Neurofeedback-Training bei Kindern mit einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung

Effekte

auf Verhaltens- und neurophysiologischer Ebene

Dissertation zur Erlangung des Doktorgrades der Mathematisch-Naturwissenschaftlichen

Fakultäten der Georg-August Universität zu Göttingen

Vorgelegt von Holger Gevensleben aus Göttingen

Göttingen 2012

Anleiter: Prof. Dr. Aribert Rothenberger

Referent: Prof. Dr. Marcus Hasselhorn

Korreferentin: Prof. Dr. Birgit Kröner-Herwig

Tag der mündlichen Prüfung:

Danke!

Ich möchte mich bei allen teilnehmenden Kindern und Eltern bedanken, ohne deren engagierte Beteiligung diese Studie nicht hätte durchgeführt werden können. Mein besonderer Dank gilt meinem Freund und Kollegen Hartmut Heinrich, mit dem ich gemeinsam dieses Projekt gestaltet habe und Prof. Dr. A. Rothenberger und Prof. Dr. G. H. Moll, die uns dieses Projekt ermöglicht und die Güte des Projekts maßgeblich mitgeprägt haben. Prof. M. Hasselhorn und Fr. Prof. B. Kröner-Herwig danke ich für die Geduld und die wohlwollende Begutachtung der Arbeit. Björn Albrecht, Christa Dahlmann und Petra Studer möchte ich stellvertretend für alle Kolleginnen und Kollegen der beteiligten Kliniken danken, die uns bei der Durchführung des Projekts unterstützt haben.

Mein ganz besonderer Dank gilt den beteiligten studentischen Hilfskräften, die nicht nur großartige Arbeit geleistet, sondern auch den gemeinsamen Spaß bei der Arbeit gewährleistet haben. Insbesondere gilt mein Dank dabei Karin Scholze, Nicola Wöstmann, Maren Schütze, Katrin Paland, Jasmin Ernst, Un-Hee Lee und Andrea Flaig, die dieses Projekt in Göttingen begleiteten.

Gewidmet ist diese Arbeit Kristina, Finn und Frida, die mir jeden Tag vor Augen führen, was im Leben tatsächlich von Bedeutung ist.

Inhalt

1. Einleitung

Neurofeedback (NF) und seine Anwendung bei Kindern ist prinzipiell zwar ein schon länger bekanntes Verfahren (Rockstroh et al., 1990), es stellt aber in seiner Weiterentwicklung mittlerweile ein innovatives, neurobiologisches, theoriegeleitetes Verfahren zur Behandlung von Kindern mit einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) dar (Heinrich et al., 2007; Holtmann et al., 2004). Es findet zunehmend Interesse, nicht zuletzt aufgrund bekannter Limitierungen oder negativer Begleiterscheinungen derzeit verfügbarer verhaltenstherapeutischer und medikamentöser Behandlungsoptionen bei ADHS (Taylor et al., 2004; Banaschewski et al., 2006; van der Oord et al., 2008).

Das Therapierational des NF-Trainings bei Kindern mit ADHS basiert auf z. T. gut replizierten empirischen Befunden, die bei Kindern mit ADHS spezifische Abweichungen unterschiedlicher Parameter hirnelektrischer Aktivität (EEG-Frequenzbänder; ereignisbezogene Potentiale, EPs) aufzeigten (Banaschewski & Brandeis, 2007). NF setzt an der Selbstregulation dieser hirnelektrischen Parameter an, ermöglicht den Patienten ein bestimmtes hirnelektrisches Muster unter Verwendung operanter Verstärkung gezielt zu verändern und diese Regulationskompetenz in Form erlernter Selbstinstruktionsstrategien in den Alltag zu transferieren. Das Verfahren überträgt damit dem Patienten die Kontrolle über seinen Aufmerksamkeitszustand und versetzt ihn in die Lage, gezielt und eigenständig einen möglichst situationsangemessenen, aufmerksamen Zustand einzunehmen, im Sinne eines optimierten Selbstmanagements. NF umfasst Elemente neurophysiologischer, lerntheoretischer und kognitiver Ansätze. Ergebnisse bisheriger Studien weisen darauf hin, dass Neurofeedback ein weiteres hilfreiches Modul kognitiv-verhaltenstherapeutischer Interventionsansätze für die Therapie von ADHS sein könnte.

Ziel meines Forschungsprojekts, auf dessen Resultaten die vorliegende Arbeit beruht, war es, eine möglichst gut kontrollierte und umfassende Evaluation unseres Neurofeedback-Trainingsprogramms durchzuführen, denn trotz bereits vielfacher praktischer Anwendungen sind sorgfältige Evaluationen kaum vorhanden. Das Neurofeedback-Training setzte sich aus zwei unterschiedlichen Trainingsprotokollen (einem Frequenzband-Training und einem Training der langsamen kortikalen Potentiale) zusammen, um nicht nur die Wirkung gegenüber einer Kontrollgruppe zu erfassen, sondern auch spezifische Effekte der unterschiedlichen Protokolle aufzuzeigen. Die Kontrollgruppe absolvierte ein vergleichbar gestaltetes computergestütztes Aufmerksamkeitstraining. Die Effekte der Trainings wurden auf unterschiedlichen Ebenen erfasst. Dazu zählten Verhaltenseinschätzungen (durch Eltern und Lehrer), die Ableitung neurophysiologische Parameter (Spontan-EEG, ereignisbezogene Hirnpotentiale) und die Erfassung neuropsychologischer Testleistungen. Die vorliegende Arbeit umfasst vier Originalpublikationen, die jeweils die Ergebnisse auf den verschiedenen Ebenen darstellen. Auf Basis unserer Ergebnisse ziehe ich den Schluss, dass Neurofeedback als ein weiterer sinnvoller Baustein in der Behandlung einer ADHS angesehen werden kann.

Für die Originalpublikation 1 (Gevensleben et al., 2009a: „Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial") erhielt ich im Rahmen des Kongresses des „Europäischen Netzwerkes für Hyperkinetische Störungen" (EUNETHYDIS) in Amsterdam (26. – 28.05.2010) den „Kramer-Pollnow-Young-Investigators-Award 2010", eine Auszeichnung an junge Wissenschaftler für „exciting new findings in the field of ADHD". Die Originalpublikation 2 (Gevensleben et al., 2010: „Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial" wurde im Rahmen des Kongresses der Europäischen Gesellschaft für Kinder- und Jugendpsychiatrie (ESCAP;

Helsinki, 2011) zur besten Publikation des Jahres zum Thema ADHS („ADHD-paper of the year”) der Zeitschrift “European Child and Adolescent Psychiatry” gekührt.

Die positive Resonanz auf unsere Veröffentlichungen drückt sich u. a. darin aus, dass den Veröffentlichungen Gevensleben et al. (2009a) und Wangler et al. (2011) jeweils die Editorials der veröffentlichenden Zeitschriften gewidmet wurden (Pine, 2009; Brandeis, 2010). Die zugrundeliegende Studie gilt bislang als die weltweit größte und valideste Studie zum Thema Neurofeedback bei ADHS (Arns et al., 2009; Coghill, 2010).

Die vorliegende Arbeit gliedert sich in einen kurzen Überblick über den aktuellen Forschungsstand in den Bereichen ADHS (Kapitel 2.) und Neurofeedback (Kapitel 3.), eine einleitende Darstellung der wesentlichen Ziele und methodischen Aspekte unseres Forschungsprojekts, an die sich die Darstellung der Ergebnisse in Form der Originalpublikationen anschießt (Kapitel 4), gefolgt durch eine abschließende kurze Zusammenfassung (Kapitel 5). Teile der Arbeit beruhen auf kürzlich erschienenen Artikeln (Gevensleben et al., 2010b; Gevensleben et al., 2011). Das Projekt wurde gefördert durch Mittel der Deutschen Forschungsgemeinschaft (RO 698-5-1, RO 698-5-2, RO 698-5-3).

2. Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung

2.1 Symptomatik

Die Aufmerksamkeitsdefizit- und Hyperaktivitätsstörung (ADHS; auch Hyperkinetische Störung, ICD-10: F90) zählt mit einer Prävalenz von ca. 5% (Huss et al., 2008; Polanzyk et al., 2007) zu den häufigsten Störungen im Kindes- und Jugendalter (Faraone et al., 2003). In den USA nahm in der ambulanten medizinischen Versorgung die Quote der Kinder mit der Diagnose ADHS von 1987 bis 1997 von 0,9% auf 3,4% zu (Olfson et al., 2003). Der Verlauf wird als chronisch angesehen, ein bedeutsamer Anteil an Fällen persistiert ins Erwachsenenalter. Zwischen 1,3 bis 5% der Erwachsenen leiden (weiterhin) unter ADHS (Kessler et al., 2006; Rösler et al., 2010; Sobanski & Alm, 2004).

Die Kernsymptomatik der Aufmerksamkeitsdefizit- und Hyperaktivitätsstörung (ADHS) besteht aus einer beeinträchtigten Aufmerksamkeitssteuerung (u. a. hohe Ablenkbarkeit, fluktuierende Aufmerksamkeitsleistungen, chaotisch anmutende Selbstorganisation, Aversion gegen kognitive Herausforderungen) sowie erhöhter motorischer Aktivität und Impulsivität (z. B. Ruhelosigkeit, nicht still sitzen können, nicht abwarten können), die vor dem 7. Lebensjahr situationsübergreifend und zeitstabil auftreten und dem sonstigen allgemeinen Entwicklungsniveau eines Kindes nicht entsprechen. Die Symptome führen zu einer bedeutsamen Beeinträchtigung unterschiedlicher Lebensbereiche (Schule/Lehre/Arbeit, Familie, soziales Umfeld) und erklären sich nicht durch das Vorliegen einer anderen psychiatrischen Störung (DSM-IV; APA, 1994). Man kann zwischen verschiedenen Subtypen einer ADHS unterscheiden. Die beiden gängigen Klassifikationssysteme psychiatrischer Störungen, das DSM-IV sowie die ICD-10 (WHO, 1994) unterscheiden sich dabei in ihrer Kategorisierung. Das DSM-IV grenzt den Mischtyp einer ADHS, der die beschriebene Vollsymptomatik aufweist (DSM-IV: 314.01; ICD-10: F 90.0: einfache Aufmerksamkeits- und Hyperaktivitätsstörung) vom vorwiegend unaufmerksamen Subtypen der Störung ab (DSM-IV: 314.00, vorwiegend unaufmerksamer Typus; ICD-10: F98.8, reine Aufmerksamkeitsstörung), bei dem die Beeinträchtigung sich v. a. auf die Aufmerksamkeitssteuerung beschränkt. Desweiteren unterscheidet das DSM-IV den vorwiegend hyperaktiv-impulsiven Typus (314.002; keine Entsprechung in der ICD-10), bei dem Hyperaktivität und Impulsivität gegenüber der Aufmerksamkeitsproblematik im Vordergrund stehen.

Bis zu 80 % der Kinder mit ADHS weisen Komorbiditäten auf (Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie u. a., 2007). Häufigste negative Begleiterscheinungen einer ADHS in Form von Komorbiditäten sind Auffälligkeiten im Sozialverhalten (betrifft bis zu 60%) und emotionale Störungen (Depression/Angst, bis zu 40%) sowie das Auftreten umschriebener Entwicklungsstörungen (bis zu 50%; Gilberg et al., 2004). Patienten mit einer ADHS haben langfristig ein erhöhtes Risiko, schulisch und / oder beruflich unter ihren Möglichkeiten zu bleiben, sind schlechter sozial integriert und haben eine erhöhtes Risiko für Substanzmissbrauch/-abhängigkeit und Gesetzeskonflikte / Delinquenz (Barkley et al., 2004; 2006; Kessler, 2006).

2.2 Grundlagen und Modelle

Zur Erklärung von Aufmerksamkeitsdefizit- und Hyperaktivitätsstörungen stehen Hypothesen und Modelle unterschiedlicher Fachdisziplinen bereit, die in unterschiedlichem Maße genetische, neurobiologische, (neuro-)psychologische und soziale Variablen einbeziehen (aktueller Überblick bei Steinhausen et al., 2010). Das komplexe Zusammenwirken unterschiedlicher Variablen versucht z. B. Döpfners „integratives klinisches Modell“ (2009) abzubilden. Demnach haben sowohl genetische sowie soziale Faktoren einen bedeutsamen kausalen Einfluss auf die Entfaltung einer ADHS-Symptomatik. Auf Basis der genetischen Ausstattung, unter Einfluss epigenetischer und exogener Faktoren (Schädigungen des Zentralnervensystems durch Traumen oder metabolische / toxische Einflüsse, z. B. Schwangerschafts-/Geburtskomplikationen, pränatale Nikotin-, Alkohol- oder Benzodiazepin-Exposition, Biederman ,2005), resultieren demnach unterschiedliche, jeweils spezifische Auffälligkeiten in neurobiologischen und / oder neuropsychologischen Variablen (die als unterschiedliche anatomische, biochemische, neurophysiologische oder neuropsychologische Endophänotypen charakterisiert werden können), die modulierend auf Erleben und Verhalten wirken und somit das beobachtbare Symptomcluster mitbestimmen, das sich letztlich in Interaktion mit den gegeneben sozialen und psychologischen Faktoren (Familie, allgemeines psychosoziales Umfeld) entwickelt (umfassendere Darstellung bei Döpfner et al., 2010).

Neurobiologische Grundlagen

Zwillingsstudien legen die Annahme eines deutlichen Einflusses genetischer Faktoren auf die Entwicklung einer ADHS-Symptomatik nahe (Faraone et al., 2005). Es wurden Hinweise auf den Zusammenhang von ADHS mit unterschiedlichen DNA-Varianten gefunden, u. a. DRD4, DRD5, DAT, SLC6A3, SNAP-25, HTR1B (Brooks et al., 2006), wobei der Zusammenhang einzelner Risikoallele mit der ADHS-Symptomatik oft nur gering bis moderat ausgeprägt scheint und das Zusammenwirken mehrerer verschiedener Genvarianten miteinander und mit unterschiedlichen Umweltfaktoren weitgehend ungeklärt ist (Banaschewski, 2010). Während Zwillingsstudien eine Heritabilitätsrate von 60 – 90 % nahelegen, lassen sich davon bislang weniger als 5% durch das Zusammenwirken unterschiedlicher Kandidaten-Gene aufklären (Hudziak & Faraone, 2010).

Aus einer Reihe neurobiologischer Studien liegen Befunde über Störungen in der Regulation bzw. Interaktion verschiedener Neurotransmittersysteme vor, in Form eines Ungleichgewichts der Verfügbarkeit und Aufnahme katecholaminerger Neurotransmitter, in erster Linie Dopamin und Noradrenalin (Madras et al., 2005; Solanto 2002; Volkow et al., 2001, 2009). Übereinstimmend damit gibt es eine Reihe Befunde über morphologische und funktionelle Auffälligkeiten in neuronalen Schaltkreisen unter Beteiligung des präfrontalen Kortex, Thalamus und Striatum (cortical-striatal-thalamic-cortical loops; CSTC; Übersicht bei Willis, 2005), die primär auf Basis katecholaminerger Neurotransmittersysteme interagieren und denen ein bedeutsamer Anteil an der Verhaltenssteuerung im Allgemeinen und sog. exekutiven Funktionen, also top-down geleiteter kognitiver Prozesse der Handlungsplanung und -regulierung (z. B. Arbeitsgedächtnis, motorische Inhibition, Interferenzkontrolle etc., Übersicht bei Chan et al., 2008) im Speziellen zugeschrieben wird (Halperin & Healey, 2010).

Im Rahmen neurophysiologischer Studien fanden sich Auffälligkeiten in unterschiedlichen Frequenzbereichen sowohl im Ruhezustand als auch während aufmerksamkeitsfordernder Aufgaben. Kinder mit ADHS wiesen dabei v. a. Auffälligkeiten im Elektroenzephalogramm (EEG) in Form erhöhter Theta- und reduzierter Beta-Aktivität auf (El Sayed, 2002; Monastra et al., 2002, Übersicht bei Barry et al., 2003a). In Studien ereignisbezogener Potentiale (EP) lag der Fokus auf späten Komponenten mit Latenzen > 300ms wie die P300 und die kontingente negative Variation (contingent negative variation, CNV; Überblick bei Banaschewski & Brandeis, 2007). Unter verschiedenen kognitiven Aufgaben konnten bei Kindern mit ADHS eine reduzierte P300 beobachtet werden, die auf Defizite in der Aufmerksamkeitssteuerung bzw. der motorischen Kontrolle hindeuten. Die CNV stellt ein langsames kortikales Potential dar (engl., slow cortical potential, SCP[1]) und kann unter verschiedenen experimentellen Paradigmen beobachtet werden, wie z.B. bei einem Continuous Performance Test mit Warnreiz (CPT). Es wird davon ausgegangen, dass die Ausprägung der CNV das neurophysiologische Korrelat antizipatorischer bzw. präparatorischer kognitiver Prozesse darstellt (Lüttge et al., 2009). Kinder mit ADHS wiesen in verschiedenen Studien auch eine reduzierte CNV auf. Dieser Befund steht im Einklang mit Modellvorstellungen, dass Kinder mit ADHS eine dysfunktionale Regulation energetischer Verarbeitungsressourcen aufweisen (Sergeant 2000).

Fasst man den aktuellen Forschungstand aus bildgebenden und neurophysiologischen Untersuchungen zusammen lässt sich festhalten, dass sich Auffälligkeiten v. a. in thalamo-kortikalen und striatalen neuronalen Substraten aufzeigen ließen, die als neuroanatomische Grundlage exekutiver Funktionen sowie basaler Selbststeuerungsmechanismen angesehen werden.

Neuropsychologische Befunde und Modelle

Exekutive Funktionen stehen angesichts der auf Verhaltensebene augenscheinlichen Probleme von Kindern mit ADHS im Fokus neuropsychologischer Forschungsbemühungen. Auf der Suche nach spezifischen neuropsychologischen Defiziten ließ sich eine Vielzahl von Auffälligkeiten (u. a. in den Bereichen Inhibition, Daueraufmerksamkeit, geteilte

---

1

Langsame kortikale Potentiale sind Aktivitätsänderungen der elektrischen kortikalen Aktivität im Zeitverlauf mehrerer hundert Millisekunden bis zu mehrerer Sekunden. Diese Veränderungen spiegeln die kurzzeitige Mobilisierung aufgabenabhängiger, kortikaler Verarbeitungsressourcen wider. Während negative SCPs erhöhte Aktivierungsbereitschaft repräsentieren (z. B. während der kognitiven Vorbereitung auf eine Aufgabe, etwa eine schnelle Reaktion), repräsentieren positive SCPs eine Verminderung der Aktivierungsbereitschaft der zugrundeliegenden neuronalen Netzwerke (z. B. während motorischer Inhibitionsprozesse, Birbaumer et al., 1990).

Aufmerksamkeit, Interferenzkontrolle oder Arbeitsgedächtnis) bei Kindern mit ADHS im Vergleich mit Kontrollkindern aufzeigen (Crosbie et al., 2008; Frazier et al., 2004). Es resultierte jedoch eine ausgesprochen heterogene und instabile Befundlage, die daran zweifeln lässt, dass sich eine einheitliche Erklärung der ADHS-Symptomatik auf Basis einer umschriebene neuropsychologischen Dysfunktion finden lässt, wie etwa bei Barkley (1997) im Rahmen des Inhibitionsmodells proklamiert. Bislang zeigte sich in einer Vielzahl neuropsychologischer Untersuchungen eine Vielzahl an Unterschieden zwischen Kindern und Jugendlichen mit ADHS und Kontrollprobanden in einer Vielzahl unterschiedlicher Aufgaben, ohne dass sich ein generelles Defizits oder ein selektives Muster spezifischer Defizite in Form eines neuropsychologischen Profils bei Kindern und Jugendlichen mit ADHS aufzeigen ließ (Übersichten bei Doyle, 2006; Willcutt et al., 2005). Vielmehr scheint es so, dass eine spezifische Gemeinsamkeit von Kindern und Jugendlichen mit ADHS die Instabilität der Leistung, d. h. die intra-individuelle Fluktuation der Aufgabenperformanz ist: „one of the most consistent manifestations of ADHD is the high prevalence of moment-to-moment variability and inconsistency in performance“ (Castellanos et al., 2006; siehe auch Albrecht et al., 2008; Uebel et al., 2010).

Erklärungsmodelle sind demnach gefordert, einen generell instabilen, inkonsistenten Arbeitsstil bei Kindern mit ADHS abzubilden (Castellanos et al., 2005; Perry et al., 2010). Es rücken damit auch motivationale und energetisierende Aspekte der Performanz in den Vordergrund (Sagvolden et al. 2005, Sonuga-Barke et al., 2005). Aktuelle Modelle betonen dabei die Bedeutsamkeit der Interaktion kognitiver Verarbeitungsprozesse im engeren Sinne, bei Castellanos et al. (2006) sog. \`kalter\` exekutiver Funktionen (z. B. Arbeitsgedächtnis oder motorische Inhibition) mit sog. \`heißen\` exekutiven Funktionen, die eher emotional-motivational geprägte Regulationsmechanismen umfassen und Aspekte wie geringere

Toleranz gegenüber Verzögerung, verringerte Fähigkeit zum Bedürfnisaufschub oder Belohnungs-Resistenz zur Folge haben (Sonuga-Barke, 2002; Luman et al., 2005; Vloet et al., 2010). Sergeant (2005) unterscheidet zwischen Problemen in Form von „process dysfunctions“ und „state dysregulations“, die bei Kindern mit ADHS beobachtet werden können. Sergeants „cognitive energetic model“ (2000; 2005, vgl. Abb. 1) differenziert zwischen einer übergeordneten exekutiven (Management-)Ebene (umfasst Selbstmanagement-Ressourcen wie strategische Auswahl und Reflexion von Verhalten), einer basalen Verarbeitungsebene (umfasst umschriebene kognitive Operationen wie Enkodierung, Abgleich mit gespeichertem Wissen, Reaktionsauswahl, motorische Abläufe) und einer mittleren, energetisierenden (Antriebs-)Ebene, die drei handlungsantreibenden Module beinhaltet. *Effort* (Reaktion auf Verstärkung, Motivation, Modulierung von Arousal und Activation), *Arousal* (phasisch, stimulusbezogen, abhängig von Neuheit und Intensität des Reizes) und *Activation* (tonische physiologische Bereitschaft auf Umweltgegebenheiten zu reagieren, Ressource für motorische Kontrolle). Seargent (2005) zufolge können – unterschiedlichen Endophänotypen entsprechend - bei Kindern und Jugendlichen mit ADHS Probleme auf allen Ebenen auftreten. Die energetisierende Ebene nimmt dabei eine zentrale Rolle ein. Hinweise auf Auffälligkeiten in den Bereichen Arousal und Activation liegen aus neurophysiologischen Untersuchungen bei Kindern und Jugendlichen mit ADHS vor (Abweichungen in der Aktivität unterschiedlicher Frequenzbereiche des Spontan-EEG, verminderte P300, CNV, Übersicht bei Banaschewski & Brandeis, 2007; Barry et al., 2003 a, b). Probleme auf dieser Ebene können funktionelle Defizite auf den anderen Ebenen nach sich ziehen und sich z. B. auch durch häufige kurzfristige Aussetzer in der Aufmerksamkeitssteuerung bemerkbar machen (vgl. Castellanos et al., 2005).

2.3 Behandlungsoptionen

Die AWMF-Leitlinien zur Behandlung der Hyperkinetischen Störung (Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie u. a., 2007) sehen ebenso wie die europäischen Leitlinien (Taylor et al., 2004) eine multimodale Behandlung als erforderlich an und schlagen eine Reihe unterschiedlicher Module aus verschiedenen Bereichen vor:

- Psychoedukation aller Beteiligten
- Elterntraining / Interventionen in der Familie
- Interventionen in Schule bzw. Kindergarten
- Bausteine aus dem Bereich kognitiv-verhaltenstherapeutischer Therapieansätze (Selbstinstruktions-, Selbstmanagementansätze)
- Pharmakotherapie

Erwähnung als möglicherweise erfolgreiche Optionen finden darüber hinaus ernährungsbasierte Ansätze (oligoantigene Diät; Omega-3/Omega-6 Supplementierung) sowie Neurofeedback. Es wird jedoch weitere Forschung für beide letztgenannten Interventionsansätze eingefordert.

Eine medikamentöse Behandlung wird für diejenigen Kinder empfohlen, bei denen nicht-medikamentöse Interventionen keine ausreichende Besserung versprechen bzw. erbringen, was v. a. ab einem höheren Schweregrad der Symptomatik zu erwarten ist. Bei einzelnen kognitiv-verhaltenstherapeutisch basierten Interventionsstrategien (Selbstinstruktions-Programme; Selbstmanagement-Programme) wird von vornherein keine ausreichende, d. h. klinisch bedeutsame Wirksamkeit angenommen, so dass sie nur in Kombination mit anderen Interventionen als angezeigt angesehen werden (vgl. auch Abikoff, 1991).

