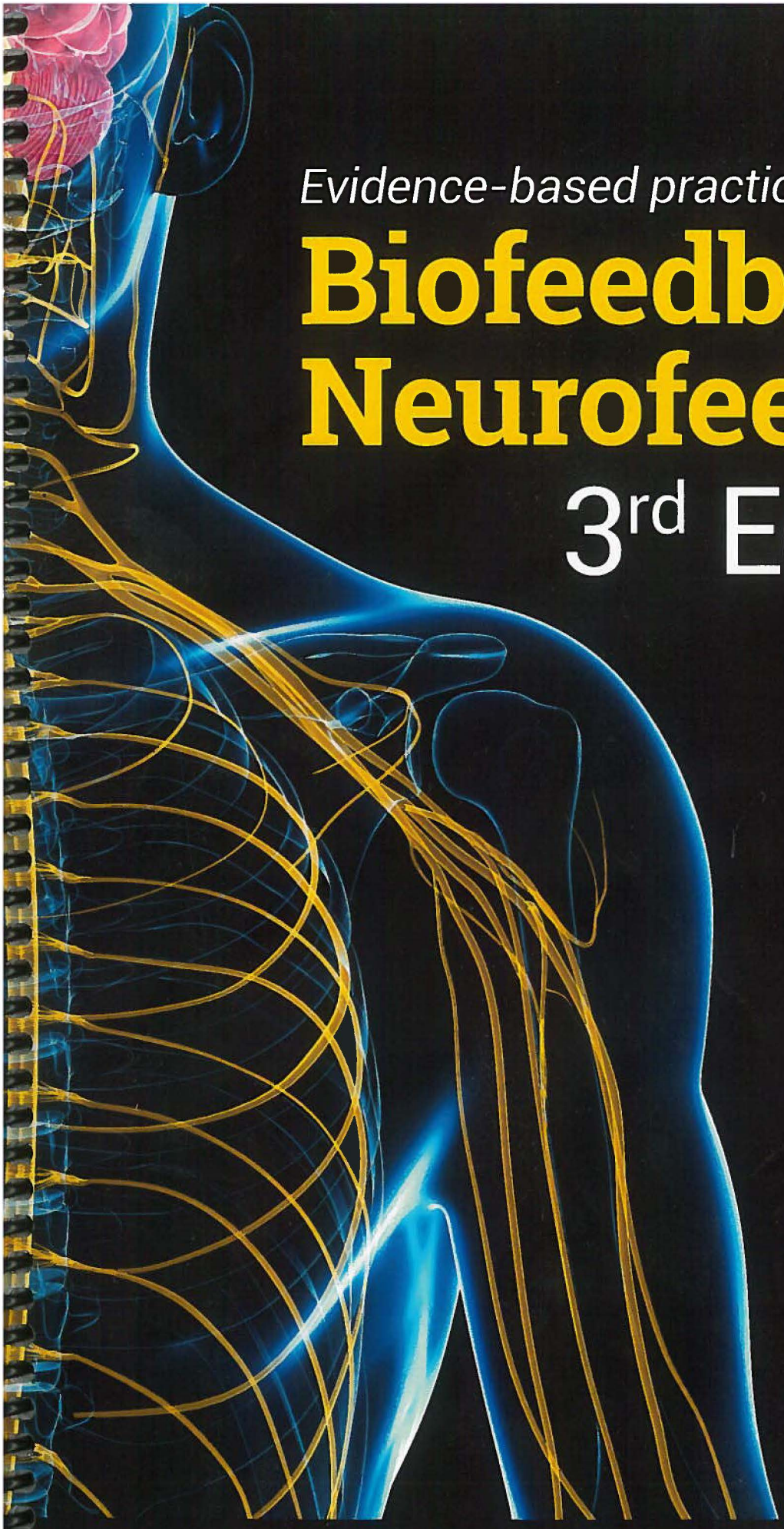

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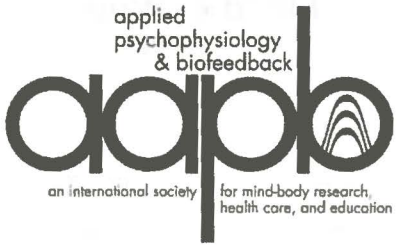

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Chapter 6 – Attention Deficit Hyperactivity Disorder (ADHD) Level 5: Efficacious and Specific

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At present, stimulant medication and behavior therapy are the most often applied and accepted treatments for attention deficit hyperactivity disorder or 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 behavior 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, specifically with regard to its current evidence base level using the APA/AAPB criteria.

A Brief History

Several years after Sterman's first demonstration of anticonvulsant effects of sensorimotor rhythm (SMR) neurofeedback (Sterman & Friar, 1972), Lubar and Shouse (1976) described the application of this same SMR neurofeedback in a child with hyperkinetic syndrome. Employing an ABA design, they reported improvements in hyperactivity and distractibility when SMR was uptrained, and found that symptoms worsened when reversal training was employed (Lubar & Shouse, 1976). Several years later, these findings were replicated in a larger study (Shouse & Lubar, 1979). These reports can now be considered the first demonstrations of clinical effects after neurofeedback in what we today refer to as ADHD.

Walter et al. in 1946 were the first to describe the Contingent Negative Variation (CNV). The CNV is very slow electrophysiological brain activity, characterized by a negative shift, in anticipation of an expected event such as waiting for a traffic light to turn green. Interestingly, in the same era when the earlier-mentioned frequency neurofeedback was first described, McAdam, Irwin, Rebert, and Knott (1966) were the first to describe that subjects could exert *voluntary control* over their CNV (McAdam et al., 1966), and this technique was further pioneered by Elbert and Birbaumer (Elbert, Rockstroh, Lutzenberger, & Birbaumer, 1980; Lutzenberger, Elbert, Rockstroh, & Birbaumer, 1979). Later in 1993, it was found that this slow cortical potential, or SCP, neurofeedback had anticonvulsive properties (Rockstroh et al., 1993) and in 2004, Heinrich and colleagues were the first to report clinical effects of this protocol in ADHD (Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004). In these early days of neurofeedback, other neurofeedback protocols such as alpha enhancement were also investigated, however, this alpha enhancement protocol failed to show effects in hyperkinetic syndrome (Nall, 1973) and in epilepsy (Rockstroh et al., 1993), suggesting some specificity in the

EEG parameter trained in neurofeedback. For a more detailed overview of the history of neurofeedback, also see Arns, Heinrich, and Strehl (2014).

Evidence Level

In the last decade, an increasing number of well-controlled studies have been conducted to evaluate the effects of neurofeedback in the treatment of ADHD. Most studies have investigated theta/beta (TBR), SMR, and/or SCP protocols in the treatment of ADHD. Since these three protocols are well investigated in ADHD and have well-established efficacy in ADHD, this review will only focus and apply to the application of these protocols in the treatment of ADHD. For these three neurofeedback protocols, theoretical models have been developed that explain their efficacy in ADHD (for review see: Arns & Kenemans, 2012; Gevensleben et al., 2013). Given the many recent studies, we will only deal with randomized controlled trials (RCTs). For a review and meta-analysis beyond RCTs, the reader is referred to Arns et al. (2009) and Arns, Heinrich, and Strehl (2014).

Randomized Controlled Trials (RCTs)

The first two RCTs compared neurofeedback to a waiting list control group and found improvements on attention and hyperactivity (Lévesque, Beauregard, & Mensour, 2006; Linden, Habib, & Radojevic, 1996). More recently, four RCTs have been published either using a cognitive training (Gevensleben et al., 2009; Holtmann et al., 2009; Steiner et al., 2014) or an electromyogram (EMG)-based biofeedback training (Bakhshayesh et al., 2011) as a control condition. These control conditions aimed at controlling for non-specific effects of neurofeedback such as the time of computer interaction, amount of client-therapist interaction, etc. Finally, one other RCT compared SCP with TBR neurofeedback, and found similar effects for both treatments on ADHD symptoms.

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 effect size [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 these control groups possibly 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 (but no effects for inattention and hyperactivity), 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 three of these RCTs, follow-up was performed and the clinical effects were maintained at 6-month follow-up (Gevensleben et al., 2010; Steiner et al., 2014; Strehl et al., 2006) and 2 years (Gani, Birbaumer, & Strehl, 2008). Two of these RCTs were multicentre studies with large sample sizes of $N = 102$ and $N = 104$, respectively (Gevensleben et al., 2009; Steiner et al., 2014).

Neurofeedback Compared to Methylphenidate

Several studies have compared the efficacy of neurofeedback to stimulant medication. Older nonrandomized studies (Fuchs et al., 2003; Monastra et al., 2002; Rossiter, 2004; Rossiter & La Vaque, 1995), reported comparable effects of neurofeedback and methylphenidate for measures of inattention, impulsivity, and hyperactivity. However, all these were nonrandomized studies, and families self-selected their preferred treatment, maximizing effects of expectancy in both groups. Recently, two RCTs have been published where neurofeedback was compared to methylphenidate using a randomized group assignment (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel et al., 2013). In both studies, methylphenidate was

not superior to neurofeedback training, confirming the findings from the earlier nonrandomized 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 firm conclusions about the equivalence of medication with neurofeedback. However, the consistency of results of these six studies comparing methylphenidate to neurofeedback is promising and suggestive of a similarity in clinical effects.