Das für Deutschland gültige Versorgungs-Konzept der „qualitätsgesicherten Versorgung von Kindern und Jugendlichen mit ADHS/ADS“ der Kassenärztlichen Bundesvereinigung (KBV, 2008) sieht zunächst einen Behandlungsversuch ohne Medikamente vor sowie die Begleitung einer medikamentösen Therapie durch weitere psychoedukative, (sozial-) psychiatrische und psychotherapeutische Interventionen.

Wenngleich keine vollständigen empirischen Daten für die Bundesrepublik Deutschland vorliegen, kann man davon ausgehen, eine medikamentöse Behandlung mit Metylphenidat die häufigste Behandlungsform von ADHS darstellt; Methylphendiat-Präparate zählen in den Altersgruppen von 7-10 und 11-13 Jahren zu den am häufigsten verschriebenen Mitteln (Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen, 2009). Die Menge der verschriebenen Tagesdosen erhöhte sich von 8 Millionen im Jahre 1999 auf 53 Millionen anno 2009 (Schwabe & Paffrath, 2009). In den USA erhielten etwa 93% der Kinder mit ADHS (zumindest zeitweise) eine medikamentöse Behandlung (knapp 86% davon mit Stimulanzien), lediglich 26% nahmen psychotherapeutische Sitzungen in Anspruch (Olfson et al., 2003). Am häufigsten erfolgt die medikamentöse Behandlung zwischen dem 6 und 12 Lebensjahr (Zuvekas et al., 2006). Dieses ist das Alter, in dem Kinder mit ADHS am häufigsten medizinische Konsultationen in Anspruch nehmen (Schlander, 2010).

Im Vergleich der bestimmenden Behandlungsmethoden bei ADHS („Methylphenidat“, „kognitive Verhaltenstherapie; VT“, „Kombination aus MPH+VT“, „Treatment as usual“) im Rahmen der bislang größten Vergleichsstudie (MTA-Studie, MTA-Cooperative Group, 1999) erwies sich eine medikamentöse Therapie im kurz- und mittelfristigen Verlauf (Intent-to-Treat-Analyse, Follow-Up nach 14 Monaten) als den nicht-medikamentösen Interventionskombinationen überlegen (MTA-Cooperative-Group, 2004). In der Follow-Up Untersuchung nach 22 Monaten ließ sich jedoch kein Unterschied zwischen den Behandlungsgruppen mehr nachweisen (Swanson et al., 2008). Da alle teilnehmenden Patienten zu diesem Zeitpunkt den zugewiesenen Behandlungsarm bereits schon länger wieder verlassen hatten und vermutlich unterschiedliche Anschlussbehandlungen in

Anspruch nahmen, ist eine eindeutige Interpretation dieses Resultats nicht möglich (Banaschewski et al., 2009). Eine bedeutsame Schlussfolgerung der Autoren lieg darin, dass eine zunächst gut wirkende medikamentöse Behandlung mit Methylphenidat für einen bedeutsamen Anteil der Kinder mit ADHS langfristig eine geringere Wirkung zeige (Swanson et al., 2007).

Medikamentöse Therapieoptionen

Das Mittel der Wahl unter den medikamentösen Behandlungsmöglichkeiten stellen Psychostimulanzien dar (Methylphenidat, D-L-Amphetamin), in erster Linie Methylphenidat (MPH). MPH blockiert die Wiederaufnahme freigesetzten Dopamins und Noradrenalins an der Axonterminale, wodurch eine größere Menge des Botenstoffs im Synaptischen Spalt verfügbar gehalten wird (Engert & Pruessner, 2008; Volkow et al., 2001). Alternativ kommt inzwischen auch verschiedene Nicht-Stimulanzien (am häufigsten das trizyklische Antidepressivum Atomoxetin, ein selektiver Noradrenalin-Wiederaufnahme-Hemmer) zur Behandlung von ADHS zum Einsatz (Übersicht bei Banaschewski et al., 2004; Garnock-Jones & Keating, 2009).

Die klinische Wirkung unterschiedlicher Stimulanzien sowie des Atomoxetins (Effektstärke in etwa 0.7 – 1.0) ließ sich in einer Reihe methodisch sehr gut kontrollierter Studien deutlich aufzeigen (lt. Biederman & Spencer, 2008, liegen inzwischen mehr als 170 kontrollierte Studien vor, die mehr als 9000 Probanden einbezogen), auch für retardierte MPH-Präparate, die durch eine verzögerte Freisetzung des Wirkstoffs eine längere Wirkdauer (bis zu ca. 10 - 12 Std.) gewähren als die konventionellen Präparate (Übersicht bei Banaschewski et al., 2006; Faraone & Buitelaar, 2009). Die o. g. medikamentöse Behandlung ist aber auch mit verschiedenen Schwierigkeiten verknüpft. So liegen die Response-Raten für unterschiedliche

Präparate i. d. R. zwischen 45-70% (Methylphenidat ca. 70%, Banaschewski & Rothenberger, 2010; Atomoxetin ca. 45 %, Newcorn et al., 2008), so dass ein durchaus beträchtlicher Anteil von Kindern- und Jugendlichen mit ADHS von einer (rein) medikamentösen Therapie nicht oder nur unzureichend profitiert (Biederman & Spencer, 2008). Wenngleich sowohl Stimulanzien als auch Atomoxetin generell als gut verträglich angesehen werden können, treten zuweilen unterschiedliche Nebenwirkungen bzw. Begleiterscheinungen auf, die eine medikamentöse Therapie entweder ausschließen, oder zumindest dazu führen, dass eine medikamentöse Therapie nicht langfristig aufrechterhalten wird (Wigal, 2009). Man kann davon ausgehen, dass etwa die Hälfte der medikamentösen Behandlungsversuche nicht länger als ein Jahr dauern (Adler & Nierenberg, 2010; Atzori et al., 2009; Hack & Chow, 2001).Das kann zum Teil, aber wohl nicht ausschließlich, auf Nebenwirkungen der Medikation zurückgeführt werden (Gau et al., 2008). Viele Eltern lehnen eine psychopharmakologische Behandlung aus Prinzip ab (Berger et al., 2008). Der Entscheidungsprozess für oder gegen eine medikamentöse Behandlung scheint von einer Reihe unterschiedlicher Faktoren abzuhängen, z. B. des Störungsmodells der Eltern, des Vertrauens zum Behandler oder der generellen Einstellung gegenüber Medikamenten (DosReis & Myers, 2008; Corkum et al., 1999).

Zu den häufigsten Nebenwirkungen einer Stimulanzientherapie zählen Schlaflosigkeit, Nervosität, depressive Verstimmung und Appetitlosigkeit (Taylor et al., 2004). Darüber hinaus ist eine Stimulanzientherapie möglicherweise mit dem Risiko einer Wachstumsverzögerung verbunden (Faraone et al., 2008). Beschrieben wird auch ein unerwünschter Einfluss von Stimulanzien als auch Atomoxetin auf das kardiovaskuläre System in Form einer Erhöhung von Herzschlagrate und Blutdruck (Stiefel & Besag, 2010; Wernicke, 2003).

Kognitiv-verhaltenstherapeutische Therapieoptionen

Unter den nicht-medikamentösen Behandlungsmöglichkeiten liegen in erster Linie Wirksamkeitsnachweise für verhaltenstherapeutisch orientierte eltern- und schul-, bzw. kindergartenzentrierte Interventionsprogramme vor, die sich auf die Kontrolle und Gestaltung relevanter Umweltfaktoren (Verstärkung erwünschten Verhaltens; Auslöser und Konsequenzen unerwünschter Verhaltensweisen) des betroffenen Kindes in Familie und Umfeld richten (Übersicht bei Chronis et al., 2006). Als weniger wirksam werden Interventionen angesehen, die sich einzig und direkt an das betroffene Kind richten, i. d. R. in Form von Selbstinstruktions- oder Konzentrationstrainings (Abikoff, 1991; Pelham et al., 1998; 2008). Eine Ausnahme unter den kindzentrierten Verfahren bildet dabei derzeit ein Training unterschiedlicher Arbeitsgedächtnisfunktionen (Klingberg et al.,2002; Prins et al., 2011), für das in einer randomisierten, kontrollierten Studie trainingsnahe, aber auch Transfereffekte (Verhaltensbeurteilung durch Eltern und Lehrer) aufgezeigt werden konnten (Klingberg et al., 2005).

Für den deutschsprachigen Raum liegen unterschiedliche, z. T. standardisierte Aufmerksamkeits- bzw. Selbstinstruktionstrainings vor, also Trainings, die primär auf kognitive Kontrolle, Mobilisierung und Selbststeuerung (spezifischer) kognitiver Ressourcen abzielen (Marburger Konzentrationstraining, Krowatschek et al., 2004; Attentioner, Jacobs & Petermann, 2008; Basisfertigkeiten und Strategieeinsatz bei Lauth & Schlottke, 2009) und sich direkt an das betroffene Kind richten (der Einbezug der Eltern ist auf einzelne Sitzungen beschränkt). Daneben liegt mit dem Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten (THOP) ein Programm vor, das deutlicher auf das mit ADHS einhergehende expansive, regelüberschreitende Verhalten eingeht, Module zur Steigerung der sozialen Kompetenz und familiären Interaktion beinhalten und mit einem engeren Einbezug der Eltern einhergehen (THOP, Döpfner et al., 2007). Neben ermutigenden Effekten einzelner Evaluationsstudien (Klingberg, 2005; Lauth & Schlottke, 1996) liegt eine Reihe von Untersuchungen vor, die bezüglich der Wirksamkeit auf die ADHS-Kernsymptomatik im Alltag (Aufmerksamkeitssteuerungsprobleme, Impulsivität, Hyperaktivität) eher ernüchternde Ergebnisse lieferten (Dreisörner 2006; Beck, 1998). Eine differenzierte Übersicht der aktuellen Befundlage bieten z. B. Metternich & Döpfner (2010) oder Bachmann et al. (2008). Randomisierte kontrollierte Evaluationsstudien zu den gängigsten deutschen Therapiemanualen liegen derzeit nicht vor. Der aktuelle Evaluationsstand hinkt damit z. B. beim Marburger Konzentrationstraining der weiten Verbreitung und Anwendung hinterher.

Für den deutschen Sprachraum stehen mit Triple P (Positive Parenting Program; Sanders, 1999); und PEP (Präventionsprogramm für expansives Problemverhalten; Plück et al., 2006) zwei strukturierte und evaluierte Trainingsprogramme für Eltern von Kindern mit expansivem Verhalten zur Verfügung, die sich generell in der Prävention von expansiven Verhaltensstörungen als wirksam erwiesen haben (Bodenmann et al., 2008; Hautmann et al., 2008), sich aber auch speziell in der Anwendung bei Kindern mit ADHS bewährt haben (Bor et al., 2002; Hanisch et al., 2010).

Die Forderung bzw. der Wunsch nach nicht-medikamentösen Behandlungsoptionen sowie die begrenzte (langfristige) Wirksamkeit bisheriger Interventionsstrategien weisen den Bedarf nach weiteren bzw. ergänzenden Behandlungsmodulen für Kinder und Jugendlichen mit ADHS aus, die z. B. die langfristig nachlassende Wirksamkeit einer medikamentösen Behandlung bzw. die nicht ausreichende Wirkung bisheriger kognitiv-verhaltenstherapeutischer Ansätze ergänzen.

3. Neurofeedback – Methodische Grundlagen

3.1 Neurofeedback

Neurofeedback zielt auf die bewusste und gezielte selbstgesteuerte Veränderung neurophysiologischer Parameter ab. Durch die kontingente und kontinuierliche Rückmeldung einzelner als relevant erachteter EEG-Parameter soll der Trainierende in die Lage versetzt werden, selbständig in die Regulation umschriebener hirnelektrisches Muster einzugreifen. Entsprechend operanten Lernmechanismen, werden Aktivitätsveränderungen in die gewünschte Richtung kontinuierlich verstärkt. Welche Prozesse genau dem Regulationserwerb zugrunde liegen, ist dabei bislang ebenso ungeklärt, wie die Mechanismen, die mögliche positive Verhaltensänderungen im Alltag bewirken. Es kann angenommen werden, dass einerseits durch die Stärkung neuronaler Verbindungen, die für die Aufmerksamkeitssteuerung mitverantwortlich sind (vgl. 1.1.2), eine verbesserte Verhaltenssteuerung resultiert. Demnach würde sich Neurofeedback die neuronale Plastizität des sich entwickelnden kindlichen Gehirns zu Nutzen machen und zu einer verbesserten Ausgestaltung neuronaler Netzwerke führen. Hinweis darauf ergeben Veränderungen in unterschiedlichen neurophysiologischen Parametern im Anschluss an ein Neurofeedback-Training (Gevensleben et al., 2009b; Levesque et al., 2006; Doehnert et al., 2008; Wangler et al., 2011). Andererseits versucht man im Rahmen eines Trainings auch durch den bewussten Einsatz der erworbenen Regulationskompetenz im Alltag (in Form von Selbstinstruktionen) Verhaltensänderungen zu erreichen (Heinrich et al., 2007). Eine Einschränkung der Anstrengungsbereitschaft und Selbstwirksamkeitserwartung der Probanden und der Verzicht auf aktive Bemühungen der Probanden um den Transfer erlernter Strategien in den Alltag scheint die Wirksamkeit eines Trainings deutlich einzuschränken (Lansbergen et al., 2010; Logeman et al., 2010). Das Verfahren überträgt damit dem Patienten Verantwortung und Kontrolle über seinen Aufmerksamkeitszustand und setzt ihn in die Lage, gezielt und eigenständig einen möglichst situationsangemessenen, aufmerksamen Zustand einzunehmen, im Sinne eines optimierten Selbstmanagements. NF umfasst somit Elemente neurophysiologischer, kognitiver und lerntheoretischer Ansätze.

3.2 Neurophysiologische Grundlagen und Trainings-Protokolle

Das Elektroencephalogramm (EEG) kann in unterschiedliche Frequenzbereiche unterteilt werden. Die relative Aktivität der Frequenzbänder zueinander spiegelt u. a. Reifungsprozesse als auch mentale bzw. Bewusstseins-Zustände wider (Banaschewski & Brandeis, 2007). So geht etwa ein aufmerksamer, interessiert-gespannter Zustand einer relativen Erhöhung der Beta-Aktivität und reduzierten Theta-Aktivität einher. Situationsabhängig lassen sich darüber hinaus spezielle Verarbeitungsmuster hirnelektrischer Aktivität (Ereignisbezogene Potentiale, EP) ableiten, die als neurophysiologische Äquivalente kognitiver Verarbeitungsprozesse gelten. (Falkenstein et al., 2003; Rockstroh et al., 1993).

Langsame kortikale Potentiale repräsentieren den Depolarisationsgrad apikaler Dendriten kortikaler Pyramidenzellen und stellen Aktivitätsänderungen der elektrischen kortikalen Aktivität im Zeitfenster von mehreren hundert Millisekunden bis zu mehreren Sekunden dar. Sie spiegeln die kurzzeitige Mobilisierung aufgabenabhängiger, kortikaler Verarbeitungsressourcen wider. Während negative SCPs erhöhte Aktivierungsbereitschaft repräsentieren (z. B. während der kognitiven Vorbereitung auf eine Aufgabe, etwa eine schnelle Reaktion), repräsentieren positive SCPs eine Verminderung der

Aktivierungsbereitschaft der zugrundeliegenden neuronalen Netzwerke (z. B. während motorischer Inhibitionsprozesse, Birbaumer et al., 1990). Sowohl in der relativen Aktivität unterschiedlicher Frequenzbänder als auch bei der Generierung langsamer kortikaler Potential ließen sich bei Kindern mit ADHS Auffälligkeiten nachweisen (Übersicht bei Barry et al., 2003 a, b; Banaschewski & Brandeis, 2007).

Diesen neurophysiologischen Auffälligkeiten entsprechend finden bei Kindern mit ADHS in erster Linie zwei unterschiedliche Neurofeedback-Trainingsprotokolle Anwendung (Heinrich, 2010): Das *Theta/Beta-Training*, bei dem die Probanden trainieren, Aktivität im Theta-Bereich zu reduzieren und parallel dazu Aktivität im Beta-Bereich zu erhöhen, adressiert tonische Aspekte kortikaler Aktivierung. Das *Training langsamer kortikaler Potentiale* (SCP-Training) zielt dagegen auf phasische Aspekte kortikaler Exzitabilität ab. Die Teilnehmer haben die Aufgabe, Potentialverschiebungen in positiver Richtung („Positivierung"; Abnahme der Exzitabilität) oder negativer Richtung („Negativierung"; Zunahme der Exzitabililtät) über dem sensomotorischen Kortex zu generieren.

3.3 Bisherige Datenlage

Neurofeedback-Studien, die bei Kindern mit ADHS in den vergangenen Jahren durchgeführt wurden, ergaben übereinstimmend positive Effekte auf der Verhaltensebene. Die durchweg ermutigenden Ergebnisse der einzelnen Studien (Drechsler et al., 2007; Fuchs et al., 2003; Heinrich et al., 2004; Monastra et al., 2002; Strehl et al., 2006) sowie das optimistische Fazit einer ersten Meta-Analyse[2] zur Wirksamkeit von NF bei ADHS (Arns et al., 2009) sollten

---

[2] Die in der vorliegenden Arbeit zusammengefasste Studie ist auch in die Meta-Analyse eingegangen.

dabei nicht darüber hinwegtäuschen, dass grundlegende Anforderungen an eine möglichst strenge wissenschaftlich Prüfung zu etablierender Therapieverfahren (vgl. Loo & Barkley, 2005) von den Studien nicht erfüllt waren und eine methodisch relevante Vergleichsstudie (Randomisierung, ausreichende Teststärke) mit einer adäquaten Kontrollbedingung nicht durchgeführt worden war. Einzelne Studien, die in die Meta-Analyse einbezogen wurden, geben keinen Hinweis, wie die Auswahl der Probanden erfolgte, was die Interpretation der Ergebnisse gerade bei Nachfrage-Populationen (d. h. Teilnehmern, die sich bewusst für ein Training und gegen eine medikamentöse Behandlung entschieden haben) privater, auf finanziellen Gewinn angewiesener Institutionen besonders schwierig macht. Insgesamt zeigte sich bei Arns et al. (2009) für das Neurofeedback-Training eine klinisch relevante Reduzierung in den Bereichen Unaufmerksamkeit (ES = 0.8) und Impulsivität (0.69), in verringertem Maße auch für den Bereich Hyperaktivität (0.4). Die Ergebnisse weisen darauf hin, dass zumindest bei einem Teil der Teilnehmer eines Neurofeedback-Trainings positive Effekte zu erwarten sind, besonders in einer Nachfragepopulation.

Hinweise auf spezifische Effekte ergeben sich aus dem Vergleich der Effekte auf neurophysiologischer Ebene. So gingen in verschiedenen Studien Veränderungen in unterschiedlichen neurophysiologischen Parametern (Spontan-EEG, ERP) mit dem Neurofeedback-Training, nicht jedoch mit dem Kontrolltraining einher (Doehnert et al., 2008; Gevensleben et al., 2009b; Levesque et al., 2006; Wangler et al., 2011).

4. Evaluation des Neurofeedbackprogramms

4.1 Ziele, Design und spezifische Fragestellungen

Ziel unserer Studie war es, methodische Mängel bisheriger Studien zu überwinden und eine möglichst aussagekräftige und strenge Überprüfung von Wirksamkeit und Wirkweise eines Neurofeedback-Trainings durchzuführen. Hauptfragestellungen waren dabei:

- Ist Neurofeedback-Training bei Kindern mit ADHS wirksamer als ein computergestütztes Aufmerksamkeitstraining (engl.: attention skills training, AST)?

- Können erzielte Effekte als dauerhaft angesehen werden?

- Können für ein Neurofeedback-Training bzw. die NF-Protokolle Theta/Beta-Training und SCP-Training spezifische Effekte insbesondere auf neurophysiologischer Ebene aufgezeigt werden?

- Lassen sich Prädiktoren ableiten, die den Erfolg eines Trainings vorhersagen?

Hierzu sind verschiedene englischsprachige Originalarbeiten unserer Arbeitsgruppe veröffentlicht (Ergebnisse auf Verhaltensebene nach Trainingsende: Gevensleben et al. (2009a) bzw. 6 Monate nach Trainingsende (Follow-up): Gevensleben et al. (2010a); Effekte auf neurophysiologischer Ebene einschließlich Prädiktorvariablen: Ruhe-EEG: Gevensleben et al. (2009b), ereignisbezogene Potentiale: Wangler et al. (2011).

Zwischen Mai 2005 und Dezember 2007 nahmen Insgesamt 102 Kinder mit ADHS (8 – 12 Jahre, mittleres Alter 9,6 +/- 1,2 Jahre; 82% Jungen) an dieser randomisierten, kontrollierten Studie teil, die von den kinder- und jugendpsychiatrischen Abteilungen der Universitätskliniken Erlangen und Göttingen sowie dem Heckscher Klinikum in München durchgeführt wurde. Die Kinder absolvierten entweder ein Neurofeedback-Training (N=59) oder ein computergestütztes Aufmerksamkeitstraining (N=35). Die Zuteilung zu den Gruppen erfolgte in einem Verhältnis 3:2 zu Gunsten des Neurofeedback-Trainings u. a. um den intraindividuellen Vergleich der beiden Neurofeedback-Protokolle an einer größtmöglichen Stichprobe durchführen zu können. Die Kalkulation der Stichprobengröße richtete sich nach einem erwarteten mittleren Effekt von 0.5 im Hauptzielkriterium (Gesamtwert der Elternversion des Fremdbeurteilungsbogen für hyperkinetische Störungen, FBB-HKS; Döpfner & Lehmkuhl 2000) bei einer Teststärke von 0.8 (einseitige Testung, $\alpha = 0.05$).

Kinder mit der Diagnose einer Aufmerksamkeitsdefizit- und Hyperaktivitätsstörung entsprechend der DSM-IV Kriterien (American Psychiatric Association, 1994; Mischtyp oder unaufmerksamer Typus) konnten an dem Projekt teilnehmen. Eine detaillierte Darstellung des diagnostischen Vorgehens findet sich in Gevensleben et al. (2009a). Hervorzuheben gilt, dass der überwiegende Teil der Kinder (> 90%) medikamentennaiv waren und begleitende Interventionen nicht erlaubt waren. Die Studie wurde nach den CONSORT Richtlinien für randomisierte Studien durchgeführt (Boutron et al., 2008). Ethik-Voten der Kommissionen aller beteiligten Standorte lagen vor. Die Kinder beider Trainingsgruppen (Neurofeedback vs. computergestütztes Aufmerksamkeitstraining) absolvierten insgesamt 36 Trainingseinheiten a 50 Minuten. Jeweils 2 Trainingseinheiten wurden zu einer Sitzung (dementsprechend a 100 Minuten, unterbrochen durch eine kurze Pause von 5 – 10 Minuten) zusammengefügt. Die Sitzungen wurden auf 2 Blocks von jeweils 9 Sitzungen aufgeteilt. Zwischen den Blocks lag eine Pause von 2-3 Wochen. Es fanden 2-3 Sitzungen pro Woche statt, so dass ein Block 3-4 Wochen dauerte. Das NF-Training stellte eine Kombination aus einem Block Frequenzband-Training und einem Block SCP-Training dar.

Zu insgesamt drei Testzeitpunkten (vor Beginn der Trainings, prä; zwischen beiden Trainingsblöcken, inter, und nach Abschluss des 2. Blocks, post) beurteilten Eltern und Lehrer die Kern- und Begleitsymptomatik anhand gängiger und etablierter Verfahren (z.B. FBB-HKS, Döpfner & Lehmkuhl, 2000). Außerdem wurden neuropsychologische / -physiologische Parameter (Spontan-EEG, EPs beim Attention Network Test, Fan et al., 2002) erhoben. 6 Monate nach Abschluss des Trainings erfolgte eine katamnestische Erhebung auf Verhaltensebene (Elterneinschätzung).

Zusätzlich wurden mittels „Placebo-Skalen“ u. a. Therapieerwartungen und -zufriedenheit der Eltern kontrolliert. Wir versuchten, die Eltern bezüglich der Trainingsgruppe des Kindes blind zu halten.

Durchführung der Trainings - Parallelisierung

Beide Trainingsformen (Neurofeedback vs. computergestütztes Aufmerksamkeitstraining) wurden so vergleichbar wie möglich konzipiert, sowohl vom Setting als auch vom Anforderungscharakter der Aufgaben.

Die Kinder beider Gruppen absolvierten aufmerksamkeitsfordernde Aufgaben am Computer, erarbeiteten sich dabei Strategien zur besseren Steuerung ihrer Aufmerksamkeit (in Form von Selbstinstruktionen) und übten diese in verschiedenen Alltagssituationen ein. Etwa die Hälfte der Trainingszeit bestand direkt aus der Bearbeitung der Aufgaben am Computer. Die andere Hälfte aus der Reflexion des Aufmerksamkeitsstatus während der Aufgaben, dem Ableiten angemessener und individueller Selbstinstruktionen, der Auswahl und Planung von Situationen im Alltag, in denen die erworbenen Strategien zielgerichtet eingesetzt werden sollten, im jeweils letzten Drittel eines Trainingsblocks auch in der Bearbeitung mitgebrachter Schulaufgaben unter Anwendung der erworbenen Strategien. Die Trainings beider Trainingsgruppen erfolgten unter Leitung eines/r Diplompsychologen/in, unterstützt durch eine studentische Hilfskraft. Die Trainings wurden in Zweiergruppen durchgeführt. Jedem Kind stand ein Trainingssystem zur Verfügung.