Placebo-Controlled Studies

Only one small placebo-controlled study used SMR neurofeedback with a sample size of nine children (Perreau-Linck et al., 2010). This study did not find clinical effects of neurofeedback; however, the small sample size (a result of recruitment issues due to the double blind nature of the study and thus a premature termination of the study) precludes us from evaluating specific effects of neurofeedback in this study (Perreau-Linck et al., 2010).

Three other placebo-controlled studies have been performed; however, the protocols and EEG locations trained in those studies deviate to such an extent that they cannot be generalized to SCP, TBR, or SMR neurofeedback protocols (for a more detailed overview, see Arns, Heinrich, & Strehl, 2014; Arns & Kenemans, 2012). Based on these studies we may conclude that neurofeedback protocols like Engagement Index (Arnold et al., 2012; DeBeus & Kaiser, 2011), alpha enhancement neurofeedback (Nall, 1973), and bilateral frontal and parietal SMR training (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011; van Dongen Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013) probably have no or at best limited clinical effects in the treatment of ADHD, particularly when applied with automatically updated thresholds and/or with exciting computer games (see Sherlin et al., 2011, for a review of learning principles and neurofeedback efficacy).

Meta-Analyses

The results of neurofeedback studies conducted up to 2009 (including nonrandomized studies) were rather coherent, as confirmed in a meta-analysis by Arns and colleagues (2009). This meta-analysis incorporated 15 studies (of which 5 were RCTs: Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2007; Gevensleben et al., 2009; Holtmann et al., 2009; Leins et al., 2007; Lévesque, Beauregard, & Mensour, 2006), and found that neurofeedback resulted in large and clinically relevant effect sizes for inattention and impulsivity and a medium effect size for hyperactivity. Recently, Sonuga-Barke and colleagues published a systematic review and meta-analysis on randomized controlled trials in the treatment of ADHD that also included neurofeedback (Sonuga-Barke et al., 2013). For so-called most-proximal ratings (typically from parents), they demonstrated comparable ES to the meta-analysis by Arns and colleagues (2009), whereas for "probably blinded" ratings (primarily teacher ratings), there was a tendency towards significance (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 focusing on standard training protocols). If only RCTs are considered where TBR or SCP training was applied and cognitive training or EMG biofeedback training was used as control conditions, a significant effect is also obtained for teacher ratings (Arns & Strehl, 2013). Therefore, it may be concluded that these two meta-analyses substantiate at least the medium effects for TBR, SMR, and SCP neurofeedback protocols on ADHD symptoms.

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 was found (Gani, Birbaumer, & Strehl, 2008; Gevensleben et al., 2010; Leins et al., 2007; Steiner et al., 2014; Strehl et al., 2006).

The ES for neurofeedback on symptoms of inattention appear to be comparable to the ES reported for methylphenidate (see Arns et al., 2009; Faraone & Buitelaar, 2009; Sherlin, Arns, Lubar, & Sokhadze, 2010). These results tend to be in line with the earlier referenced studies that compared neurofeedback to stimulant medication and suggest that at least for inattention the effects are similar.

Other Aspects

Beyond the criteria for determining efficacy level for biofeedback interventions regarding a specific condition or clinical disorder, two further points are worth mentioning. Support for the specificity of effects induced by SCP and TBR neurofeedback protocols mentioned above is also provided by significant associations between effects at the neurophysiological level (learned self-regulation, EEG, and event-related potentials) and clinical improvements, particularly differential patterns for different neurofeedback protocols (see Arns, Heinrich, & Strehl, 2014 for review). Finally, up to now, safety (adverse events) of neurofeedback in ADHD has not been systematically documented (Lofthouse et al., 2010). To our knowledge, side effects have only been systematically documented in two studies that used other than TBR and SCP protocols (Arnold et al., 2012; Lansbergen et al., 2011). Future studies should more systematically assess adverse events and other safety aspects of neurofeedback.

Conclusion

Neurofeedback in the treatment for ADHD, limited to SCP, TBR, and SMR protocols, can thus be considered a *Level: 5 Efficacious and Specific* treatment. This is based specifically on the following evidence:

- At least two independent multicenter RCTs with large sample sizes (N >100) where neurofeedback was compared to cognitive training (a *credible sham*: Gevensleben et al., 2009; Steiner et al., 2014) and the effects were maintained for at least 6 months (Gevensleben et al., 2010; Steiner et al., 2014).
- At least two independent RCTs where methylphenidate was not superior to neurofeedback in the treatment of ADHD (Duric et al., 2012; Meisel et al., 2013), and overall comparable effect sizes of neurofeedback and methylphenidate from recent meta-analyses (Arns et al., 2009; Faraone & Buitelaar, 2009).

This conclusion is further supported by one meta-analysis (Arns et al., 2009), and indirectly supported by another meta-analysis when restricted to standard protocols (Arns & Strehl, 2013; Sonuga-Barke et al., 2013).

Acknowledgement

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