Um die NF-Trainingseffekte möglichst isoliert betrachten zu können, wurde auf einige begleitende Interventionen verzichtet, die in der Praxis obligatorisch sind. Dies kann die Effektivität des Trainings beeinträchtigen. So wurde, um etwaige konfundierende Effekte auszuschließen, auf die Ergänzung des Trainings durch weitere Lern- und Arbeitsstrategien verzichtet, der Einbezug der Eltern minimiert. Die Durchführung zweier NF-Protokolle in getrennten Blöcken, um jeweils spezifische Effekte der einzelnen Protokolle darstellen zu können, stellt ein eher akademisches Setting dar. Dies ging auf Kosten des Trainingsumfangs für ein einzelnes Protokoll. Die Anzahl von 18 Trainingseinheiten pro Protokoll stellt eher ein Kurzzeit-Training dar. In der Regel werden 30-45 Sitzungen angestrebt; vgl. Doehnert et al. (2008): 30 Einheiten; Fuchs et al.(2003): 36 Einheiten; Leins et al. (2007): 30 Einheiten; Monastra et al. (2002): 43 Einheiten.

Neurofeedback-Training

Für das Neurofeedback-Training wurden ein von unserer Arbeitsgruppe zu Forschungszwecken entwickeltes System (SAM; Self-regulation and Attention Management) eingesetzt, das unterschiedliche Animationen bietet, die v. a. für Kinder konzipiert sind (siehe Abb. 2). Die Kinder haben dabei die Aufgabe, Elemente auf dem Bildschirm durch die Veränderung spezifischer Parameter ihrer Gehirnaktivität zu steuern. Während eines SCP-Trainings mussten Strategien gefunden werden, eine Kugel im unteren Teil des Bildschirms nach oben (Negativierung; Zuwendung von Aufmerksamkeit) oder nach unten (Positivierung; entspannter, gelassener Zustand) zu lenken.

Während des Theta/Beta-Trainings sollte durch Einnehmen eines fokussierten, aufmerksamen Zustandes ein Balken am linken Bildschirmrand (Theta) verkleinert und zeitgleich ein Balken am rechten Bildschirmrand (Beta) vergrößert werden. Verstärkung für richtige Regulation erfolgte in Form von Punkten für erfolgreiche Durchgänge oder den Fortlauf der Animation.

(a) (b)

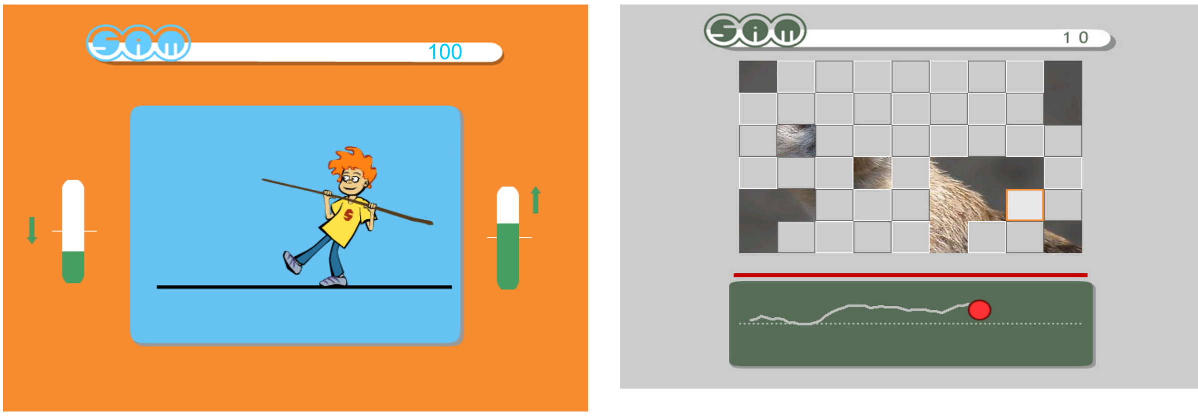


Abbildung 1: Beispiele für Neurofeedback-Animationen

(a) Theta/Beta-Training: Ein Junge (Sam) balanciert auf einem Seil. Er kommt nur voran, wenn die Theta-Aktivität im EEG reduziert und die Beta-Aktivität erhöht wird (bezogen auf Baseline-Werte). Für die Schritte, die Sam vorangeht, erhält das trainierende Kind Punkte. Diese werden auf dem Bildschirm oben rechts angezeigt. Die Aktivität in den beiden Frequenzbändern wird über den Flüssigkeitsstand in den Säulen rückgemeldet (linke Säule: Theta-Aktivität; rechte Säule: Beta-Aktivität).

(b) SCP-Training: Die Kugel, die in jedem Trial von links nach rechts fliegt, soll in Negativierungstrials nach oben und in Positivierungstrials nach unten gelenkt werden: Die vertikale Position der Kugel gibt die SCP-Amplitude wider. Mit jedem erfolgreichen Trial wird ein Teil des verdeckten Bildes aufgedeckt.

Bei der Animation „Puzzle" wurde für einen erfolgreichen Durchgang /Abschnitt ein Teil eines verdeckten Bildes aufgedeckt. Bei einer Animation namens „GöFi-Spiel" wurde zu Beginn eines Durchgangs ein Spielkärtchen mit einer bestimmten Punktzahl angezeigt, um das mit einem vom Computer simulierten Gegner konkurriert wurde. Derjenige, der über den nächsten Durchgang bzw. Abschnitt besser regulierte, bekam die Punkte gutgeschrieben. Wer am Ende des Spiels die meisten Punkte hatte, war Gewinner. Nähere Informationen (incl. technischer Details) finden sich in Originalpublikation 2: Gevensleben et al. (2009b).

Computergestütztes Aufmerksamkeitstraining

Das Kontrolltraining basierte auf Skillies (Auer Verlag, Donauwörth, Deutschland), einem mehrfach ausgezeichneten Computerprogramm, das basale Grundfertigkeiten unterschiedlicher Grundschulleistungen fördern soll. Das Programm läuft als Spiel ab, in dem man als Teil einer Schiffscrew sieben unterschiedliche Inseln bereist, um dort jeweils spezifische Aufmerksamkeit fordernde Aufgaben zu bearbeiten. Gefordert sind dabei u. a. Vigilanz, visuelle und auditive Wahrnehmung, Daueraufmerksamkeit und Reaktionsgeschwindigkeit. Auf der Insel „buntes Riff“ z. B. schwimmen Fische unterschiedlicher Farbe von Bildschirmrand zu Bildschirmrand hin und her. Mit jedem Richtungswechsel ändern sie ihre Farbe. Durch Klicken auf die Fische kann die Farbe durch den Spieler geändert werden. Die Aufgabe besteht darin, alle Fische in die gleiche Farbe zu bringen. Durch diese Aufgabe werden v. a. Vigilanz und Reaktionsschnelligkeit angesprochen. Auf der Insel „verwunschener Teich“ müssen z. B. Memory ähnliche Aufgaben gelöst werden. Evaluationsstudien zu diesem Programm liegen leider bislang nicht vor.

4.2 Kurz – und langfristige Effekte auf Verhaltensebene

94 Kinder der ursprünglichen Stichprobe (NF-Gruppe: N=59; Kontrollgruppe: N=35) konnten in die Auswertung einbezogen werden. Eine detaillierte Darstellung der Ergebnisse findet sich in Gevensleben et al. (2009a). Eltern und Lehrer füllten eine Reihe von Fragebogen zur

Erfassung der Kern- als auch der Begleitsymptomatik aus, wobei sowohl pauschale Symptombewertungen als auch das Vorliegen von Symptomen in spezifischen, konkreten Situationen erfragt wurden: Neben dem FBB-HKS (Erfassung der Kardinalsymptomatik der ADHS; Döpfner & Lehmkuhl, 2000) wurden der Fremdbeurteilungsbogen SSV (FBB-SSV, erfasst Auffälligkeiten im Sozialverhalten, Döpfner & Lehmkuhl 2000), der Strength and Difficulties Questionnaire (SDQ) zur Erfassung eines breiteren Spektrums von Verhaltensstärken und -problemen (Woerner et al., 2004) sowie die Homework Problems Checklist (HPC-D, Döpfner et al. 2007) und der Home Situations Questionnaire (HSQ –D, Döpfner et al. 2007) eingesetzt.

In beiden Gruppen zeigte sich eine signifikante Reduzierung der Symptomatik im Hauptzielkriterium (FBB-HKS Gesamtwert). Dabei erwies sich die Verbesserung in der NF-Gruppe der in der AST-Gruppe als signifikant überlegen. Der Unterschied in den Verbesserungen zwischen den beiden Gruppen erreichte eine mittlere Effektgröße von .60. In den Unterskalen Unaufmerksamkeit und Hyperaktivität / Impulsivität betrug die Verbesserung in der Neurofeedback-Gruppe 25-30% (vgl. Abb. 2).

Auch bezogen auf die Begleitsymptomatik (FBB-SSV, SDQ) schnitt das NF-Training in wesentlichen Parametern besser ab (kleine bis mittlere Effektstärken). Bzgl. situationsspezifischer Verhaltensmuster (HSQ-D, HPC-D) gab es nach Trainingsende zwar in beiden Gruppen signifikante Verbesserungen, die Effekte in der NF-Gruppe und in der AST-Gruppe unterschieden sich jedoch nicht signifikant. Spezifische Unterschiede in der Wirkung zwischen den beiden NF-Protokollen (Theta/Beta- vs. SCP-Training) zeigten sich nicht.

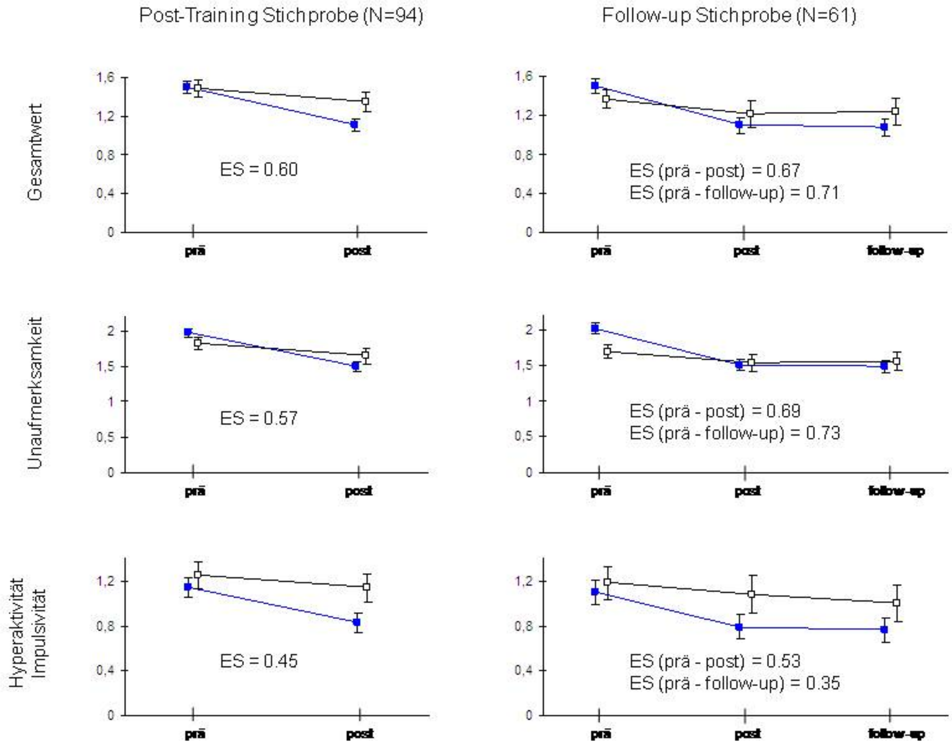


Abb. 2: Trainingsergebnisse für den FBB-HKS Gesamtwert sowie die Unterskalen Unaufmerksamkeit und Hyperaktivität / Impulsivität. Die Post-Training Stichprobe umfasst die Kinder, die ihr Training abgeschlossen hatten; die Follow up-Stichprobe schließt die Kinder ein, für die 6 Monate nach Abschluss des Trainings Fragebogenbeurteilungen der Eltern vorlagen und die keine weitere Therapie (z.B. Medikation) im Follow up-Intervall begonnen hatten, Die Werte für die NF-Gruppe sind jeweils in blau (gefüllt) dargestellt, die Werte für die Kontrollgruppe jeweils in schwarz (transparent).

Die Lehrerurteile ergaben ein vergleichbares Ergebnismuster mit Effektstärken in der gleichen Größenordnung wie die Elternurteile. Auch hier erwies sich das Neurofeedback-Training als dem Kontrolltraining im Hauptzielkriterium FBB-HKS signifikant überlegen und im Vergleich der Veränderungswerte zwischen den beiden Gruppen vom Prä- zum Posttest-Zeitpunkt resultierte im Lehrerurteil eine der Elterneinschätzung vergleichbare mittlere Effektgröße von .64. Der Vergleich der Therapieeffekte für die Symptombereiche

Unaufmerksamkeit und Impulsivität/Hyperaktivität (FBB-HKS Subskalen-Niveau) zeigte sich für den Bereich Unaufmerksamkeit eine signifikante Überlegenheit des Neurofeedbacks (mittlere Effektstärke von .50). Im Bereich Impulsivität/Hyperaktivität unterschieden sich beide Trainingsformen in der Lehrerbeurteilung nicht signifikant voneinander, es ergab sich aber eine Tendenz in Richtung Überlegenheit des Neurofeedback-Trainings (Effektstärke .40). In der Beurteilung des Sozialverhaltens (FBB-SSV) sowie in der Beurteilung der allgemeinen psychopathologischen Belastung (Gesamtwert des SDQ) ergaben sich keine signifikanten Wirksamkeitsunterschiede zwischen den beiden Trainingsgruppen. Lediglich in der Unterskala Hyperaktivität des SDQ erwies sich das Neurofeedback-Training als der Kontrollbedingung signifikant überlegen (Effektstärke .48)

Anhand einer selbst entwickelten, erfahrungsbasierten Itemsammlung (Froemke-Inventar, unveröffentlicht) wurde eine globale Beurteilung der Eltern erhoben bezüglich der Erwartungen an das Training, Zufriedenheit mit dem Training, Bewertung der Motivation der Kinder und eine Einschätzung, an welchem Training (NF, AST) das Kind wohl teilnehme. In beiden Gruppen konnten etwa 40% der teilnehmenden Eltern nicht verlässlich einschätzen, welches Training ihr Kind absolvierte. Das ist gemessen an der vermutlichen Verblindungs-Quote bei Medikamenten-Studien (mit einer Verblindungs-Quote von z. T. weniger als 20%, Morin et al., 1995; Margraf et al., 1991) ein akzeptables Ergebnis. Bezüglich der globalen Beurteilung des Trainings durch die Eltern (Erwartungen an das Training, allgemeine Zufriedenheit mit dem Training) und deren Einschätzung der Motivation der Kinder, unterschieden sich die Bewertungen zwischen den Gruppen nicht.

Das festgelegte Erfolgs-Kriterium einer Verbesserung von mindestens 25% erreichten 52 % der Kinder der NF-Gruppe (insgesamt 30) und 28 % der AST-Gruppe (10 Kinder). Die Responder-Rate lag damit in der NF-Gruppe signifikant höher (odds ratio: 2.68). Dennoch zeigte sich, dass knapp die Hälfte der Kinder der NF-Gruppe das (relativ niedrige) Erfolgskriterium verfehlte. In der AST-Gruppe waren es mehr als 2/3. Die eher niedrige Rate an Respondern kann dabei möglicherweise zumindest teilweise dem akademischen Setting des NF-Trainings geschuldet sein. Evtl. hätten mehr Kinder von dem Training profitiert, wenn sie nicht zwei kurze Protokolle (von jeweils nur 9 Sitzungen), sondern ein Protokoll intensiver (18 Sitzungen) trainiert hätten oder wenn die Trainingsprotokolle aufeinander abgestimmt gewesen wären.

4.2.1 Originalpublikation 1: Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial.

THE JOURNAL OF
CHILD PSYCHOLOGY AND PSYCHIATRY

Journal of Child Psychology and Psychiatry 50:7 (2009), pp 780–789 doi:10.1111/j.1469-7610.2008.02033.x

Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial

Holger Gevensleben,[1] Birgit Holl,[3] Björn Albrecht,[1] Claudia Vogel,[2] Dieter Schlamp,[3] Oliver Kratz,[2] Petra Studer,[2] Aribert Rothenberger,[1] Gunther H. Moll,[2] and Hartmut Heinrich[2,3]

[1]Child & Adolescent Psychiatry, University of Göttingen, Germany; [2]Child & Adolescent Psychiatry, University of Erlangen-Nürnberg, Germany; [3]Heckscher-Klinikum, München, Germany

Background: For children with attention deficit/hyperactivity disorder (ADHD), a reduction of inattention, impulsivity and hyperactivity by neurofeedback (NF) has been reported in several studies. But so far, unspecific training effects have not been adequately controlled for and/or studies do not provide sufficient statistical power. To overcome these methodological shortcomings we evaluated the clinical efficacy of neurofeedback in children with ADHD in a multisite randomised controlled study using a computerised attention skills training as a control condition. **Methods:** 102 children with ADHD, aged 8 to 12 years, participated in the study. Children performed either 36 sessions of NF training or a computerised attention skills training within two blocks of about four weeks each (randomised group assignment). The combined NF treatment consisted of one block of theta/beta training and one block of slow cortical potential (SCP) training. Pre-training, intermediate and post-training assessment encompassed several behaviour rating scales (e.g., the German ADHD rating scale, FBB-HKS) completed by parents and teachers. Evaluation ('placebo') scales were applied to control for parental expectations and satisfaction with the treatment. **Results:** For parent and teacher ratings, improvements in the NF group were superior to those of the control group. For the parent-rated FBB-HKS total score (primary outcome measure), the effect size was .60. Comparable effects were obtained for the two NF protocols (theta/beta training, SCP training). Parental attitude towards the treatment did not differ between NF and control group. **Conclusions:** Superiority of the combined NF training indicates clinical efficacy of NF in children with ADHD. Future studies should further address the specificity of effects and how to optimise the benefit of NF as treatment module for ADHD. **Keywords:** Neurofeedback, attention deficit/hyperactivity disorder (ADHD), slow cortical potentials (SCPs), theta/beta training, randomised controlled trial (RCT), EEG.

Attention deficit/hyperactivity disorder (ADHD) is characterised by developmentally inappropriate levels of inattention, impulsiveness and hyperactivity. It is one of the most common psychiatric disorders in children and adolescents (prevalence: about 5%; Rothenberger, Döpfner, Sergeant, & Steinhausen, 2004; Polaczyk, Silva de Lima, Horta, Biederman, & Rohde, 2007). ADHD is often accompanied by impaired social adjustment, academic problems and high likelihood of psychiatric diagnosis leading to lower adaptive functioning in major life activities in adulthood (Gilberg et al., 2004). So far, medication (methylphenidate) is the most effective treatment though it has disadvantages and limitations, like a considerable rate of non-responders, side-effects and reservations against medication (Taylor et al., 2004; Banaschewski et al., 2006). Even in responders, there is still room for improvement.

European clinical guidelines for hyperkinetic disorder recommend a multimodal treatment, encompassing medication, cognitive behavioural and family treatments (Taylor et al., 2004). However, previous child-oriented cognitive-behavioural intervention strategies have not always proven to be sufficiently effective, especially in terms of generalisation and long-term effects (Abikoff, 1991; Pelham, Wheeler, & Chronis, 1998). Thus there remains a need for effective treatment strategies in improving attentional and self-management capabilities in children with ADHD.

In the search for additional or alternative treatment options for children with ADHD, NF emerged as one of the most promising options (Heinrich, Gevensleben, & Strehl, 2007). NF is a neurobehavioural treatment aimed at acquiring self-control over certain brain activity patterns and implementing these skills in daily-life situations. Two training protocols – training of slow cortical potentials (SCPs) and theta/beta training – are typically used in children with ADHD.

A training of slow cortical potentials[1] is related to phasic regulation of cortical excitability. Surface-negative SCPs ('negativities') and surface-positive SCPs ('positivities') have to be generated over the sensorimotor cortex. Negative SCPs reflect increased

Conflict of interest statement: No conflicts declared.

[1] SCPs lasting from several hundred milliseconds to several seconds are related to the level of excitability of underlying cortical regions. They originate in the apical dendritic layers of the neocortex (Birbaumer, Elbert, Canavan, & Rockstroh, 1990).

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

excitation and occur, e.g., during states of behavioural or cognitive preparation. Positive SCPs are thought to indicate reduction of cortical excitation of the underlying neural networks and appear, e.g., during behavioural inhibition.

In theta/beta training the goal is to decrease activity in the theta band (4–8 Hz) and to increase activity in the beta band (13–20 Hz) of the electroencephalogram (EEG) which corresponds to an alert and focused but relaxed state. Thus, this training paradigm addresses tonic aspects of cortical arousal.

The rationale of applying these paradigms in ADHD is based on findings from EEG and event-related potentials (ERP) studies. For the contingent negative variation (CNV; a typical SCP), reduced amplitude was measured during cued continuous performance tests (CPT) in children with ADHD (for review see Banaschewski & Brandeis, 2007). This finding may be seen in line with the dysfunctional regulation/allocation of energetical resources model of ADHD (Sergeant, Oosterlaan, & Van der Meere, 1999).

In the resting EEG, increased slow wave activity (theta, 4–8 Hz) and/or reduced alpha (8–13 Hz) and beta (13–30 Hz) activity, especially in central and frontal regions, might be associated with ADHD, probably reflecting under-arousal of the central nervous system (for review see Barry, Clarke, & Johnstone, 2003). However, empirical evidence is contradictory and different findings might depend on technical and motivational factors among others.

On the other hand, notwithstanding a (hypothetical neurophysiological) dysfunction, NF can be seen simply as a tool for enhancing specific cognitive or attentional states in certain situations, as it is practised in peak performance applications in arts or sports (Egner & Gruzelier, 2003; Landers et al., 1991). In this respect, children with ADHD may learn compensatory strategies in NF training, underlining the necessity to support participants in acquiring self-regulation abilities and implementing them in critical life situations.

A series of studies provide evidence for positive effects of NF treatment in children with ADHD. For theta/beta training as well as for SCP training a decrease of behavioural problems and improved cognitive performance have been reported (Drechsler et al., 2007; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger 2004; Monastra, Monastra, & George, 2002; Strehl et al., 2006).

However, the studies conducted thus far have obvious shortcomings, such as small sample sizes, lack of an adequate control group, no randomisation, mixed multiple intervention strategies or disregard of long-term outcome. These shortcomings preclude unambiguous interpretation or generalisation of the results (Heinrich et al., 2007; Loo & Barkley, 2005).

In the present trial, the main aim was to control for unspecific effects (e.g., the fact that training is an attention-demanding task) and confounding variables (e.g., parental engagement). Therefore, we chose a computerised attention skills training (AST) as a control condition, with both trainings being conceived as similarly as possible. Sample size was calculated to be large enough to reach sufficient statistical power to reveal at least moderate treatment effects. Since theta/beta and SCP training are thought to address different aspects of cortical regulation – both being important for an optimal attentive behaviour (Rockstroh, Elbert, Lutzenberger, & Birbaumer, 1990; Heinrich et al., 2007) – we intended to integrate both protocols in the NF training, also allowing us to compare the protocols at the intra-individual level.

We hypothesised that improvements in the NF group exceeded the training effects in the control group with respect to all ADHD symptom domains. We expected comparable 'global' effects for the two NF training protocols but were also interested to know whether a distinct pattern may occur at the symptom level.

Methods and materials

Subjects

One hundred and two children with ADHD, aged 8 to 12 years (mean age: 9.6 ± 1.2 years), participated in an NF training or an attention skills training (training period: May 2005 to December 2007). Patients of the outpatient departments of the participating clinics with no urgent need for medication were informed about the project and families who had heard about the study from local professionals applied to take part. Subjects were randomly assigned to one of the two study groups (ratio NF:AST = 3:2). There were no pre-training differences between the NF and AST groups concerning demographic, psychological and clinical variables (see Tables 1 and 2).

All patients fulfilled DSM-IV criteria for ADHD (American Psychiatric Association, 1994). Diagnoses were based on a semi-structured clinical interview (CASCAP-D; Döpfner, Berner, Flechtner, Lehmkuhl, & Steinhausen 1999) and confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD (Döpfner & Lehmkuhl, 2000) by a child and adolescent psychiatrist or a clinical psychologist, supervised by a board-certified child and adolescent psychiatrist. Children with comorbid disorders other than conduct disorder, emotional disorders, tic disorder and dyslexia were excluded from the study. All children lacked gross neurological or other organic disorders. All children were drug-free and without concurring psychotherapy for at least 6 weeks before starting the training. Most of the children (N = 87, see Table 1) were drug-naïve.

The study follows the CONSORT guidelines for randomised trials (Boutron et al., 2008). It was approved by the local ethics committees of the participating clinics and conducted according to the Helsinki

Table 1 Demographic and clinical characteristics of the NF group and the control group: at the pre-training level there were no significant differences between the groups. Dropouts (see text) are not included in the table

	NF group $n = 59$	AST group $n = 35$
No. of patients treated by centre (Erlangen/ Göttingen/München)	23/19/17	16/08/11
Age (years; month)	9;10 ± 1;3	9;4 ± 1;2
Sex (boys/girls)	51/8 (86.4%/13.6%)	26/9 (74.3%/25.7%)
IQ (HAWIK-III, Tewes et al. 2000)	106.1 ± 13.2	104.5 ± 12.9
DSM-IV subtype		
Combined type	39 (66.1%)	27 (77.1%)
Inattentive type	20 (33.9%)	8 (22.9%)
Drug-naive	54 (91.5%)	33 (97.1%)
Associated disorders		
Conduct disorder	10 (16.9%)	7 (20.0%)
Emotional disorder	3 (5.1%)	3 (8.6%)
Tic disorder	3 (5.1%)	0 (.0%)
Dyslexia	12 (20.3%)	10 (28.6%)

declaration. Assent was obtained from the children and written informed consent from their parents.

Design of the study

Both trainings consisted of two blocks of 18 sessions (conducted as nine double sessions of about 2 × 50 minutes each, separated by a short break), with two to three double sessions a week, adapted to the families' routine activities during their weekly schedule (2.74 ± .62 double-sessions per week; no significant differences between the groups). Thus, each block lasted for three to four weeks. Pre-training assessment took place during the week prior to the course. Intermediate and post-training assessment was done about one week after the last session of the first and second training blocks, respectively. The NF training consisted of an SCP block and a theta/beta block (balanced order).

Subjects were randomly assigned to the groups by the administering psychologist. Children trained in pairs but children from different treatment groups were not paired together. Each centre prepared time slots for

Table 2 Parents and teachers behaviour ratings (mean values ± standard deviation)

	NF group (n = 59)		AST group (n = 35)			
Behaviour ratings	Pre-training	Change	Pre-training	Change	Effect-size (Cohen's d)	t-test (1-sided)
Parents						
FBB-HKS						
Total score	1.50 ± .45	−.39 ± .37	1.49 ± .50	−.14 ± .44	.60	$p < .005$
Inattention	1.97 ± .51	−.48 ± .47	1.83 ± .52	−.19 ± .55	.57	$p < .005$
Hyperactivity/ impulsivity	1.14 ± .66	−.31 ± .44	1.25 ± .68	−.12 ± .42	.45	$p < .05$
FBB-SSV						
Oppositional behaviour	1.06 ± .66	−.25 ± .44	1.11 ± .66	−.07 ± .53	.38	$p < .05$
Delinquent and physical aggression	.13 ± .13	−.02 ± .12	.15 ± .13	+.03 ± .15	.37	$p < .05$
SDQ						
Total score	16.0 ± 4.8	−2.29 ± 4.95	16.2 ± 4.9	−.03 ± 3.90	.51	$p < .01$
Emotional symptoms	3.54 ± 2.02	−.37 ± 1.89	3.50 ± 2.60	+.03 ± 2.04		
Conduct problems	2.74 ± 1.80	−.39 ± 1.65	3.03 ± 1.68	−.09 ± 1.79		
Hyperactivity	6.93 ± 1.81	−1.29 ± 1.84	7.00 ± 1.76	−.24 ± 1.62	.60	$p < .005$
Peer problems	2.79 ± 2.23	−.24 ± 1.77	2.65 ± 2.02	+.27 ± 1.59	.30	$p < .1$
Prosocial behaviour	7.32 ± 2.28	+.06 ± 1.51	7.32 ± 2.00	−.18 ± 1.81		
Problem situations in family (HSQ-D)	40.6 ± 24.5	−9.3 ± 20.1	30.2 ± 18.3	−5.0 ± 14.1		
Homework (HPC-D)	35.9 ± 9.1	−5.2 ± 9.5	37.8 ± 16.9	−5.2 ± 8.8		
Teachers						
FBB-HKS						
Total score	1.25 ± .59	−.29 ± .33	1.37 ± .66	−.03 ± .47	.64	$p < .01$
Inattention	1.71 ± .62	−.35 ± .51	1.75 ± .59	−.06 ± .64	.50	$p < .05$
Hyperactivity/ impulsivity	.87 ± .82	−.21 ± .42	1.90 ± .89	.01 ± .59	.40	$p < .1$
FBB-SSV						
Oppositional behaviour	.67 ± .76	−.13 ± .37	.74 ± .82	+.01 ± .45	.34	
Delinquent and physical aggression	.06 ± .11	−.01 ± .08	.09 ± .15	−.03 ± .09		
SDQ						
Total score	13.3 ± 6.1	−2.00 ± 4.30	15.2 ± 6.7	−1.35 ± 4.47		
Emotional symptoms	2.00 ± 2.31	−.39 ± 2.17	2.78 ± 2.39	−.82 ± 2.10		
Conduct problems	1.87 ± 1.99	−.36 ± 1.52	2.44 ± 2.31	−.24 ± 1.92		
Hyperactivity	6.18 ± 2.27	−1.01 ± 1.57	7.11 ± 2.65	−.18 ± 1.88	.48	$p < .05$
Peer problems	3.21 ± 2.41	−.22 ± 1.84	2.89 ± 2.89	−.12 ± 2.03		
Prosocial behaviour	5.79 ± 2.80	+.53 ± 2.25	5.61 ± 2.62	−.12 ± 1.73		

Change = post-training minus pre-training values (negative change scores indicate improvement, except SDQ-Prosocial behaviour). Effect sizes (Cohen's d) ≥ .3 are reported. All t-tests and effect sizes refer to comparisons between the groups.

each treatment and the participants were allocated via lots to these treatment slots.

Parental estimations were controlled via evaluation scales ('placebo scales'; questionnaires assessing expectations, evaluation and satisfaction with the treatment). Parents were explicitly not informed about the treatment condition of their child and, as a rule, did not enter the room during treatment.

Assuming a detectable effect size slightly above .5 for the primary outcome measure[2] (German ADHD rating scale, FBB-HKS total score; Döpfner & Lehmkuhl, 2000) and a dropout rate of 5%, we calculated that we needed to include about 100 children to reach a power of .8 (one-sided, .05-level test; ratio NF:AST = 3:2).

Design of the training programs

Both training programs were designed as similarly as possible concerning the setting and the demands placed upon the participants. Treatment of both groups entailed computer-game-like tasks that demanded attention, development of strategies for focusing one's attention and practising of acquired strategies at home and in school. Both treatments were introduced to the parents and children as experimental, but promising treatment modules for ADHD.

The children of both treatment groups completed their trainings in pairs, with each child working at one computer. About three tasks at the computer lasting for about 25–30 minutes were accomplished in one session.

The training programs were administered by the same clinical psychologists with the support of a student assistant who were instructed to take a neutral attitude concerning the effects of the individual training programs. In both trainings, the therapists had to introduce the next task, discuss problems with the task and the use of strategies ('What did you do to succeed?', 'What was your strategy?', 'How did it work?', 'Did you spend much effort?', 'Were you focused or did something distract you?', 'How could you deal with that?'). In addition, the trainers were asked to motivate and praise the children. Thus, the quality and quantity of interaction were comparable for both trainings.

From the 8th session on, children of both groups had to practise one of their strategies in a specific situation for about 10 minutes each day in daily-life situations (e.g., while reading a book, while playing football). Children were instructed to identify situations in which these strategies would be important, aimed at increasing the children's responsibility for attention control in certain situations. Exercises were documented by keeping a log and controlled at the beginning of the next session. Homework was kept identical in quantity and quality between the groups. Parents were instructed to support the children with the transfer of the learned strategies to everyday life. This parent counselling did not exceed two hours.

[2] This estimation was derived from the effects described in a SCP training study (Heinrich et al., 2004) and a sensorimotor training study (Banaschewski et al., 2001).

Neurofeedback training

The neurofeedback system SAM (Self-regulation and Attention Management), which was developed by our study group, was used for neurofeedback training. It contains several feedback animations to keep the training diversified and appropriate for children. During training, children sat in front of a monitor and controlled a kind of computer game by modulating their brain electrical activity. In the course of the SCP training the task was to find appropriate strategies to direct a ball upwards (negativity trials) or downwards (positivity trials). In the theta/beta-protocol a bar on the left of the screen (representing theta activity) had to be reduced while simultaneously a bar on the right (representing beta activity) had to be increased.

In each SCP training session approximately 120 trials were performed. Negativity (50%) and positivity trials (50%) were presented in random order. A trial lasted for 8 seconds (baseline period: 2 s, feedback period: 6 s). Intertrial interval was set to 5 ± 1 s.

Trials of the theta/beta training lasted for 5 minutes at the start of training and were extended to 10 minutes as the training proceeded. Feedback was calculated from Cz (reference: mastoids, bandwidth: 1–30 Hz for theta/beta training and .01–30 Hz for SCP training, respectively, sampling rate: 250 Hz). Baseline values were determined at the beginning of each session (3 minutes). An adjustment within a session was not scheduled. Vertical eye movements, which were recorded with electrodes above and below the left eye, were corrected online using slightly different regression-based algorithms for theta/beta training (Semlitsch, Anderer, Schuster, & Presslich, 1986) and SCP training (Kotchoubey, Schleichert, Lutzenberger, & Birbaumer, 1997). For segments containing artefacts exceeding ±100 μV in the EEG channel and ±200 μV in the EOG channel, no feedback was calculated.

Transfer trials, i.e., trials without contingent feedback, were also conducted (about 40% at the beginning of a training block and about 60% at the end of a training block).

The children of the NF group were required to practise their focused state (which was practised in the sessions) at home, in different situations (one situation per day, e.g., 'try to be very focused while reading', 'try to stay focused on the ball while playing football this afternoon').

Attention skills training

The attention skills training was based on 'Skillies' (Auer-Verlag, Donauwörth, Germany), an award-winning German learning software, which primarily exercises visual and auditory perception, vigilance, sustained attention, and reactivity. In 'Skillies', the children had to sail to several islands. On each island, a defined task – each requiring different attention-based skills – has to be solved; e.g., on an island named 'Coloured Reef', fish of different colours swim from one side of the screen to the other and back. All fish must be the same colour. The colour can be modified by clicking on a fish. With every change of direction the fish change their colour (fixed order). Thus, the main aim of this task is to improve vigilance and reactivity.

The training was complemented by some self-directed interventions from cognitive therapy to assure comparability to NF, i.e., the children were to compile (meta-)cognitive strategies such as focusing attention, careful processing of tasks and impulse control. Corresponding to the NF group, children of the AST group should practise one of the strategies needed to solve a task of the computer-game ('watch like a hawk'), in daily-life situations (as described in the NF section above).

Parameterisation

Parent and teacher ratings were assessed at three points (pre-training, intermediate, post-training). Pre-training questionnaires were evaluated the week before the first training session, intermediate and post-training ratings followed about one week after the last session of the first and second block, respectively.

- German ADHD rating scale (FBB-HKS; Döpfner & Lehmkuhl 2000): The FBB-HKS is a 20-item questionnaire related to DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorders, frequently used in Germany in the evaluation of medical and cognitive behavioural treatment of ADHD (i.e., Sevecke, Döpfner, & Lehmkuhl, 2004). It was completed by parents and teachers. The severity of each item was rated from 0 to 3. Outcome measures were the main FBB-HKS total score, i.e., the mean value of all items as well as subscores for inattention and hyperactivity/impulsivity. The FBB-HKS total score of the parents constituted the primary outcome measure of the study.
- German Rating Scale for Oppositional Defiant/Conduct Disorders (FBB-SSV; Döpfner & Lehmkuhl, 2000), which allows parameterising oppositional behaviour and delinquent and physical aggression.
- Strength and Difficulties Questionnaire (SDQ; German version; Woerner, Becker, & Rothenberger, 2004), which addresses both positive and negative attributes.
- The Home Situations Questionnaire (HSQ, German version) was used to assess behaviour problems of the child in specific home situations. The HSQ consists of 16 situations in which problematic child behaviour can occur. Parents rate whether the problem behaviour is present in that setting; if so, they rate its severity on a 9-point scale. (Döpfner, Schürmann, & Frölich, 2002).
- Problem behaviour during homework was assessed using the Homework Problem Checklist (HPC, German version). This parent checklist consists of 20 items, rated on a 4-point frequency scale (Döpfner et al., 2002).
- Evaluation scales (Froemke Inventory, 2005; unpublished): a 9-item questionnaire developed by our working group. The first part is made up of items about the assumptions of parents regarding the type of treatment their child receives (neurofeedback, attention skills training, or a combination of both). The second part comprises evaluative questions about the helpfulness of the training (treatment adequacy, satisfaction, and effectiveness) and the motivation of their child on a five-point-scale (0 = in no way/never; 4 = absolute/ever). All items are easy to understand and easy to answer. Psychometric properties of the scales are unexamined.

If post-training ratings of the parents were missing, intermediate ratings were included in the analysis (last-observation-carried-forward approach, LOCF).

Data analysis

Since we had directed hypotheses (larger improvements in the NF group compared to the AST group), one-sided Student's *t*-tests were applied for the analysis of training effects. For these between-group comparisons, change scores (post-training minus pre-training) of parents and teachers ratings were used. Intra-group pre-post comparisons were tested for the primary outcome measure (*t*-test, one-tailed). For comparison of pre-training measures of the NF and AST group and the evaluation of the treatment by the parents ('placebo scales'), two-sided *t*-tests were computed.

For the comparison of the NF protocols, an ANOVA with within-subject factor 'protocol' (theta/beta vs. SCP) and between-subject factor 'order' (of the protocols) was calculated.

To compare the ratio of responders (≥25% reduction of the primary outcome measure) in the NF group and the control group, the odds ratio was calculated.

For all statistical procedures significance was assumed if $p < .05$.

Results

From the 102 children with ADHD who were initially assessed and randomly assigned to a training group, 8 children had to be excluded (NF: $n = 5$; AST: $n = 3$) due to immediate need for medical treatment ($n = 3$), organisational problems of the parents ($n = 2$), loss of motivation ($n = 1$) or protocol violation ($n = 2$). Hence, 94 children were included in the analysis (NF: $n = 59$; AST: $n = 35$) with last-observation-carried-forward in 7 children (NF: $n = 4$; AST: $n = 3$). With mean FBB-HKS total scores of about 1.5, ADHD symptomatology was moderately pronounced in both groups.

Parent ratings

Parent and teacher ratings are summarised in Table 2.

FBB-HKS: Improvement of the NF group in the FBB-HKS total score (primary outcome measure) was superior compared to the AST group ($t(91) = -2.88$; $p < .005$). This effect reached a medium effect size of .60 (Cohen's d).[3] In both treatment groups, a significant improvement resulted (NF: $t(57) = -7.90$; $p < .001$, CI(95%):−.49, −.29; AST: ($t(34) = -1.95$; $p = .03$, CI(95%):−.29, .01).

[3] Considering boys only, the effect size was .56. So, slightly (but not significantly) different gender ratios in the two groups did not affect the main result of our study.

On the subscale level, improvements in inattention and hyperactivity/impulsivity of about 25–30% in the NF group were significantly larger compared to about 10% in the AST group (inattention: $t(91) = -2.71$; $p < .005$); hyperactivity/impulsivity: $t(91) = -2.01$; $p < .05$).

Referring to oppositional and conduct behaviour, the reductions in both *FBB-SSV* subscales in the NF group exceeded the changes in the AST group (oppositional behaviour: $t(91) = -1.82$; $p < .05$; delinquent and physical aggression: $t(91) = -1.81$; $p < .05$).

For the *SDQ* total score as well as for the hyperactivity subscale, the decrease in the NF group was significantly larger than in the AST group (total score: $t(91) = -2.25$; $p < .01$), hyperactivity: $t(91) = -2.71$; $p < .005$). For the remaining SDQ subscales, no significant effects were observed.

Concerning problematic behaviour in family situations (*HSQ-D*) and homework problems *(HPC-D)*, both groups did not differ significantly from each other (HSQ-D: $t(83) = -1.05$, n.s.; HPC: $t(87) = .02$; n.s.). Post-hoc *t*-tests (two-tailed) conducted for the two groups separately indicated improvements in the NF group (HPC: $t(55) = -4.08$, $p < .001$; HSQ: $t(52 = -3.36$; $p < .001$) as well as the AST group (HPC: $t(32) = -3.40$, $p < .002$; HSQ: $t(31) = -2.02$, $p < .1$).

The *responder rate* in the NF group was superior to the rate in the AST group. Thirty children of the NF group (51.7%) and 10 children of the AST group (28.6%) improved more than 25% in the primary outcome measure (odds ratio: 2.68, $p < .05$: CI(95%) = 1.10–6.48).

Parental evaluation/placebo scales: Evaluation scales of 90 participants assessed at the end of the training were available. There was no significant difference between the groups in parents' attitude towards the treatment (e.g., effectiveness: NF group: 3.19 ± .82; AST group: 3.13 ± .90; $t(88) = .30$; $p = .77$) and how parents rated the motivation of their children ('My child does not like the training': NF group: .64 ± .77; AST group: .56 ± 1.13; $t(88) = .37$; $p = .71$).

Forty-two percent of the parents in the NF group and 37% of the parents in the control group could not reliably quote treatment assignment of their child (i.e., these parents voted 'I don't know which training my child attends', 'My child attends a combination of a NF and an AST training' or the parents just estimated the wrong group).

Teacher ratings

For about 70% of the children, pre-training and post-training ratings of the same teacher could be assessed. Missing data, which did not differ significantly between the two groups (χ^2-test: $p = .25$), resulted from school or teacher changes or lack of compliance. For the *FBB-HKS* total score, the reduction in the NF group was superior to the effect in the AST group ($t(60) = -2.55$; $p < .01$). A significant effect was also found for the inattention subscale ($t(60) = -1.94$; $p < .05$) and a trend for the hyperactivity/impulsivity subscale ($t(60) = -1.59$; $p < .1$). Effect sizes of .40 to .64 (medium effect sizes) were in the same range as for the parent ratings (see Table 2).

Analysing FBB-SSV and SDQ ratings of the teachers, a significant effect resulted for the hyperactivity subscale of the SDQ ($t(54) = -1.72$; $p < .05$).

Comparison of theta/beta and SCP training

For both training protocols (theta/beta, SCP), parents rated comparable improvements in the FBB-HKS total score as well as in the inattention and the hyperactivity/impulsivity subscales (see Table 3). Statistics revealed a trend towards better improvement in the FBB-HKS total score, when theta/beta training preceded SCP training ($F(1,50) = 3.00$; $p < .1$).

Discussion

In the present study, the effects of neurofeedback training for children with ADHD were evaluated in comparison to a computerised attention skills training aiming to provide further information about the efficacy of neurofeedback. In contrast to previous studies, the control treatment was designed to parallel the neurofeedback treatment as closely as possible with respect to unspecific factors, using larger

Table 3 *Theta/beta-training vs. SCP-training* (FBB-HKS, parent rating). Each participant of the NF group took part in a SCP- and a theta/beta-protocol block (balanced order). The table shows differences (absolute scores) between the ratings before and after a block

FBB-HKS change	Theta/beta training	SCP training	ANOVA
Total score	−.22 ± .40	−.19 ± .42	Protocol: $F(1,50) = .09$, n.s. Order: $F(1,50) = 3.00$, $p < .1$ P × O: $F(1,50) = .13$, n.s.
Inattention	−.26 ± .52	−.24 ± .56	Protocol: $F(1,50) = .03$, n.s. Order: $F(1,50) = 1.89$, n.s. P × O: $F(1,50) = 1.78$, n.s.
Hyperactivity/impulsivity	−.18 ± .41	−.15 ± .43	Protocol: $F(1,50) = .17$, n.s. Order: $F(1,50) = 1.99$, n.s. P × O: $F(1,50) = 1.31$, n.s.

sample sizes and a randomised group assignment. Neurofeedback was not confounded with additional interventional strategies such as medication, cognitive skills training or parental counselling.

Behaviour ratings by parents and teachers revealed a superiority of the NF training in decreasing ADHD symptomatology. Medium effect sizes of about .6 for the FBB-HKS in parent and teacher ratings indicate that NF effects are substantial and of practical importance. Our results confirm findings of previous NF studies even under strict control conditions.

Positive effects do not appear to be restricted to core ADHD symptoms, but also affected accompanying problems of social adaptation as indicated by the decreases in the FBB-SSV subscales, the SDQ total score, the HSQ and HPC rating.

Control condition

Children in the control group repeatedly practised attentional tasks and their application in daily life. Thus, the control training targets attention management skills directly, i.e., it may have specific aspects (Subrahmanyam, Greenfield, Kraut, & Gross, 2001). Compared to a placebo condition, the use of an attention skills training may have raised the bar for the NF training.

According to scientific standards, a double-blind, placebo-controlled design is suggested to isolate specific effects and is lacking in NF research (Loo & Barkley, 2005). However, such a design, in which participants as well as raters are actually 'blind', is hard to realise for an NF study and must even be questioned for medication studies, which are usually not controlled for the validity of the blinding procedure (Margraf et al., 1991).

Beyond ethical considerations discussed, e.g., in Heinrich et al. (2007), regulation of brain electrical parameters poses certain practical problems for the placebo design. It is difficult to gain mastery over cortical self-regulation. For example, in SCP training up to 60% of the trials are regulated successfully if a subject has appropriate regulation strategies (Leins, 2004), which leaves 40% or more of the trials unsuccessful. Being aware of the possibility of practising a placebo condition may lead to an enhanced impression of uncontrollability, which in turn may result in a loss of motivation and diminished effort (learned helplessness) and thus worsen treatment outcome.

Specific vs. unspecific training effects

The control training was designed to be comparable with respect to training setting, demands upon participants and therapeutic support in general. Since parents of the NF group and the control group did not differ in expectations or satisfaction with the treatment, these factors should not have influenced the results. Thus, our findings support the notion that, first and foremost, specific factors account for the superiority of the NF training.

On the other hand, mainly due to the non-blind design, it is possible that additional factors not considered in our study may have affected the results; e.g., we did not assess the children's attitude towards and satisfaction with the training directly. It cannot entirely be ruled out that expectations, comprehension and effort may have been different between the children of the two groups, even though both trainings were paralleled.

Besides controlling for these factors in future studies, further evidence for the specificity of training effects may be gained by relating neurophysiological measures (e.g., estimates of NF regulation capabilities or pre- to post-training changes in EEG and ERP parameters) to the clinical outcome.

NF training setting

The improvement in the primary outcome measure (FBB-HKS total score) of about 26% after neurofeedback training is comparable to our previous study (Heinrich et al., 2004), as well as behavioural improvements obtained by other groups (Strehl et al., 2006; Drechsler et al., 2007; Fuchs et al., 2003). Actually, we had expected larger effects of about 30–35% since the children had more training sessions and practised both theta/beta training (aiming at tonic aspects of cortical arousal) and SCP training (related to phasic regulation of excitability underlying attentive behaviour). However, one block of 18 sessions might have been too short to build up stable regulation competence. The two protocols were not coordinated but trained in different blocks in order to compare the two protocols at the intra-individual level. To all appearances, several children seemed to be unable to distinguish regulation and transfer strategies of the SCP vs. the theta/beta protocol, but this information was not assessed systematically.

In addition, in order to avoid confounding variables we abstained from some basal elements to enhance effectiveness, such as combination with cognitive/learning strategies and involvement of parents and teachers (Pelham et al., 1998; Drechsler et al., 2007).

Owing to these restrictions of our training setting, it may not be appropriate to indirectly compare the efficacy of NF based on our results with RCTs of other treatment approaches (e.g., long-acting medications with effect sizes of about .6 to 1.0; Banaschewski et al., 2006).

Responders vs. non-responders

As a consequence of the non-optimal training setting, the rate of responders (about 52%) in the neurofeedback group, though superior compared to the control condition (about 29%), fell short of our expectations.

But what differentiates responders from non-responders, i.e., from children who could benefit from NF training but to a smaller degree – or not at all? In a further step it should be investigated if clinical, psychosocial factors as well as neuropsychological and physiological parameters may predict the outcome of NF training. Thus, it could be possible to establish criteria that indicate in which cases NF could be particularly useful as well as identify factors that require particular attention during the training.

General differences between the NF protocols, i.e., theta/beta and SCP training, could not be obtained in our study. However, this does not preclude that an individual child could benefit more from one protocol than the other. Our data also suggest that a certain order of protocols might be advantageous. So the above-mentioned issue of response prediction should also be extended to the question of which factors could influence improvement following a distinct protocol or which combination of protocols might be appropriate for an individual child.

NF in a multimodal treatment setting

Owing to the heterogeneity of children with ADHD and a multiplicity of behavioural and psychosocial factors, it does not seem reasonable to expect sufficient clinical improvement in all children following neurofeedback as the only intervention, particularly if more severely impaired children than those who participated in our study are considered. Further research will show how to combine NF optimally with additional cognitive behavioural and social intervention strategies, parental counselling, and medication within the framework of a multimodal treatment setting. For example, medication might help children benefit more from NF training, or NF could help reduce medication dosage or prevent relapse.

Conclusion

Our results indicate that NF may be considered as a clinically effective module in the treatment of children with ADHD. Further studies are needed not only to replicate our findings but also to control for factors not covered in our study, to further isolate specific effects of NF and to address inter alia how to optimise NF training, also taking the long-term outcome into account.

Note

Trial registry: ISRCTN87071503 – Comparison of neurofeedback and computerised attention skills training in children with attention-deficit/hyperactivity disorder (ADHD). (http://www.controlled-trials.com/ISRCTN87071503).

Acknowledgements

The authors thank Christa Dahlmann, Martin Deinzer, Susanne Wangler and all student assistants for their valuable support as well as all participating families for their contribution and effort. This study was supported by the German Research Foundation (with a joint grant to H.H., G.H.M, and A.R.; HE 4536/2, MO 726/2, RO 698/4).

Correspondence to

Hartmut Heinrich, Heckscher-Klinikum, Deisenhofener Straße 28, D-81539 München, Germany; Tel: (+49)89/9999-1116; Fax: (+49)89/9999-1111; Email: hheinri@arcor.de

Key points

- For children with ADHD, a reduction of inattention, impulsivity and hyperactivity by neurofeedback (NF) has been reported in several studies. To overcome methodological shortcomings of previous studies, we evaluated clinical efficacy in a randomised controlled study using a computerised attention skills training as a control condition.
- For parent and teacher ratings, improvements in the neurofeedback group were superior to those of the control group (medium effect size).
- This is the first randomised controlled trial on neurofeedback in children with ADHD indicating clinical efficacy with sufficient statistical power.

References

Abikoff, M. (1991). Cognitive training in ADHD children: less to it than meets the eye. *Journal of Learning Disabilities*, *24*, 205–209.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Press.

Banaschewski, T., Besmens, F., Zieger, H., & Rothenberger, A. (2001). Evaluation of sensorimotor training in children with ADHD. *Perceptual and Motor Skills*, *92*, 137–149.

Banaschewski, T., & Brandeis, D. (2007). Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective. *Journal of Child Psychology and Psychiatry*, *48*, 415–435.

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., Dankaerts, M., Döpfner, M., Faraone, S.V., Rothenberger, A., Sergeant, J., Steinhausen, H.C., Sonuga-Barke, E.J.S., & Taylor, E. (2006). Long-acting medications for the hyperkinetic disorders: A systematic review and European treatment guideline. *European Child and Adolescent Psychiatry*, *15*, 476–495.

Barry, R.J., Clarke, A.R., & Johnstone, S.J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, *114*, 171–183.

Birbaumer, N., Elbert, T., Canavan, A.G., & Rockstroh, B. (1990). Slow potentials of the cerebral cortex and behavior. *Physiological Reviews*, *70*, 1–41.

Boutron, I., Moher, D., Douglas, G., Altman, G., Schulz, F., & Ravaud, P. (2008). Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and elaboration. *Annals of Internal Medicine*, *148*, 295–310.

Döpfner, M., Berner, W., Flechtner, H., Lehmkuhl, G., & Steinhausen, H.C. (1999). *Psychopathologisches Befund-System für Kinder und Jugendliche (CASCAP-D)*. Göttingen: Hogrefe.

Döpfner, M., & Lehmkuhl, G. (2000). *DISYPS-KJ – Diagnostik-System für psychische Störungen im Kindes- und Jugendalter*. Bern: Hans Huber.

Döpfner, M., Schürmann, S., & Frölich, J. (2002). *Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten (THOP)*. Weinheim: Beltz.

Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H.C., & Brandeis, D. (2007). Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention-deficit/hyperactivity disorder (ADHD). *Behavioural and Brain Functions*, *3*, 35.

Egner, T., & Gruzelier, J.H. (2003). Ecological validity of neurofeedback: Modulation of slow wave EEG enhances musical performance. *Neuroreport*, *14*, 1221–1224.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J.H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. *Applied Psychophysiology and Biofeedback*, *28*, 1–12.

Gilberg, C., Gillberg, I.C., Rasmussen, P., Kadesjö, B., Söderström, H., Råstam, M., Johnson, M., Rothenberger, A., & Niklasson, L. (2004). Co-existing disorders in ADHD – implications for diagnosis and intervention. *European Child and Adolescent Psychiatry*, *15*, 80–92.

Heinrich, H., Gevensleben, H., Freisleder, F.J., Moll, G.H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: Evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry*, *55*, 772–775.

Heinrich, H., Gevensleben, H., & Strehl, U. (2007). Annotation: Neurofeedback – train your brain to train behaviour. *Journal of Child Psychology and Psychiatry*, *48*, 3–16.

Kotchoubey, B., Schleichert, H., Lutzenberger, W., & Birbaumer, N. (1997). A new method for self-regulation of slow cortical potentials in a timed paradigm. *Applied Psychophysiology and Biofeedback*, *22*, 77–93.

Landers, D.M., Petruzello, S.J., Salazar, W., Crews, D.J., Kubitz, K.A., Gannon, T.L., & Han, M. (1991). The influence of electrocortical biofeedback on performance in pre-elite archers. *Medicine and Science in Sports and Exercise*, *23*, 123–129.

Leins, U. (2004). Train your brain: Neurofeedback für Kinder mit einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS). Dissertation, University of Tübingen.

Loo, S.K., & Barkley, R. (2005). Clinical utility of EEG in attention-deficit/hyperactivity disorder. *Applied Neuropsychology*, *12*, 64–76.

Margraf, J., Ehlers, A., Roth, W.T., Clark, D.B., Sheikh, J., Agras, W.S., & Taylor, C.B. (1991). How 'blind' are double-blind studies? *Journal of Consultant and Clinical Psychology*, *59*, 184–187.

Monastra, V., Monastra, D., & George, S. (2002). The effects of stimulant therapy, EEG-biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback*, *27*, 231–249.

Pelham, W.E., Wheeler, T., & Chronis, A. (1998). Empirically supported psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child Psychology*, *27*, 190–205.

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., & Rohde, L.A. (2007). The world-wide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*, 942–948.

Rockstroh, B., Elbert, T., Lutzenberger, W., & Birbaumer, N. (1990). Biofeedback: Evaluation and therapy in children with attentional dysfunction. In A. Rothenberger (ed.), *Brain and behaviour in child psychiatry* (pp. 345–357). Berlin: Springer Verlag.

Rothenberger, A., Döpfner, M., Sergeant, J., & Steinhausen, H.C. (Eds.). (2004). ADHD beyond core symptoms – not only a European perspective. *European Child and Adolescent Psychiatry*, *13*(Suppl.1).

Semlitsch, H.V., Anderer, P., Schuster, P., & Presslich, O. (1986). A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology*, *23*, 695–703.

Sergeant, J.A., Oosterlaan, J., & Van der Meere, J.J. (1999). Information processing and energetic factors in attention-deficit/hyperactivity disorder. In H.C. Quay, & A. Hogan (Eds.), *Handbook of disruptive behavior disorders* (pp. 75–104). New York: Plenum Press.

Sevecke, K., Döpfner, M., & Lehmkuhl, G. (2004). The effectiveness of stimulants of retard forms in children and adolescents with ADHD – a systematic overview.

Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, *32*, 265–278.
Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Birbaumer, N. (2006). Self-regulation of slow cortical potentials: A new treatment for children with attention-deficit/hyperactivity disorder. *Pediatrics*, *118*, 1530–1540.
Subrahmanyam, K., Greenfield, P., Kraut, R., & Gross, E. (2001). The impact of computer use on children's and adolescents' development. *Applied Developmental Psychology*, *22*, 7–30.
Taylor, E., Döpfner, M., Sergeant, J., Asherson, P., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Rothenberger, A., Sonuga-Barke, E., Steinhausen, H.C., & Zuddas, A. (2004). European clinical guidelines for hyperkinetic disorder – first upgrade. *European Child and Adolescent Psychiatry*, *13*(Suppl. 1), I7–30.
Tewes, U., Rossmann, P., & Schallberger, U. (2000). *Hamburg-Wechsler-Intelligenztest für Kinder III (HAWIK-III)*. Göttingen: Hogrefe.
Woerner, W., Becker, A., & Rothenberger, A. (2004). Normative data and scale properties of the German parent SDQ. *European Child and Adolescent Psychiatry*, *13*(Suppl. 2), 11–16.

Manuscript accepted 10 September 2008

4.2.2 Originalpublikation 2: Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial

Sechs Monate nach Abschluss des Trainings lagen von 61 teilnehmenden Kindern, die keine weitere Therapie (z.B. Medikation) begonnen hatten, Fragebogenbeurteilungen der Eltern vor (Gevensleben et al., 2010a). 11 Kinder der NF-Gruppe und 6 Kinder aus der AST-Gruppe hatten im Katamnese-Intervall eine medikamentöse Behandlung mit Methylphenidat begonnen. Auch bei der Follow-up Erhebung zeigte sich eine Überlegenheit des NF-Trainings bzgl. des Hauptzielkriteriums gegenüber der AST-Gruppe mit einer mittleren Effektgröße von .71 (im Vergleich der Verbesserung von Trainingsbeginn bis zum Follow up-Zeitpunkt zwischen NF- und Kontrollgruppe, siehe Abb. 2). Auch für die begleitenden Instrumente (FBB-SSV, SDQ) erhielten sich die Verbesserungen aufrecht. Außerdem wurden größere Effekte für das NF-Training bezüglich der Problembereiche Familie (kleine Effektstärke, ES = 0.33) und Hausaufgaben (mittlere Effektstärke, ES = 0.60) gefunden.

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-010-0109-5

ORIGINAL CONTRIBUTION

Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial

Holger Gevensleben · Birgit Holl · Björn Albrecht · Dieter Schlamp · Oliver Kratz · Petra Studer · Aribert Rothenberger · Gunther H. Moll · Hartmut Heinrich

Received: 8 September 2009 / Accepted: 31 March 2010

Abstract Neurofeedback (NF) could help to improve attentional and self-management capabilities in children with attention-deficit/hyperactivity disorder (ADHD). In a randomised controlled trial, NF training was found to be superior to a computerised attention skills training (AST) (Gevensleben et al. in J Child Psychol Psychiatry 50(7): 780–789, 2009). In the present paper, treatment effects at 6-month follow-up were studied. 94 children with ADHD, aged 8–12 years, completed either 36 sessions of NF training ($n = 59$) or a computerised AST ($n = 35$). Pre-training, post-training and follow-up assessment encompassed several behaviour rating scales (e.g., the German ADHD rating scale, FBB-HKS) completed by parents. Follow-up information was analysed in 61 children (ca. 65%) on a per-protocol basis. 17 children (of 33 dropouts) had started a medication after the end of the training or early in the follow-up period. Improvements in the NF group ($n = 38$) at follow-up were superior to those of the control group ($n = 23$) and comparable to the effects at the end of the training. For the FBB-HKS total score (primary outcome measure), a medium effect size of 0.71 was obtained at follow-up. A reduction of at least 25% in the primary outcome measure (responder criterion) was observed in 50% of the children in the NF group. In conclusion, behavioural improvements induced by NF training in children with ADHD were maintained at a 6-month follow-up. Though treatment effects appear to be limited, the results confirm the notion that NF is a clinically efficacious module in the treatment of children with ADHD.

Keywords ADHD · Neurofeedback · Randomised controlled trial (RCT) · Follow-up · Children

Introduction

For attention-deficit/hyperactivity disorder (ADHD), European guidelines recommend a multimodal treatment tailored to the requirements of the child [29]. Medication (first-line treatment: methylphenidate), cognitive-behaviour therapy and parental training have proven to be effective [22, 31]. But there is still a need for further effective treatment strategies in improving attentional and self-management capabilities in children with ADHD, especially concerning long-term effects [20, 23]. Recent neurofeedback (NF) studies obtained encouraging results and raise the hope of closing the gap in providing children strategies for better self-regulation and -management [9, 12, 28].

NF aims at acquiring self-control over certain brain activity patterns, deriving self-regulation strategies, and implementing these self-regulation skills in daily life.

Trial registry: ISRCTN87071503. Comparison of neurofeedback and computerised attention skills training in children with attention-deficit/hyperactivity disorder (ADHD; http://www.controlled-trials.com/ISRCTN87071503).

H. Gevensleben · B. Albrecht · A. Rothenberger
Child and Adolescent Psychiatry, University of Göttingen, v.Siebold-Str. 5, 37075 Göttingen, Germany

O. Kratz · P. Studer · G. H. Moll · H. Heinrich
Department of Child and Adolescent Mental Health, University of Erlangen-Nürnberg, Schwabachanlage 6+10, 91054 Erlangen, Germany

B. Holl · D. Schlamp · H. Heinrich (✉)
Heckscher-Klinikum, Deisenhofener Straße 28, 81539 Munich, Germany
e-mail: hheinri@arcor.de

Published online: 25 May 2010

Two training protocols—theta/beta training and training of slow cortical potentials (SCPs)—are typically used for children with ADHD [15].

In theta/beta training, children learn to reduce activity in the theta band of the EEG (4–8 Hz) and to increase activity in the beta band (13–20 Hz). In the resting EEG, increased slow wave (theta) activity and/or reduced relative alpha (8–13 Hz) and beta activity was reported in several studies on children with ADHD (for review, see [2, 3]). Thus, theta/beta training may address an underlying neuronal dysfunction. On the other hand, NF may simply be seen as a tool for enhancing specific cognitive or attentional states (an alert and focused but relaxed state in theta/beta training), irrespective of supposed neurophysiological deviations [15].

SCPs are changes of cortical electrical activity lasting from several hundred milliseconds to several seconds. They are thought to represent task-dependent short-term mobilisations of cortical processing resources. While negative SCPs reflect increased excitation (e.g., during states of behavioural or cognitive preparation), positive SCPs indicate reduction of cortical excitation of the underlying neural networks (e.g., during behavioural inhibition) [4].

The contingent negative variation (CNV) is an SCP that reflects anticipation and/or preparation [18]. It is, for example, elicited in cue trials of a continuous performance test. In event-related potential studies, the CNV was found to be reduced in children with ADHD (for review, see [2]). Training of SCPs leads to an increase of the CNV [14]. Thus, SCP training, in which surface-negative and surface-positive SCPs have to be generated over the sensorimotor cortex, could help children with ADHD to improve their assumed dysfunctional regulation of energetical resources [26].

In the last decade, several NF studies in children with ADHD have been published which manage to overcome the methodological shortcomings of earlier studies [9, 10, 14, 21, 28]. In all of these studies, positive behavioural, cognitive and/or neurophysiological effects were described. Our group conducted a randomised controlled trial encompassing 102 children with ADHD. In this trial, behavioural and neurophysiological effects of NF, which included one training block of theta/beta training and one block of SCP training, were analysed in comparison to a computerised attention skills training (AST) [12, 13, 32]. According to parent and teacher ratings, children of the NF group showed larger behavioural improvements than those of the control group (medium effect size of 0.6 for the primary outcome measure, total score of the German ADHD rating scale, FBB-HKS [7]). Due to comparable settings and demands for NF and the control training, superiority of NF was first and foremost ascribed to specific factors. A tendency for larger improvements was observed if theta/beta training preceded SCP training [12].

At the neurophysiological level (resting EEG, event-related potentials), specific associations with behavioural improvements could be revealed for theta/beta and SCP training (e.g., association between decrease of theta activity and reduction of ADHD symptomatology) [13, 32]. These neurophysiological effects contribute to a better understanding of the mechanisms underlying a successful training and indicate specificity of NF training effects.

Both behavioural and neurophysiological findings of our trial indicate that NF may be considered as a clinically efficacious module in the treatment of children with ADHD.

One of the questions which has not been studied under controlled conditions is whether NF training effects remain stable after completing the training. Leins et al. [17] reported that children with ADHD, who had participated in either a theta/beta training or an SCP training, were able to learn cortical self-regulation accompanied by significant improvements in behaviour and cognition. These effects remained constant after 6 months. For a subgroup of 23 (from initially 47) children, 2-year follow-up data could also be assessed [11]. Neuroregulation skills were still preserved. Behavioural and cognitive effects were reported to be stable or even further enhanced. However, due to the lack of a control group, the effects cannot be differentiated from the natural course.

This paper reports follow-up behavioural data assessed 6 months after completion of the training (either NF training or AST) for the children with ADHD of our previous paper [12]. We hypothesised that behavioural improvements in the NF group remain stable and superior to those of the control group.

Materials and methods

Subjects

102 children with ADHD (8–12 years) participated in a NF training or an AST. Subjects were randomly assigned to one of the two study groups (ratio NF, control training = 3:2; see also Fig. 2). Eight children (NF, $n = 5$; AST, $n = 3$) discontinued the study due to immediate need for medical treatment ($n = 3$), organisational problems of the parents ($n = 2$), loss of motivation ($n = 1$) or protocol violation ($n = 2$). Sample size had been estimated a priori to be large enough to detect a medium effect size of about 0.5 with a power of 0.8 (one-sided, 0.05-level test).

Table 1 summarises inter alia demographic, psychological and clinical variables of the children completing their training. Concerning these variables, there were no

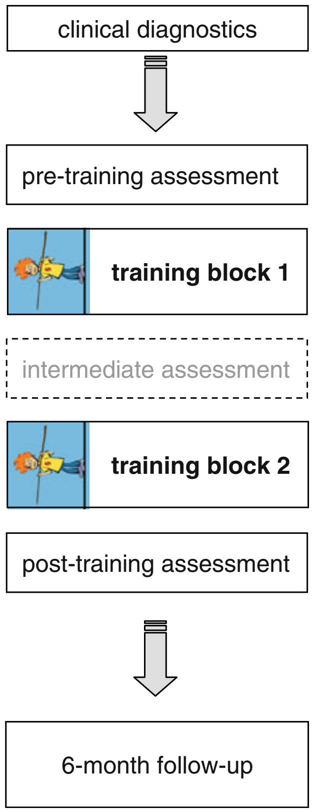


Fig. 1 Schematic illustration of the design of the randomised trial in children with ADHD. The training (neurofeedback, NF; attention skills training) was divided into two blocks. Children of the NF group conducted theta/beta training in one block and SCP training in the other block (balanced order). Behavioural ratings used for follow-up evaluation were assessed before the training started, directly after the end of the training and 6 months after the end of the training

significant differences between NF group ($n = 59$) and control group ($n = 35$).[1]

All patients fulfilled DSM-IV criteria for ADHD [1]. Diagnoses were based on a semi-structured clinical interview (CASCAP-D [6]) and confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD [7] by a child and adolescent psychiatrist or a clinical psychologist, supervised by a board-certified child and adolescent psychiatrist. With mean total FBB-HKS scores of about 1.5 (range 0–3; see Table 2), ADHD symptomatology was moderately pronounced in both training groups. Children with comorbid disorders other than conduct disorder, emotional disorders, tic disorder and dyslexia were excluded from the study. All children lacked gross neurological or other organic disorders. All children were drug-free for at least 6 weeks before starting the training and without concurring psychotherapy.

The study follows the CONSORT guidelines for randomised trials [5]. It was approved by the local ethics committees of the participating clinics and conducted according to the declaration of Helsinki. Assent was obtained from the children and written informed consent from their parents.

Design of the study

The design of the study is illustrated in Fig. 1. NF and AST both consisted of 36 units of 50 min each. Both treatments were divided in two blocks of 18 units. These 18 units were combined in 9 sessions. These sessions took place two to three times a week. The NF training consisted of 1 block of 18 units of theta/beta training and 1 block of 18 units of SCP training (balanced order). For both NF and AST training, there was a break of 2–3 weeks between the two treatment blocks. The NF and the AST training were designed as similarly as possible concerning the setting and the demands upon the participants, e.g., both treatments encompassed attention demanding tasks on a computer (to a comparable amount, 25–30 min per training unit), acquirement of strategies for focussing attention, and efforts to transfer learned strategies into daily life [12]. Parents were not explicitly informed about the treatment condition of their child (NF vs. AST).[2]

Parent ratings were assessed in the week before the training course started (*pre-training*), about 1 week after the last session of the first (*intermediate*[3]) and second training block (*post-training*), respectively, and 6 months after the end of the training (*follow-up*).

In contrast to the other assessment points, neuropsychological/physiological data were not measured at follow-up.

Training programs

Neurofeedback

The NF system SAM ("self-regulation and attention management") which was developed by our study group was used for NF training.

In theta/beta training, the task was to reduce theta and enhance beta activity. A bar on the left of the screen (representing theta activity) had to be reduced while simultaneously a bar on the right (representing beta

---

[1] t tests were computed for age and IQ ($|t(92)| < 1.54$), for all other variables χ^2 tests were applied ($\chi^2 < 2.19$).

[2] At the post-training assessment, about 40% of the parents could not reliably quote treatment assignment of their child. The attitude of the parents in the two groups towards the treatment of their child and post hoc evaluation of the training did not differ (rated via "placebo scales").

[3] These ratings will not be considered for the evaluation of follow-up results in this paper.

Table 1 Demographic and clinical characteristics of the NF group and the control group

	NF group		Control group	
	Post-training sample ($n = 59$)	Follow-up sample ($n = 38$)	Post-training sample ($n = 35$)	Follow-up sample ($n = 23$)
Age (years; month)	9;10 ± 1;3	9;11 ± 1;4	9;4 ± 1;2	9;5 ± 1;1
Sex (boys/girls)	51/8 (86.4%/13.6%)	32/6 (84.2%/15.8%)	26/9 (74.3%/25.7%)	16/7 (69.6%/30.4%)
IQ (HAWIK-III [30])	106.1 ± 13.2	106.5 ± 13.3	104.5 ± 12.9	106.8 ± 13.0
DSM-IV subtype				
Combined type	39 (66.1%)	23 (60.5%)	27 (77.1%)	17 (73.9%)
Inattentive type	20 (33.9%)	15 (40.5%)	8 (22.9%)	6 (26.1%)
Drug-naive	54 (91.5%)	36 (94.7%)	33 (97.1%)	22 (95.7%)
Associated disorders				
Conduct disorder	10 (16.9%)	5 (13.2%)	7 (20.0%)	3 (13.0%)
Emotional disorder	3 (5.1%)	2 (5.2%)	3 (8.6%)	1 (4.3%)
Tic disorder	3 (5.1%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Dyslexia	12 (20.3%)	8 (21.1%)	10 (28.6%)	6 (26.1%)

Data are presented for the children who had completed their training ("post-training sample") and, separately, for the children for whom follow-up data were available ("follow-up sample"). At the pre-training level, there were no significant differences between the groups (neither for the post-training sample nor for the follow-up sample)

activity) had to be increased. In each unit, about five or six trials of 5 min each, or up to three trials of 10 min each, were performed. Baseline values of theta and beta activity were determined at the beginning of each session (3 min). Children were instructed to reach a relaxed but attentive state and to find individual strategies to control the bars.

In SCP training, the children had to generate negative or positive SCPs. They had to find appropriate strategies to direct a ball upwards (negativity trials) or downwards (positivity trials). Negativity (50%) and positivity trials (50%) were presented in random order. A trial lasted for 8 s (baseline period: 2 s, feedback period: 6 s). Children were instructed to reach an attentive (negativity trials) or relaxed state (positivity trials). In each SCP training unit, approximately 120 trials were performed, divided into 2–3 blocks of 40–60 trials in each treatment unit.

For both NF protocols, feedback was calculated from Cz (reference: mastoids, bandwidth: 1–30 Hz for theta/beta training and 0.01–30 Hz for SCP training, respectively, sampling rate: 250 Hz). Vertical eye movements, which were recorded with electrodes above and below the left eye, were corrected online using slightly different regression-based algorithms for theta/beta training [25] and SCP training [16]. For segments containing artefacts exceeding ±100 μV in the EEG channel and ±200 μV in the EOG channel, no feedback was calculated.

Transfer trials, i.e., trials without contingent feedback, were conducted about one-third at the beginning of a training block and about two-third at the end of a training block. These transfer trials, as well as homework, were intended to improve generalisation of treatment effects.

Attention skills training

The AST was based on "Skillies" (Auer-Verlag, Donauwörth, Germany), a German learning software programme which primarily exercises visual and auditory perception, vigilance, sustained attention, and reactivity. In "Skillies", the children had to sail to several islands. On each island, a clearly defined task—each requiring different attention-based skills—had to be solved (for further information, see [12]). The training was complemented by some self-directed interventions from cognitive therapy to assure comparability to NF, i.e., the children were to compile (meta-)cognitive strategies such as focusing attention, careful processing of tasks and impulse control. Corresponding to the NF group, children of the AST group should practice their compiled strategies in daily life situations.

Behavioural assessment

The following questionnaires (assessed at pre-training, post-training and follow-up) were completed by parents to evaluate the follow-up results:

- German ADHD rating scale (FBB-HKS) [7]: The FBB-HKS is a 20-item questionnaire related to DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorders, frequently used in Germany in the evaluation of medical and cognitive behavioural treatment of ADHD (e.g. [27]). The severity of each item is rated from 0 to 3. Outcome measures were the main FBB-HKS total score, i.e., the mean value of all items as well

Table 2 Parent behaviour ratings (mean values ± standard deviation) assessed at pre-training, post-training and follow-up for the children with ADHD for whom follow-up data were available ("follow-up sample")

Behaviour Ratings	Pre	Post	Follow-Up	Pre	Post	Follow-Up	Effect sizes (Cohen's d)	
Follow-up sample	**NF group (n=38)**			**Control group (n=23)**			**Pre-post**	**Pre-follow-up**
FBB-HKS								
Total score	1.50 ± 0.44	1.10 ± 0.51	1.08 ± 0.51	1.37 ± 0.46	1.22 ± 0.65	1.24 ± 0.66	0.67	0.71
Inattention	2.02 ± 0.50	1.51 ± 0.46	1.49 ± 0.55	1.70 ± 0.46	1.54 ± 0.60	1.56 ± 0.60	0.69	0.73
Hyperactivity / impulsivity	1.10 ± 0.67	0.79 ± 0.69	0.76 ± 0.68	1.18 ± 0.68	1.08 ± 0.79	1.00 ± 0.78	0.53	0.35
FBB-SSV								
Oppostional behaviour	1.16 ± 0.70	0.89 ± 0.70	0.86 ± 0.74	1.13 ± 0.70	0.99 ± 0.74	0.97 ± 0.71		0.30
Delinquent and physical aggression	0.15 ± 0.14	0.13 ± 0.15	0.11 ± 0.16	0.15 ± 0.15	0.19 ± 0.22	0.18 ± 0.24	0.43	0.52
SDQ								
Total score	16.1 ± 5.1	13.7 ± 5.6	13.6 ± 5.8	15.9 ± 5.3	15.2 ± 5.8	15.0 ± 6.3	0.43	0.32
Hyperactivity	7.03 ± 1.76	5.62 ± 1.89	5.45 ± 2.14	6.91 ± 1.70	6.57 ± 2.12	6.32 ± 2.23	0.67	0.49
Problem situations in family (HSQ-D)	37.3 ± 20.0	29.2 ± 22.0	28.0 ± 24.4	31.0 ± 22.4	27.1 ± 24.6	28.4 ± 26.8		0.33
Homework (HPC-D)	36.5 ± 7.9	30.8 ± 9.6	28.2 ± 12.1	36.3 ± 10.1	30.6 ± 12.6	33.4 ± 13.1		0.60
Post-training sample [12]	**NF group (n=59)**			**Control group (n=35)**				
FBB-HKS								
Total score	1.50 ± 0.45	1.11 ± 0.47		1.49 ± 0.50	1.35 ± 0.62		0.60	
Inattention	1.97 ± 0.51	1.50 ± 0.56		1.83 ± 0.52	1.65 ± 0.66		0.57	
Hyperactivity / impulsivity	1.14 ± 0.66	0.83 ± 0.64		1.25 ± 0.68	1.14 ± 0.73		0.45	
FBB-SSV								
Oppostional behaviour	1.06 ± 0.66	0.81 ± 0.60		1.11 ± 0.66	1.04 ± 0.68		0.38	
Delinquent and physical aggression	0.13 ± 0.13	0.11 ± 0.14		0.15 ± 0.13	0.18 ± 0.19		0.37	
SDQ								
Total score	16.0 ± 4.8	13.7 ± 5.3		16.2 ± 4.9	15.9 ± 5.5		0.51	
Hyperactivity	6.93 ± 1.81	5.64 ± 1.82		7.00 ± 1.76	6.79 ± 2.38		0.60	
Problem situations in family (HSQ-D)	40.6 ± 24.5	33.5 ± 23.6		30.2 ± 18.3	25.2 ± 24.2			
Homework (HPC-D)	35.9 ± 9.1	30.6 ± 11.0		37.8 ± 16.9	32.6 ± 12.5			

Only effect sizes (Cohen's d) $\geq$ 0.3 are reported. All effect sizes refer to comparisons of the change scores (from pre- to post-training or from pre-training to follow-up) between the training groups. For comparison purposes, the pre-training and post-training measures of all children who had completed the training ("post-training sample") are shown in the lower part (already reported in [12])

as subscores for inattention and hyperactivity/impulsivity. The FBB-HKS total score constituted the primary outcome measure of the study.

- German Rating Scale for Oppositional Defiant/Conduct Disorders (FBB-SSV) [7]: It is comprised of 25 items. The severity of each item is rated from 0 to 3. Outcome measures were the subscales oppositional behaviour (mean value of the first 9 items) and delinquent and physical aggression (mean value of the remaining 16 items).
- The Strength and Difficulties Questionnaire (SDQ, German version) [24, 33] is comprised of 25 items which address both positive and negative attributes. Each item is rated from 0 to 2. Outcome measures were the total difficulties score as well as the five subscales (emotional symptoms, conduct problems, hyperactivity, peer problems, prosocial behaviour).
- The Home Situations Questionnaire (HSQ, German version) [8] was used to assess behaviour problems of the child in specific home situations. The HSQ consists of 16 situations in which problematic child behaviour can occur. Parents rate whether the problem behaviour is present in that setting; if so, they rate its severity on a nine-point scale.
- Problem behaviour during homework was assessed using the Homework Problem Checklist (HPC, German version) [8]. This checklist consists of 20 items, rated on a four-point frequency scale.

Data analysis

Per-protocol analysis was conducted to avoid confounding the treatment effects with additional treatment. Children were classified as dropouts and excluded if they had started another treatment (e.g., medication, psychotherapy) or if questionnaires were not returned.

Behavioural data were analysed in repeated-measures ANOVAs with between-subject factor GROUP (NF vs. control training), within-subject factor TIME (post-training, follow-up) using the baseline (pre-training) measure as a covariate. If NF training effects are still superior to the control training at follow-up, the ANOVA is expected to reveal a significant GROUP effect. If the difference between the two trainings becomes significantly greater or smaller, this effect is expected to be indicated by a significant GROUP $\times$ TIME interaction.

Effect sizes (Cohen's *d*) were calculated as the difference of the change of a measure from pre-training to an assessment point (post-training and follow-up, respectively) and the corresponding change score in the control group divided by the pooled standard deviations of these change scores. To compare the ratio of responders ($\geq$25% reduction of the primary outcome measure) in the NF group and the control group, the odds ratio was calculated.

Though limited by a smaller sample size, possible effects of the order of the NF training blocks were tested by comparing improvements in the FBB-HKS obtained at post-training and at follow-up (*t* tests).

Since there were about 35% dropouts (see "Results"), we also tested for differences in the clinical (behavioural) data between the dropouts and the remaining children. We computed ANOVAs with between-subject factors GROUP (NF vs. control training) and DROPOUT (dropout vs. follow-up data available) and within-subject factor TIME (pre-training, post-training).

SPSS (v.16) was used for statistical analysis. For all statistical procedures, significance was assumed if $p < 0.05$.

Results

Dropouts

17 children (NF group: $n = 11$, 18.6%[4]; control group: $n = 6$, 17.1%) started a medication during the follow-up interval. None of the children started any other treatment. Parents of 16 children (NF group: $n = 10$, 16.9%; control group: $n = 6$, 17.1%) did not return the questionnaires. Thus, there were 33 dropouts with percentages of dropouts not differing between NF and control group ($\chi^2 = 0.034$, $df = 2$, n.s.).

Analysis of the training effects at 6-month follow-up encompassed 61 of the 94 children completing the training (NF group: $n = 38$, control group: $n = 23$; see also Fig. 2).

Comparing the dropouts and the remaining children, dropouts were not characterised by significantly smaller training effects, i.e., no significant effect containing the factor TIME (pre- vs. post-training) was obtained in the repeated-measures ANOVAs. Dropouts tended to have higher FBB-HKS scores (FBB-HKS total score: factor DROPOUT: $F(1,90) = 3.22$; $p < 0.1$; FBB-HKS Inattention subscale: $F(1,90) = 3.18$; $p < 0.1$), mainly in the control group as indicated by a trend for the GROUP $\times$ DROPOUT interaction. For all other rating scales, no significant effect or trend containing the factor DROPOUT was obtained.

NF versus control training

Results are summarised in Table 2. Ratings of the children for whom follow-up data were available ("follow-up sample") are presented in the upper part. To facilitate comparison, the pre-training and post-training measures of all children who completed the treatment ("post-training sample") are shown in the lower part of Table 2 (already reported in [12]). Only effect sizes $\geq$ 0.3 are reported.

For the FBB-HKS total score (primary outcome measure), statistics revealed a significant GROUP effect ($F(1,58) = 10.10$; $p < 0.005$) but no significant TIME (post-training vs. follow-up) ($F(1,58) = 0.69$; n.s.) or GROUP $\times$ TIME interaction effect ($F(1,58) = 0.01$; n.s.). Hence, NF training effects were still superior to the control training at follow-up (medium effect size of 0.71 for change measure from pre-training to follow-up).

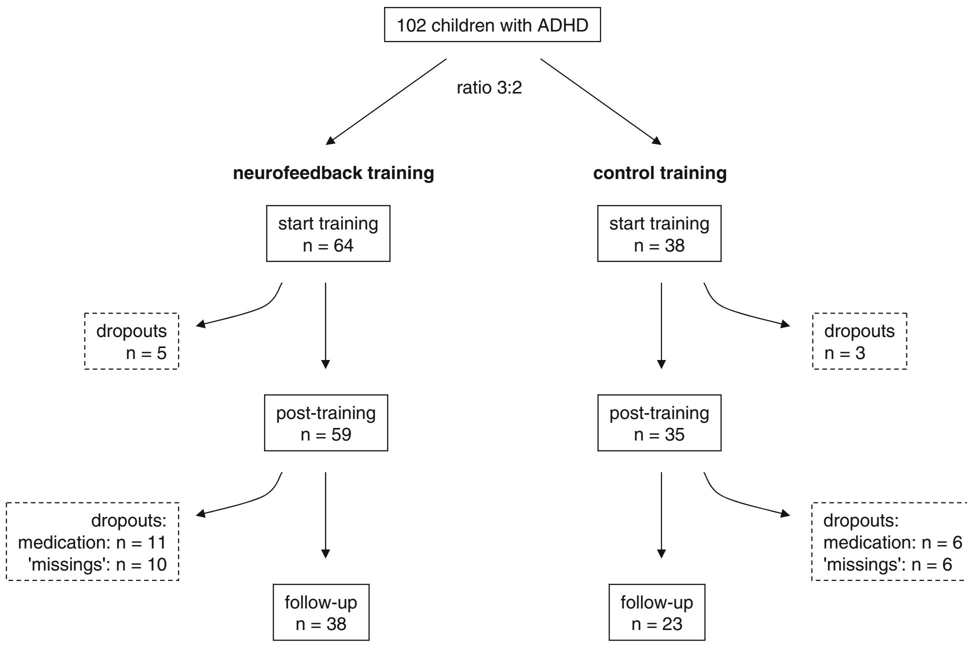
Correspondingly, a significant GROUP effect for the FBB-HKS Inattention subscale ($F(1,58) = 4.72$; $p < 0.05$) and a trend for the FBB-HKS Hyperactivity/Impulsivity subscale ($F(1,58) = 3.45$; $p < 0.1$) were obtained. Reductions of inattention and hyperactivity/impulsivity at follow-up (compared to pre-training) were about 25–30% in the NF group compared to about 10–15% in the control group.

Concerning the FBB-SSV subscale Delinquent and Physical Aggression, the ANOVA yielded a trend for the factor GROUP ($F(1,56) = 3.64$; $p < 0.1$) due to larger decreases in the NF group. Small to medium effect sizes were obtained at post-training and follow-up, respectively.

For the SDQ subscale Hyperactivity, a significant GROUP effect ($F(1,57) = 5.49$; $p < 0.05$) indicated larger improvements for the NF group in comparison to the control group still evident at follow-up. While medium effect sizes were observed for this subscale, small effect sizes resulted for the SDQ total score. For the remaining

[4] 5 (of these 11) children of the NF group starting a medication had been classified as responders at the end of the training.

Fig. 2 Patient flow diagram



SDQ subscales (not reported in Table 2), effect sizes were smaller than 0.3.

Concerning homework problems (HPC-D), the GROUP × TIME interaction turned out to be significant ($F(1,54) = 4.18$; $p < 0.05$). Post hoc, we computed an ANOVA with the follow-up score as dependent variable, GROUP as between-subject factor and the pre-training score as covariate. For this analysis, a significant GROUP effect was found ($F(1,54) = 5.48$; $p < 0.05$) indicating a larger positive effect concerning homework after NF training (compared to the control training) at follow-up (medium effect size of 0.60). Neither the decrease in NF group ($F(1,32) = 1.56$, n.s.) nor the increase in the control group from post-training to follow-up ($F(1,32) = 0.02$, n.s.) reached significance.

For the problem situations in family (HSQ-D) questionnaire, no significant effects were obtained.

Responder rate

In the follow-up sample, 50% (19 of 38) of the children of the NF group showed a reduction of 25% or more in the primary outcome measure at post-training and also 50% at follow-up. According to this criterion, 26.1% (6 of 23) of the children of the control group were responders at post-training and 30.4% (7 of 23) at follow-up. Odds ratios were 2.83 (post-training) and 2.29 (follow-up) and, thus, in the same range as in the post-training sample (odds ratio: 2.68 [12]) but failed to reach significance due to the smaller sample size (Fisher's exact test, one-sided: post-training: $p = 0.06$; follow-up: $p = 0.11$).

Order of NF protocols

For the follow-up sample, improvements in the FBB-HKS total score at post-training were non-significantly higher when theta/beta training preceded SCP training as compared to the reversed order of protocols ($t(35) = -0.75$, $p = 0.46$; $d = 0.25$). The effect size for the post-training sample had been 0.43 [12]. At follow-up, the improvements for both orders were nearly identical ($t(35) = -0.04$, $p = 0.97$; $d = 0.01$).

Discussion

The impact of a treatment significantly relies on the generalisation of treatment effects, which can be conceptualised as occurring across settings, behaviour variables and time [19]. This underlines the necessity to consider multiple indicators as well as to assess follow-up measurements concerning the stability of effects. In previous papers, we reported the immediate treatment effects of a NF training (theta/beta training and SCP training) compared to an AST on different outcome levels, encompassing behavioural and neurophysiological measures [12, 13, 32]. This paper deals with the 6-month follow-up analyses of the behavioural outcome. Since some children started medication, we conducted a per-protocol analysis in order to avoid confounding the treatment effect with medication effect. For 61 of the 94 children (ca. 65%) of this sample, 6-month follow-up data (parent ratings) could be analysed. On average, effects were sustained at follow-up and the effects in the NF group were still superior to those of the control group. For the total score of the German ADHD rating scale (primary outcome measure), a medium effect size was obtained. Further, effects were not restricted to core ADHD symptoms but could also be observed in other domains (homework situation, conduct disorder; small to medium effect sizes). Regarding order effects for the NF protocols, the tendency for larger improvements when theta/beta training preceded SCP training could not be confirmed in the follow-up sample.

Since settings and demands for NF and the control training were comparable, these findings indicate that mainly specific effects accounted for the superiority of NF compared to the ASTs.

Specificity of effects is further supported by associations between neurophysiological patterns and the outcome at the clinical (behavioural) level as reported in [13, 32]. For example, in theta/beta training, the decrease of theta activity in the resting EEG was associated with a decrease of the FBB-HKS total score [13]. Concerning SCP training, children with a higher CNV in an attention test at baseline showed larger improvements after the relatively short training block [32].

On the other hand, partly due to the non-blind design, it cannot be ruled out that unspecific effects might have also contributed to the behavioural effects.[5]

There was a relatively large number of dropouts, i.e., children who either started a medication or for whom no questionnaires were received, at follow-up (about 35%). However, dropouts were not characterised by a worse training outcome at the end of the training. These children (mainly in the control group) had slightly (but non-significantly) higher scores on the German ADHD rating scale already at the beginning of the training. In general, children for whom follow-up data were available could not be differentiated from dropouts with respect to behavioural or demographic characteristics. So, it seems unlikely that the follow-up results were strongly biased by the large portion of dropouts.

Findings are based on parent ratings only. At the post-training assessment, for only about 70% of the children, ratings of the same teacher who had completed the pre-training questionnaires were available. Expecting further high dropout rates due to change of teachers and loss of motivation to complete the questionnaires, we decided not to include teacher ratings in the follow-up analysis. It can be questioned whether teacher ratings would have supported the follow-up results obtained from parent ratings. However, in [17], parent and teacher ratings did not develop differentially from post-training to follow-up. In our study, comparable effects resulted for parent and teacher ratings at the post-training assessment [12].

50% of the children completing the training were categorised as non-responders, according to a criterion of 25% reduction in the primary outcome measure. 11 out of 59 children of the NF group started a medication during the follow-up interval. Our study was not designed to achieve maximum NF training effects but had an arguably artificial scientific setting (e.g., separating theta/beta and SCP training in two separate, non-coordinated blocks). Nevertheless, the low responder rate and the portion of children starting a medication in our study argue against NF as a stand-alone intervention for children with ADHD. The results indicate that not every child with ADHD may improve after NF treatment. In our opinion, NF should rather be seen as a treatment module for children with ADHD which can be embedded in a multimodal treatment program tailored to the individual needs of a child.

Stability of training effects at follow-up refers to the mean scores of the NF group and naturally does not apply to all individuals within the group. In our design, we used a fixed number of training sessions. This was intended to standardise number of treatment sessions across all individuals. However, qualitative analyses of our data suggest that children vary in their abilities and speed to learn and apply NF techniques. One block of 18 units for a single protocol might have been too short at least in some children to build up stable regulation capability and to establish transfer into daily life sufficiently. Further research therefore would be required to determine the optimal NF protocol (or combination of protocols) and the adequate number of treatment sessions for a particular child.

Coming back to the long-term outcome, it could be helpful at least for some of the children to conduct further training sessions with longer intervals between the training session to sustain and consolidate regulation capabilities and the transfer into daily life, just as it is usually practiced in conventional cognitive-behaviour therapy. In this respect, the possible benefit of such booster sessions should also be investigated in further studies.

Conclusions

Behavioural effects of NF training were maintained in children with ADHD at 6-month follow-up, further supporting clinical efficacy of this neurobehavioral training. NF may be recommended as a treatment module for children with ADHD besides conventional behavioural trainings and medication. Future studies should systematically address how to optimise/individualise NF training and how to embed it in a multimodal treatment in children with ADHD.

[5] For a more detailed discussion concerning the control condition, see [12].

Acknowledgments The authors thank Christa Dahlmann, Martin Deinzer, Claudia Vogel, Susanne Wangler, Nicola Wöstmann and the student assistants for their valuable support as well as all the participating families for their contribution and effort. We thank Margaret and Simon Tiffin-Richards for language editing. This study was supported by the German Research Foundation (with a joint grant to H.H., G.H.M, and A.R.; HE 4536/2, MO 726/2, RO 698/4).

References

1. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). American Psychiatric Press, Washington, DC
2. Banaschewski T, Brandeis D (2007) Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us—a child psychiatric perspective. J Child Psychol Psychiatry 48:415–435
3. Barry RJ, Clarke AR, Johnstone SJ (2003) A review of electrophysiology in attention-deficit/hyperactivity disorder. I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 114:171–183
4. Birbaumer N, Elbert T, Canavan AG, Rockstroh B (1990) Slow potentials of the cerebral cortex and behavior. Physiol Rev 70:1–41
5. Boutron I, Moher D, Douglas G, Altman G, Schulz F, Ravaud P (2008) Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 148:295–310
6. Döpfner M, Berner W, Flechtner H, Lehmkuhl G, Steinhausen HC (1999) Psychopathologisches Befund-System für Kinder und Jugendliche (CASCAP-D). Hogrefe, Göttingen
7. Döpfner M, Lehmkuhl G (2000) DISYPS-KJ—Diagnostik-System für psychische Störungen im Kindes-und Jugendalter. Hans Huber, Bern
8. Döpfner M, Schürmann S, Frölich J (2002) Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten (THOP). Weinheim, Beltz
9. Drechsler R, Straub M, Doehnert M, Heinrich H, Steinhausen HC, Brandeis D (2007) Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention-deficit/hyperactivity disorder (ADHD). Behav Brain Funct 3:35
10. Fuchs T, Birbaumer N, Lutzenberger W, Gruzelier JH, Kaiser J (2003) Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl Psychophysiol Biofeedback 28:1–12
11. Gani C, Birbaumer N, Strehl U (2008) Long term effects after feedback of slow cortical potentials and of theta-beta-amplitudes in children with attention-deficit/hyperactivity disorder. Int J Bioelectromagn 10:209–232
12. Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O, Studer P, Rothenberger A, Moll GH, Heinrich H (2009) Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. J Child Psychol Psychiatry 50(7):780–789
13. Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P, Wangler S, Rothenberger A, Moll GH, Heinrich H (2009) Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. Int J Psychophysiol. doi:10.1016/j.ijpsycho.2009.08.005
14. Heinrich H, Gevensleben H, Freisleder FJ, Moll GH, Rothenberger A (2004) Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. Biol Psychiatry 55:772–775
15. Heinrich H, Gevensleben H, Strehl U (2007) Annotation: neurofeedback—train your brain to train behaviour. J Child Psychol Psychiatry 48:3–16
16. Kotchoubey B, Schleichert H, Lutzenberger W, Birbaumer N (1997) A new method for self-regulation of slow cortical potentials in a timed paradigm. Appl Psychophysiol Biofeedback 22:77–93
17. Leins U, Hinterberger T, Kaller S, Schober F, Weber C, Strehl U (2006) Neurofeedback for children with ADHD: a comparison of SCP- and theta/beta-protocols. Prax Kinderpsychol Kinderpsychiatr 55:384–407
18. Lütcke H, Gevensleben H, Albrecht B, Frahm J (2008) Brain networks involved in early versus late response anticipation and their relation to conflict processing. J Cogn Neurosci. doi:10.1162/jocn.2008.21165
19. Mash EJ, Barkley RA (2006) Treatment of childhood disorders, 3rd edn. The Guilford Press, New York
20. Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR, MTA Cooperative Group (2009) The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 48(5):484–500
21. Monastra V, Monastra D, George S (2002) The effects of stimulant therapy, EEG-biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback 27:231–249
22. The MTA Cooperative Group (1999) A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1073–1086
23. Rothenberger A, Döpfner M, Sergeant J, Steinhausen HC (eds) (2004) ADHD beyond core symptoms—not only a European perspective. Eur Child Adolesc Psychiatry, 13 (Suppl 1)
24. Rothenberger A, Becker A, Erhart M, Wille N, Ravens-Sieberer U, the BELLA study group (2009) Psychometric properties of the parent strengths and difficulties questionnaire in the general population of German children and adolescents: results of the BELLA study. Eur Child Adolesc Psychiatry 17(Suppl 1):99–105
25. Semlitsch HV, Anderer P, Schuster P, Presslich O (1986) A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. Psychophysiology 23:695–703
26. Sergeant JA, Oosterlaan J, van der Meere JJ (1999) Information processing and energetic factors in attention-deficit/hyperactivity disorder. In: Quay HC, Hogan A (eds) Handbook of disruptive behavior disorders. Plenum Press, New York, pp 75–104
27. Sevecke K, Döpfner M, Lehmkuhl G (2004) The effectiveness of stimulants of retard forms in children and adolescents with ADHD—a systematic overview. Zeitschrift für Kinder- und Jugendpsychiatrie Psychotherapie 32:265–278
28. Strehl U, Leins U, Goth G, Klinger C, Hinterberger T, Birbaumer N (2006) Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. Pediatrics 118:1530–1540
29. Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Rothenberger A, Sonuga-Barke E, Steinhausen HC, Zuddas A (2004) European clinical guidelines for hyperkinetic disorder—first upgrade. Eur Child Adolesc Psychiatry 13(Suppl 1):I7–I30
30. Tewes U, Rossmann P, Schallberger U (2000) Hamburg-Wechsler-Intelligenztest für Kinder III (HAWIK-III). Hogrefe, Göttingen
31. van der Oord S, Prins PJ, Oosterlaan J, Emmelkamp PM (2008) Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. Clin Psychol Rev 28(5):783–800

32. Wangler S, Gevensleben H, Albrecht B, Studer P, Rothenberger A, Moll GH, Heinrich H (2010) Neurofeedback in children with ADHD: specific event-related potential findings of a randomized controlled trial (in preparation)

33. Woerner W, Becker A, Rothenberger A (2004) Normative data and scale properties of the German parent SDQ. Eur Child Adolesc Psychiatry 13(Suppl 2):11–16

4.3 Effekte auf neurophysiologischer Ebene

Die neurophysiologischen Untersuchungen fanden zu den drei Erhebungszeitpunkten statt (prä: im Verlauf der Woche vor Trainingsbeginn; inter, post: jeweils im Verlauf der Woche nach Abschluss des vorhergehenden Trainingsblocks). Der Vergleich zwischen NF- und AST-Training basiert auf der Prä- und Post-Ableitung; für den Vergleich Theta/Beta- vs. SCP-Training wurde auch die Ableitung zwischen den beiden Trainingsblöcken verwendet.

4.3.1 Originalpublikation 3: Distinct EEG effects related to neurofeedback training in children with ADHD: A randomized controlled trial

Im EEG (Ruhezustand, 2 min, Augen offen) zeigte sich in der NF-Gruppe im Gegensatz zur AST-Gruppe eine signifikante Reduzierung der Theta-Aktivität über centro-parietalen Mittellinienelektroden. Diese Reduzierung war nicht, wie ursprünglich erwartet, auf den Trainingsblock des Theta/Beta-Trainings zurückzuführen, sondern resultierte mit vergleichbarem Anteil beider Trainingsblöcke aus dem kombinierten Training. Spezifische Veränderungen im EEG in Folge eines einzelnen NF-Protokolls ließen sich nicht aufzeigen. Die relativ geringe Anzahl an Trainingseinheiten pro Protokoll mag dafür mitverantwortlich sein. Es ist vorstellbar, dass sich mit einer höheren Anzahl an Sitzungen spezifische Effekte aufzeigen lassen. Hinweise darauf finden sich in spezifischen Assoziationen, die sich zwischen EEG-Veränderungen und Reduzierung der klinischen Symptomatik für die beiden Trainingsprotokolle ergaben. So wiesen Kinder, bei denen sich die Aktivtät im Theta-Band (parietal, Mitte) nach dem Theta/Beta-Training stärker reduzierte, eine größere Verbesserung im FBB-HKS Gesamtwert auf. Bezogen auf das SCP-Training ging eine größere Zunahme der Aktivität im Alpha-Band eine größere Reduktion der ADHS-Symptomatik (inbesondere im Symptombereich Hyperaktivität/Impulsivität) einher.

International Journal of Psychophysiology 74 (2009) 149–157

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Distinct EEG effects related to neurofeedback training in children with ADHD: A randomized controlled trial ☆

Holger Gevensleben [a], Birgit Holl [c], Björn Albrecht [a], Dieter Schlamp [c], Oliver Kratz [b], Petra Studer [b], Susanne Wangler [b], Aribert Rothenberger [a], Gunther H. Moll [b], Hartmut Heinrich [b,c,*]

[a] Child and Adolescent Psychiatry, University of Göttingen, v.Siebold-Str. 5, D-37075 Göttingen, Germany
[b] Child and Adolescent Psychiatry, University of Erlangen-Nürnberg, Schwabachanlage 6+10, D-91054 Erlangen, Germany
[c] Heckscher-Klinikum, Deisenhofener Str. 28, D-81539 München, Germany

ARTICLE INFO

Article history:
Received 7 April 2009
Received in revised form 12 August 2009
Accepted 16 August 2009
Available online 25 August 2009

Keywords:
ADHD
Neurofeedback
EEG
Theta/beta training
SCP training
Specific effects

ABSTRACT

In a randomized controlled trial, neurofeedback (NF) training was found to be superior to a computerised attention skills training concerning the reduction of ADHD symptomatology (Gevensleben et al., 2009). The aims of this investigation were to assess the impact of different NF protocols (theta/beta training and training of slow cortical potentials, SCPs) on the resting EEG and the association between distinct EEG measures and behavioral improvements.

In 72 (of initially 102) children with ADHD, aged 8–12, EEG changes after either a NF training ($n=46$) or the control training ($n=26$) could be studied. The combined NF training consisted of one block of theta/beta training and one block of SCP training, each block comprising 18 units of 50 minutes (balanced order). Spontaneous EEG was recorded in a two-minute resting condition before the start of the training, between the two training blocks and after the end of the training. Activity in the different EEG frequency bands was analyzed.

In contrast to the control condition, the combined NF training was accompanied by a reduction of theta activity. Protocol-specific EEG changes (theta/beta training: decrease of posterior-midline theta activity; SCP training: increase of central-midline alpha activity) were associated with improvements in the German ADHD rating scale. Related EEG-based predictors were obtained. Thus, differential EEG patterns for theta/beta and SCP training provide further evidence that distinct neuronal mechanisms may contribute to similar behavioral improvements in children with ADHD.

1. Introduction

Neurofeedback (NF) is an operant conditioning procedure in which participants (patients) learn to gain self-control over EEG patterns (Heinrich et al., 2007). Measures representing these neurophysiological patterns are converted into visual or acoustic signals which are continuously fed back in real-time. Changes that are made in the desired direction are rewarded, i.e. positively reinforced. Neurofeedback training can be run as a kind of computer game and is thus principally attractive for children. It is increasingly studied as a treatment option in children with attention deficit/hyperactivity disorder (ADHD) with encouraging results in recent studies (Strehl et al., 2006; Drechsler et al., 2007; Gevensleben et al., 2009).

In a randomized controlled trial encompassing 102 children with ADHD, Gevensleben et al. (2009) documented clinical efficacy of NF[1]. A combined NF (18 units of theta/beta frequency band training, preceded or followed by 18 units of training of slow cortical potentials (SCPs) was compared to 2×18 units of a computerised attention skills training (AST), not encompassing neuroregulation. According to parents and teacher ratings, children of the NF group showed larger behavioral (clinical) improvements than those of the control group. Due to comparable settings and demands for NF and AST training, superiority of NF primarily was ascribed to specific factors of the NF treatment.

For the 18 units of theta/beta training and the 18 units of SCP training of the combined NF training, comparable behavioral improvements (referring to inattentiveness, hyperactivity and impulsivity) were observed. However, clear knowledge about the neurophysiological basis of the training effects of both NF protocols is lacking. Better understanding of underlying neurophysiological processes

☆ Trial registry: ISRCTN87071503 — Comparison of neurofeedback and computerised attention skills training in children with attention-deficit/hyperactivity disorder (ADHD) (http://www.controlled-trials.com/ISRCTN87071503).

* Corresponding author. Heckscher-Klinikum, Deisenhofener Straße 28, D-81539 München, Germany. Tel.: +49 89 9999 1116; fax: +49 89 9999 1111.
E-mail address: hheinri@arcor.de (H. Heinrich).

[1] EEG data of this paper were recorded in the same trial.

0167-8760/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpsycho.2009.08.005

would probably help to specify indication criteria or to prevent non response, especially in the light of potentially different EEG subtypes of ADHD (Clarke et al., 2003) suggesting different needs for specific EEG tuning.

1.1. Theta/beta frequency band training

In theta/beta frequency band training, children should learn to decrease activity in the theta band of the EEG (4–8 Hz) and to increase activity in the beta band (13–20 Hz). In several studies, ADHD was associated with increased slow wave activity (theta, 4–8 Hz) and/or reduced alpha (8–13 Hz) and/or beta activity (13–30 Hz) in the resting EEG (for review see Barry et al., 2003) as well as during attention task processing (El-Sayed et al., 2002). After theta/beta training (in combination with cognitive–behavioral and educational intervention strategies) Monastra et al. (2002) reported a decrease of the theta/beta quotient in a group of children with ADHD with an initially enhanced theta/beta quotient. Comparable results were obtained after frequency band training with slightly different but comparable NF protocols and settings (without additional interventions) by Fuchs et al. (2003) and Leins et al. (2006).

1.2. Training of slow cortical potentials (SCPs)

SCPs are changes of cortical electrical activity lasting from several hundred milliseconds to several seconds. They are thought to represent task-dependent short-term mobilizations of cortical processing resources. While negative SCPs reflect increased excitation (e.g., during states of behavioral or cognitive preparation), positive SCPs indicate reduction of cortical excitation of the underlying neural networks (e.g., during behavioral inhibition; Birbaumer et al., 1990).

The contingent negative variation (CNV) is a SCP elicited e.g. in cue trials of a continuous performance test reflecting anticipation or preparation. In event-related potential studies, the CNV was found to be reduced in children with ADHD (for review see Banaschewski and Brandeis, 2007) supporting the notion of a dysfunctional regulation of energetical resources in ADHD (Sergeant et al., 1999).

A training of slow cortical potentials, in which surface-negative and surface-positive SCPs have to be generated over the sensorimotor cortex voluntarily, could address this regulation deficit and, thus, help children with ADHD to improve their behavior.

In a previous study, we reported an increase of the CNV in a continuous performance test after SCP training in children with ADHD. The CNV enhancement was accompanied by a reduction of impulsivity errors at the performance level (Heinrich et al., 2004). This finding was partly confirmed by Doehnert et al. (2008), who performed a comparable SCP training with children with ADHD, and additionally analyzed SCP training effects on the spontaneous EEG. They found a reduction of theta/beta ratio at Cz for the children of the ADHD combined type and a slight increase of activity in the upper alpha band (10–12 Hz) for the complete group.

1.3. Aims of this study

In order to learn more about neurophysiological mechanisms underlying behavioral changes of NF training in children with ADHD, we studied the impact of a combined theta/beta and SCP training on the spontaneous EEG, in comparison to an attention skills training. We expected a reduction of theta activity and an enhancement of beta activity (reduction of the theta/beta ratio) after NF. These changes should primarily follow theta/beta treatment and were not expected for the AST. According to Doehnert et al. (2008), we also hypothesized an increase of alpha activity after SCP training.

Furthermore, we tested if distinct changes in EEG patterns were associated with behavioral improvements (reduction of ADHD symptomatology). These analyses also included the relation of EEG baseline measures to the outcome of training in order to assess the predictive value of certain EEG measures for the success of the training.

2. Materials and methods

2.1. Subjects

102 children with ADHD (8 to 12 years) participated in a NF training or an attention skills training (training period from May 2005 to December 2007). Subjects were randomly assigned to one of the two study groups (ratio NF:AST = 3:2). 8 children (NF: $n = 5$, AST: $n = 3$) were dropouts. A further 22 children (NF: $n = 13$, AST: $n = 9$) had to be excluded because of insufficient EEG signal quality (see below). In Table 1, demographic, psychological and clinical variables of the remaining children are summarized. There was no significant difference between NF and AST group concerning these variables.

Initial sample size calculation based on an assumed medium effect size for the primary outcome measure (FBB-HKS) revealed a sample size of about 100 children to reach a power of .80 (one-sided; .05-level test; ratio NF:AST = 3:2).

All patients fulfilled DSM-IV criteria for ADHD (American Psychiatric Association, 1994). Diagnoses were based on a semi-structured clinical interview (CASCAP-D, Döpfner et al., 1999) and confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD (Döpfner and Lehmkuhl, 2000). Children with comorbid disorders other than conduct disorder, emotional disorders, tic disorder and dyslexia were excluded from the study. All children lacked gross neurological or other organic disorders. All children were drug-free and without concurring psychotherapy for at least 6 weeks before starting the training. The study follows the CONSORT guidelines for randomised trials (Boutron et al., 2008). It was approved by the local ethics committees of the participating clinics and conducted according to the declaration of Helsinki. Assent was obtained from the children and written informed consent from their parents.

2.2. Design of the study

The design of the study is illustrated in Fig. 1. Neurofeedback and attention skills training both consisted of 36 units of 50 minutes each. Both treatments were divided in two blocks of 18 units. These 18 units were combined to nine (double-)sessions. Both units of a session were separated by a short break. The sessions took place two to three times a week. The NF training consisted of one block of 18 units of theta/beta training and one block of 18 units of SCP training (balanced order). For

Table 1
Demographic and clinical characteristics of the NF group and the control group.

	NF group $n = 46$	AST group $n = 26$
Age (years; month)	9;11 ± 1;3	9;5 ± 1;0
Sex (boys/girls)	41/5 (89.1%/10.9%)	20/6 (76.9%/23.1%)
IQ (HAWIK-III)	107.3 ± 13.5	103.2 ± 12.8
DSM-IV subtype		
Combined type	29 (63.0%)	19 (73.1%)
Inattentive type	17 (37.0%)	7 (26.9%)
FBB-HKS (Parents)		
Total score	1.53 ± 0.48	1.47 ± 0.51
Inattention	2.03 ± 0.54	1.88 ± 0.55
Hyperactivity/impulsivity	1.16 ± 0.69	1.16 ± 0.67
Associated disorders		
Conduct disorder	9 (19.6%)	4 (15.4%)
Emotional disorder	3 (6.5%)	3 (11.5%)
Tic disorder	3 (6.5%)	0 (0.0%)
Dyslexia	10 (21.7%)	9 (34.6%)

Only subjects for whom a pre-training and a post-training EEG recording with sufficient data quality was available are included in the table. At the pre-training level, there were no significant differences between the two groups.

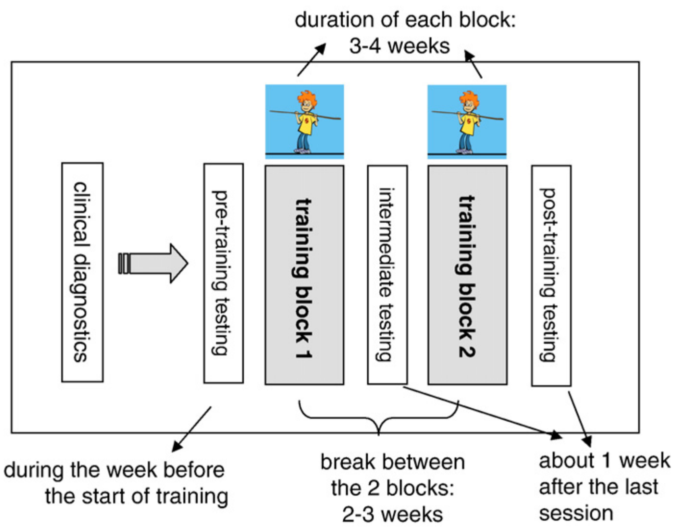


Fig. 1. Schematic illustration of the design of the randomised trial in children with ADHD. The training (neurofeedback, NF; attention skills training) was divided into two blocks. Children of the NF group conducted theta/beta training in one block and SCP training in the other block (balanced order). Behavioral assessments and recordings of resting EEG were done before the training started, between the two training blocks and after the end of the training.

both trainings (NF and AST) there was a break of 2–3 weeks between the treatment blocks. The NF and the AST were designed as similarly as possible concerning the setting and the demands upon the participants. Treatment of both groups encompassed attention-demanding tasks on a computer. Participants of both groups were instructed to develop strategies for focussing attention and to practice the acquired strategies at home and in school. Both treatments were introduced to the parents and children as experimental, but promising, treatment modules for ADHD. The children of both treatment groups completed their trainings in pairs, with each child working at one computer. About three tasks at the computer were accomplished in one unit, altogether lasting for about 25–30 minutes, which means 25–30 minutes of "pure regulation" for the NF group and the same amount of time of attention demanding "mental processing" for the AST group.

The training programs were administered by the same clinical psychologists with the support of a student assistant, who were instructed to take a neutral attitude concerning the effects of the individual training programs. In both trainings, the therapists had to introduce the next task, discuss problems with the task and the use of strategies. In addition, the trainers were asked to motivate the children. Thus, quality and quantity of interaction was comparable for both trainings.

Parents were explicitly not informed about the treatment condition of their child (NF vs. AST) and, as a rule, did not enter the room during treatment.[2]

From the 8th unit on, children of both groups had to practice one of their strategies in a specific situation for about 10 minutes each day in daily-life situations. Children were instructed to identify situations in which these strategies would be important. The goal was to increase the children's responsibility for attention control in certain situations. Exercises were documented by keeping a log, and controlled and discussed at the beginning of the next session. Homework was kept identical in quantity and quality between the groups. Parents were instructed to support the children with the transfer of the learned strategies into everyday life. This parent counselling did not exceed 2 hours.

[2] At the post-training assessment of about 40% of the parents could not reliably quote the treatment assignment of their child. The attitude of the parents in the two groups towards the treatment of their child and post hoc evaluation of the training did not differ (assessment of satisfaction with the treatment, motivation of the child etc, rated via "placebo scales"). For details see Gevensleben et al. (2009).

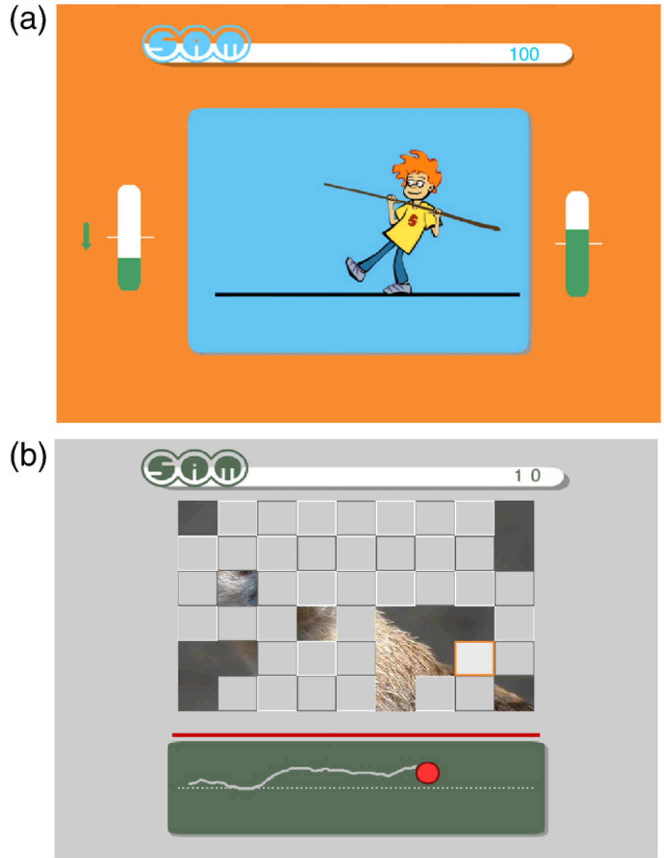


Fig. 2. Example for neurofeedback animations. (a) Theta/beta training: a boy on a rope (Sam) moves ahead if theta activity is reduced/beta activity is increased simultaneously (below/above the baseline values). The participant collects a point for every step Sam makes. Points are presented in the upper right corner of the screen. The activity of both frequency bands is represented by a bar on the screen (range of the bars: theta activity (left bar): $\pm 4\ \mu V$; beta activity (right bar): $\pm 3\ \mu V$; referred to baseline values). (b) SCP training: the ball has to be directed upwards (negativity trials) or downwards (positivity trials): the vertical position of a ball represents the SCP. With each correct trial, a part of the covert picture becomes visible.

EEG recordings, and parent and teacher ratings, were conducted at three time points (pre-training, intermediate, and post-training). Pre-training (baseline) assessment took place during the week before the training started. Intermediate assessment was done about 1 week after the last session of the first block, and post-assessment about 1 week after the second block.

2.3. Training programs

2.3.1. Neurofeedback

The neurofeedback program SAM ("Self regulation and Attention Management"), which was developed by our study group[3] and runs on an Abisam400 amplifier (Abimek, Goettingen, Germany), was used for neurofeedback training.

2.3.1.1. Theta–beta training. The task of the theta–beta training was to reduce theta and enhance beta activity. A bar on the left side of the screen (representing theta activity) had to be reduced while simultaneously a bar on the right side (representing beta activity) had to be increased (see Fig. 2a).

Butterworth filters (48 dB/octave) were applied to calculate theta and beta activity. Using a moving time window of two-second length, feedback information (root-mean-square value) was determined 10 times per second. Trials of the theta/beta training lasted for 5 minutes

[3] Not commercially available.

in the beginning of the training and were extended to 10 minutes as the training proceeded, so that the children had to sustain the focussed state for a longer period. In each unit about 5–6 trials of 5 minutes each, or up to 3 trials of 10 minutes each were performed. Baseline values were determined at the beginning of each session (3 minutes, eyes open). An adjustment within a session was not scheduled. Children were instructed to get into a relaxed but attentive state and to find individual strategies to control the bars.

2.3.1.2. SCP training. In the SCP training, negative or positive slow cortical potentials had to be generated by the participant. The participant had to find appropriate strategies to direct a ball upwards (negativity trials) or downwards (positivity trials). Children were instructed to get into an attentive (negativity trials) or relaxed state (positivity trials). An example of a SCP feedback animation is presented in Fig. 2b. Negativity (50%) and positivity trials (50%) were presented in random order. A trial lasted for 8 s (baseline period: 2 s, feedback period: 6 s). During the feedback phase, the mean SCP amplitude (moving time window: 1 s) was calculated 10 times per second. Intertrial interval was set to 5 ± 1 s. In each SCP training unit approximately 120 trials were performed (25–30 minutes).

For both NF protocols, feedback was calculated from Cz, which is frequently used for children with ADHD (Heinrich et al., 2007; reference: mastoids, bandwidth: 1–30 Hz for theta/beta training and 0.01–30 Hz for SCP training, respectively, sampling rate: 250 Hz). Vertical eye movements, which were recorded with electrodes above and below the left eye, were corrected online using slightly different regression-based algorithms for theta/beta training (Semlitsch et al., 1986) and SCP training (Kotchoubey et al., 1997). For segments containing artefacts exceeding ±100 µV in the EEG channel and ±200 µV in the EOG channel, no feedback was calculated.

Transfer trials, i.e. trials without contingent feedback, were also conducted (about 40% in the beginning of a training block and about 60% at the end of a training block). These transfer trials, as well as homework, were intended to improve generalisation of treatment effects.

2.3.2. Attention skills training

The attention skills training was based on “Skillies” (Auer-Verlag, Donauwörth, Germany), a German learning software which primarily exercises visual and auditive perception, vigilance, sustained attention, and reactivity. In “Skillies,” the children had to sail to several islands. On each island, a clearly defined task — each requiring different attention-based skills — had to be solved; e.g., on an island named ‘Coloured Reef,’ fish of different colours swim from one side of the screen to the other and back. The aim is that all fish shall have the same colour. The colour can be modified by clicking on a fish. With every change of direction the fish change their colour in a predetermined order. Thus this task aims first and foremost at increasing vigilance and reactivity.

The training was complemented by some self-directed interventions from cognitive therapy to assure comparability to NF, i.e., the children were to compile (meta-)cognitive strategies such as focussing attention, careful processing of tasks and impulse control. Corresponding to the NF group, children of the AST group should practice one of their compiled strategies (needed to solve a task of the computer game) in daily-life situations.

2.4. EEG recording and processing

We performed pre-training, intermediate and post-training testing at approximately the same time of day (for some participants variations of not more than 2 hours could not be avoided due to organizational reasons). Recording of spontaneous EEG activity was conducted as the first part of a neurophysiological/psychological test session of about 90 minutes. Participants were seated on a comfortable chair in a quiet room.

The EEG was recorded in an eyes-open resting condition while children were looking at the centre of a blank screen. In all participating clinics (Erlangen, Göttingen, Munich), the EEG was recorded with sintered silver/silver-chloride (Ag/AgCl) electrodes and Abralyt 2000 electrolyte from 23 sites according to an extended 10–20 system using a BrainAmp amplifier (Brain Products, Munich, Germany). The electrooculogram (EOG) was recorded from two electrodes placed above and below the right eye and at the outer canthi. EEG and EOG activity was recorded with FCz as recording reference at a sampling rate of 500 Hz with low and high cut-off filters set to .016 Hz and 120 Hz, respectively. The ground electrode was placed at CPz. Impedances were kept below 20 kΩ.

For data processing, the software program VisionAnalyzer (Brain Products, Munich, Germany) was used. After downsampling to 256 Hz, the EEG was re-referenced to the mastoids and filtered offline with .1–30 Hz, 12 dB/octave Butterworth filters, and a 50-Hz notch filter. Occular artefacts were corrected with the method of Gratton et al. (1983). Raw data files were divided into four-second, non-overlapping segments. If the amplitude at any EEG electrode exceeded ±100 µV, the segment was removed. Recordings were only considered for analysis if at least 10 segments without artefacts were available.

The Fast Fourier transform was calculated and spectra were averaged. For each EEG frequency band, delta (0.5–3.75 Hz), theta (4–7.75 Hz), alpha (8–12.75 Hz) and beta (13–20 Hz), voltage values were calculated. The electrodes were grouped into 9 regions as suggested by Clarke et al. (2003): left frontal (Fp1, F3, F7), midline frontal (Fpz, Fz, Fcz), right frontal (Fp2, F4, F8), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz, Oz) and right posterior (T6, P4, O2).

2.5. Behavioral assessment

The German ADHD rating scale (FBB-HKS, Döpfner and Lehmkuhl, 2000) was used to assess training effects at the behavioral level. It was completed by the parents at the same time the spontaneous EEG was recorded, i.e., before the start of the training, between the two training blocks and after the end of the training. The FBB-HKS is a 20-item questionnaire related to DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorders. The severity of each item was rated from 0 to 3. Outcome measures were the FBB-HKS total score, i.e., the mean value of all items, as well as subscores for inattention and hyperactivity/impulsivity.

2.6. Data analysis

In a first step, pre-training (baseline) EEG measures were analyzed. For each EEG frequency band and the theta/beta ratio, a separate repeated measure ANOVA was computed with GROUP (NF, AST) as between-subject factor, a lateral factor X (left, midline, right) and a sagittal factor Y (frontal, central, parietal) as within-subjects factors. AGE and IQ were defined as covariates since the spectral content of the EEG is known to depend on these parameters. Greenhouse-Geisser adjusted *p*-values are reported where appropriate.

For the analysis of pre- vs. post-training changes (NF vs. AST) an additional factor TIME (pre-training, post-training) was introduced. If effects reached significance, additional post hoc tests were run, e.g. significant effects containing the factor X or Y were studied using trend analyses (T-lin: linear trend; T-quad: quadratic trend).

For the comparison of the NF protocols (theta/beta vs. SCP), the difference between the parameters at the end and the start of a training block were calculated. These EEG change measures were subjected to ANOVAs with the within-subject factors X, Y and PROTOCOL (theta/beta, SCP), the covariates AGE and IQ, and the between-subject factor ORDER representing the order in which the protocols were applied (1: theta/beta–SCP, 2: SCP–theta/beta).

To investigate if training effects can be predicted by and/or correlate with the EEG, block-wise linear regression models were applied. In linear regression models any joint prediction (mulitcolinearity) is assigned to the earlier block, so that variables in the earlier block function as control variables (covariates) for later blocks (Heal and Rusch, 1995).

In a first block, age and IQ were considered mainly to control for spurious correlations between behavioral and EEG effects induced by those factors. In a second block, EEG baseline measures were introduced. Thus, it could be analyzed if EEG baseline measures predict the training outcome. Additionally, it could be controlled that extreme baseline values did not falsely predict possible associations between behavioral effects and the changes of EEG parameters, which were added in the third block of the regression models.

Only those EEG measures were used for the regression analysis for which at least a tendency for significance resulted for the Pearson correlation with the behavioral outcome measure.

Outcome measures were the change (post-training minus pre-training) of the FBB-HKS total score as well as the change of the subscales inattention and hyperactivity/impulsivity.

Corresponding regression analyses were computed for the NF protocols separately. Change values refer to differences between the end and the start of a training block.

SPSS (v.16) was used for statistical analysis.

3. Results

As indicated above 8 children were dropouts (NF: $n=5$; AST: $n=3$), due to an immediate urge for medical treatment ($n=3$), organizational problems of the parents ($n=2$), loss of motivation ($n=1$), or protocol violation ($n=2$)., Further 22 children (NF: $n=13$, AST: $n=9$) had to be excluded due to insufficient EEG signal quality. Thus, 72 children with ADHD (NF: $n=46$; AST: $n=26$) were included in the EEG analysis.

3.1. Pre-training (baseline) EEG activity

EEG pre-training (baseline) values are presented in Fig. 3. There were no significant differences in baseline activity between the NF and the AST group in any frequency band or the theta/beta ratio, respectively ($F(1,68)<2.41$; $p>0.10$).

For the different frequency bands, (well-known) effects concerning age, IQ and topography were obtained. With increasing age, a decrease of activity in slower frequency bands (delta: $F(1,68)=8.54$, $p<0.01$; theta: $F(1,68)=5.84$, $p<0.05$) and a reduction of the theta/beta ratio ($F(1,68)=4.89$, $p<0.05$) were observed.

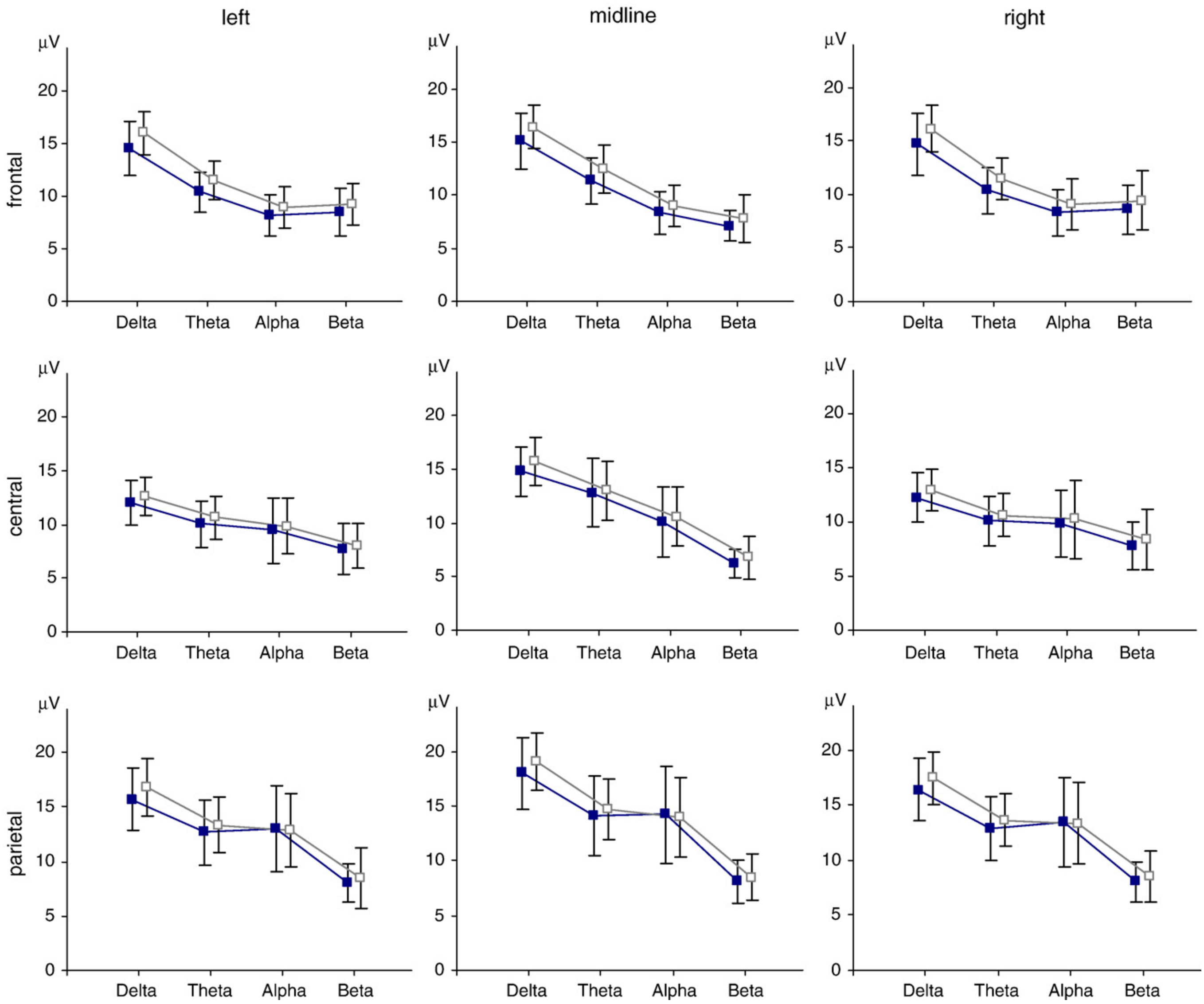


Fig. 3. EEG baseline (pre-training) measures. For each group (neurofeedback: blue, filled squares; attention skills training: gray, open squares), mean value ± standard deviation of baseline activity measured in the EEG frequency bands (delta, theta, alpha, beta) over different brain regions are plotted.

The factor IQ turned out to be significant for activity in faster frequency bands. Alpha and beta activity were larger for higher IQ (alpha: $F(1,68)=4.53$, $p<0.05$; beta: $F(1,68)=3.86$, $p<0.05$).

Topographically, delta activity was lower over central electrodes compared to frontal and parietal electrodes (factor Y: T-quad (1,68) = 8.23, $p<0.005$) and beta activity was larger over midline compared to more lateral electrodes (factor X: T-quad (1,68) = 3.75, $p<0.05$). Tendencies towards a decrease of theta activity from anterior to posterior (factor Y: T-lin (1,68) = 3.63, $p<0.1$) and towards laterally higher central theta activity (T-quad (1,68) = 3.56, $p<0.1$) were observed. The theta/beta ratio was higher over midline compared to more lateral regions (T-quad (1,68) = 17.1, $p<0.001$) and to decrease from anterior to posterior (T-lin (1,68) = 5.61, $p<0.05$).

3.2. NF vs. AST training: pre- vs. post-training comparisons

For theta activity, the repeated measure ANOVA revealed a Time x Y x Group (T-lin (1,68) = 8.51, $p<0.005$) and a Time x X x Group (T-quad (1,68) = 7.59, $p<0.01$) effect, indicating a larger reduction of theta activity in the NF group vs. the AST group over centro-parietal midline electrodes (see Fig. 4). Calculating a specific contrast (average of central-midline and parietal-midline) revealed a significant decrease for the NF group only (NF: -0.62 ± 1.16; $t(45)=-3.63$, $p<0.001$; AST: 0.09 ± 1.41; $t(25)=0.34$, $p=0.74$).

For other frequency bands (delta, alpha, and beta) and the theta/beta ratio, no significant effects containing the factors TIME and/or GROUP were obtained.

Concerning the covariates, changes in beta activity were effected by age and intelligence. A significant Time x Y x Age interaction effect ($F(2,136)=3.88$, $p<0.05$) indicated a larger decrease of frontal beta activity at post-training measurement with increasing age. This reduction of beta activity related to age was accompanied by a corresponding effect (tendency) for the theta/beta ratio (Time x Y x Age: $F(2,136)=2.49$, $p<0.1$). Furthermore, a significant Time x X x IQ interaction effect ($F(2,136)=4.03$, $p<0.05$) was observed due to a larger pre- to post-training decrease of beta activity over midline electrodes with increasing IQ.

3.3. Comparison of theta/beta and SCP training

For the comparison of theta/beta and SCP training, the EEG of the intermediate testing was additionally taken into account. A further four children had to be excluded from this analysis because of an insufficient number of artefact-free segments.

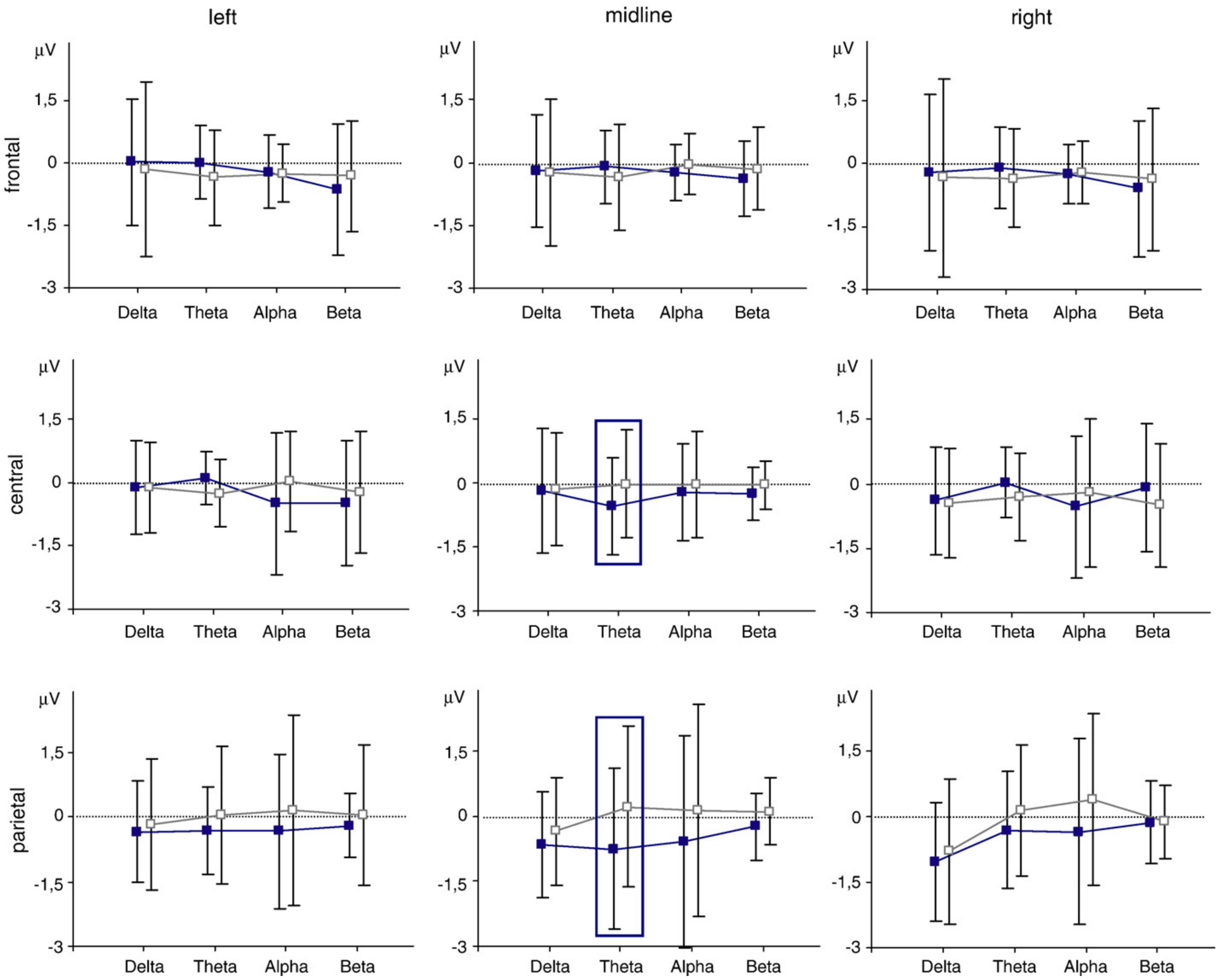


Fig. 4. EEG change (post-training minus pre-training) measures. For each group (neurofeedback: blue, filled squares; attention skills training: gray, open squares), mean value ± standard deviation of changes (post-training minus pre-training) in the EEG frequency bands (delta, theta, alpha, beta) over different brain regions are plotted. In the NF group, there was a decrease of theta activity at central-midline and parietal-midline electrodes.

Table 2
Block-wise linear regression analyses.

	Change FBB-HKS Total score	Change FBB-HKS Inattention subscale	Change FBB-HKS Hyperactivity/impulsivity subscale
Neurofeedback (theta/beta, SCP) training	–	–	–
Age, IQ			
EEG baseline measures			
EEG change measures			
Theta/beta training block	$R=0.465$ $F(2,37)=4.70$, $p=0.016$	$R=0.378$ $F(1,37)=5.84$, $p=0.021$	$R=0.399$ $F(1,37)=6.83$, $p=0.013$
Age, IQ	–	–	–
EEG baseline measures	theta-parietal-midline $\beta=-0.281$, $p=0.1$	theta-parietal-right $\beta=-0.378$, $p=0.021$	theta-parietal-midline $\beta=-0.399$, $p=0.013$
EEG change measures	theta-parietal midline $\beta=-0.330$, $p=0.05$	–	–
SCP training block	$R=0.339$ $F(1,37)=4.69$, $p=0.037$	–	$R=0.644$ $F(2,37)=12.4$, $p<0.001$
Age, IQ	–	–	–
EEG baseline measures	alpha-parietal-left $\beta=-0.339$, $p=0.037$	–	alpha-parietal-left $\beta=0.379$, $p=0.006$
EEG change measures	–	–	alpha-central-midline $\beta=-0.470$, $p=0.001$

Predictor variables under consideration: age and IQ (first block), EEG baseline measures (second block) and EEG change measures (third block). Behavioral outcome was assessed via the German ADHD rating scale (FBB-HKS) completed by parents. Analyses were done for the complete NF training, the theta/beta training block and the SCP training block.

Neither for the change of theta activity (PROTCOL: $F(1,37)=0.09$; $p=0.76$; PROTOCOL x X: $F(2,74)=0.42$; $p=0.61$; PROTOCOL x Y: $F(2,74)=1.24$; $p=0.29$) nor for any other frequency band, could a significant difference between the two NF protocols be obtained. We also computed the specific contrast concerning theta activity (average of central-midline and parietal-midline electrodes) for the theta/beta and the SCP training block separately. For both NF protocols, a tendency towards a decrease was apparent (theta/beta training: -0.31 ± 1.02; $t(41)=-1.98$; $p<0.1$; SCP training: -0.28 ± 0.97; $t(41)=-1.86$; $p<0.1$).

3.4. Relations between resting EEG and behavioral outcome

Results of the block-wise linear regression analyses are summarized in Table 2.

For the outcome of the *combined NF training*, no significant predictor variables were obtained — neither for the FBB-HKS total score nor for the inattention and hyperactivity/impulsivity subscales.

For the *theta/beta training* block, theta activity over parietal-midline sites at baseline and the change of theta activity over this region remained in the regression model for the FBB-HKS total score, accounting for about 20% of the variance ($R=0.465$; $F(2,37)=4.70$, $p=0.016$). As can be seen in Fig. 5, higher theta activity at baseline and a larger decrease of theta activity were associated with a larger decrease of the FBB-HKS total score for the theta/beta training block. For the inattention and the hyperactivity/impulsivity subscales, baseline theta activity at parietal-right and parietal-midline sites, respectively were significant predictor variables.

For the *SCP training* block, the model with the best fit (explaining about 40% of variance) was obtained for change of the hyperactivity/impulsivity subscale with alpha activity measured over parietal-left sites at baseline and the change of alpha activity over central-midline electrodes as significant predictor variables ($R=0.644$; $F(2,37)=12.4$, $p<0.001$). Lower alpha activity at baseline and a larger increase of alpha increase following SCP training were related to a larger improvement (see Fig. 6).This change of alpha activity in the SCP block also contributed substantially to the prediction of the change of the impulsivity/hyperactivity subscale for the complete NF training ($R=0.362$; $F(1,40)=5.87$, $p<0.05$). Alpha activity measured over parietal-left sites at baseline also contributed to the prediction of the change of FBB-HKS total score following SCP training ($R=0.339$; $F(1,37)=4.69$, $p<0.05$).

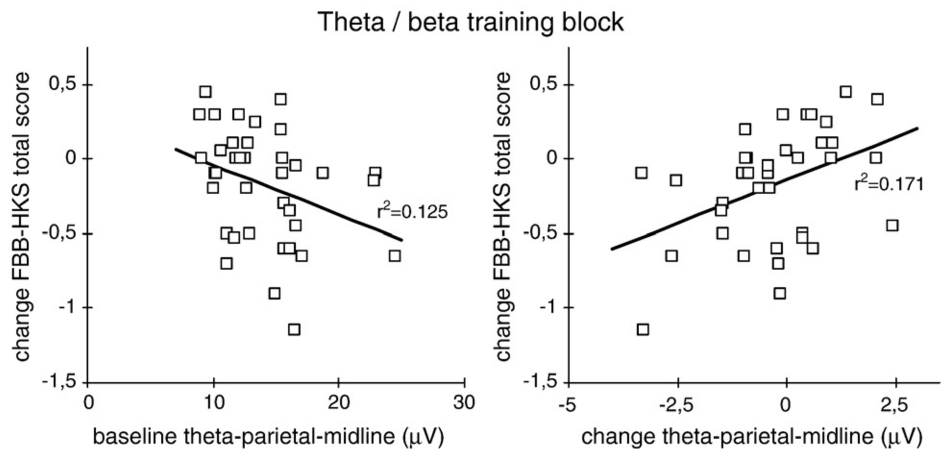


Fig. 5. Theta/beta training block. Left: change of the FBB-HKS total score vs. theta activity measured at baseline over parietal-midline electrodes. Right: change of the FBB-HKS total score vs. change of theta activity over parietal-midline electrodes. The linear regression lines are also shown.

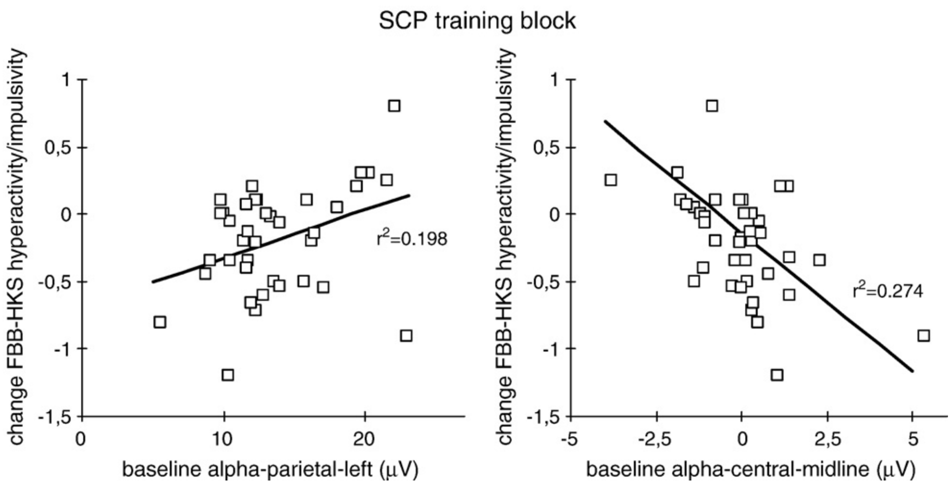


Fig. 6. SCP training block. Left: change of the FBB-HKS hyperactivity/impulsivity subscale vs. alpha activity measured at baseline over parietal-left electrodes. Right: change of the FBB-HKS hyperactivity/impulsivity subscale vs. change of alpha activity over central-midline electrodes. The linear regression lines are also shown.

For the *control training (AST)*, an increase of beta activity over parietal-midline electrodes was associated with a decrease of the impulsivity/hyperactivity subscale ($R = 0.426$; $F(1,24) = 5.11$, $p < 0.05$).

In none of the models under study, was a significant linear relationship between the behavioral outcome and age or IQ found.

4. Discussion

The impact of a combined neurofeedback training (theta/beta training, SCP training) on the resting EEG was studied in children with ADHD in comparison to an attention skills training as control. Further, EEG measures recorded at baseline as well as changes of EEG parameters from pre- to post-training were related to the clinical outcome. Results only partly confirmed the assumptions of specific protocol-dependent effects of NF training on the resting EEG. Nevertheless, some distinct EEG effects could be observed.

4.1. Pre-training vs. post-training EEG comparisons

In contrast to the control training, NF led to a reduction of theta activity in centro-parietal regions. The reduction of theta activity was comparable for the theta/beta and the SCP training block, but neither block by itself resulted in significant changes. Thus, the hypothesis that NF leads to protocol-specific changes (theta/beta vs. SCP) could not be confirmed in the pre- vs. post-training comparisons.

Further training and protocol-specific EEG effects could not be obtained, even for beta activity and the theta/beta ratio, which were targeted directly during theta/beta training.

During training, children practiced to get into an 'active', attentive state whereas, during recording of the resting EEG, they should be relaxed. Thus, our results might indicate that neuronal regulation capability does not necessarily have a corresponding impact on the resting EEG. The finding of Monastra et al. (2002), who reported a decrease of the theta/beta ratio after theta/beta training, need not be seen to contrast with our results, since EEG assessment in Monastra et al. (2002) did not rely on the resting EEG solely, but was based on an index encompassing also EEG activity during reading, listening, and drawing.

This notion is also supported by the results of NF studies in healthy adults. The group of Gruzelier, who carried out a series of studies investigating the impact of different frequency band protocols on cognitive–behavioral and neurophysiological measures, reported protocol-specific effects (improvements) in attention and working memory tasks (Egner and Gruzelier, 2004; Vernon et al., 2003). However, in the resting EEG, associations between a training protocol and changes in the spectral topography of the spontaneous EEG appeared to be ambiguous (Egner et al., 2004). In the same line, Doppelmayr et al. (2009) reported no statistically significant increase of SMR activity in the resting EEG after 25 units of SMR training, although there was a clear increase of SMR amplitudes in training trials.

When discussing pre-training to post-training effects, the number of training sessions also has to be taken into account. So far no empirical evidence is available concerning the number of units needed to obtain training effects. The number of 36 NF units in our study is comparable to recent controlled studies (Doehnert et al., 2008: 30 units; Fuchs et al., 2003: 36 units; Leins et al., 2007: 30 units; Monastra et al., 2002: 43 units of 40 minutes). In our study, children clearly improved at the behavioral/clinical level (Gevensleben et al., 2009), accompanied by reduced theta activity in the resting EEG. When comparing theta–beta and SCP training, which had been conducted in two separate blocks, the number of 18 training units for each protocol might have been too small to reveal protocol-specific effects in the resting EEG.

4.2. Protocol-specific EEG — behavior associations

Relations between EEG baseline and change measures and effects on the behavioral level were studied using block-wise linear regression models. Significant improvements in the behavior ratings of parents and teachers concerning inattention and hyperactivity/impulsivity had been obtained after NF (Gevensleben et al., 2009). Although the combined NF training was related to behavioral improvements, there was no significant association of the latter with EEG baseline or change measures.

For the theta/beta training block, improvements were related to higher pre-training theta activity, as well as to a larger reduction of theta activity, mainly at parietal-midline sites. For the SCP training block, effects in the alpha band were obtained. Smaller parietal alpha activity and a larger increase of central alpha activity were associated with larger behavioral improvements. Generally, associations were stronger for hyperactivity/impulsivity than inattention symptoms. This could be due to the resting condition studied, but might be different in an attention-demanding task.

Besides the functional significance, further studies could address which neuronal networks are involved in the EEG effects associated with NF training, including the role of thalamo-cortical synchronisation (Rothenberger, 2009). This can be done by simultaneous EEG-fMRI recordings, which allow investigation of how distributed neuronal networks correlate with the EEG frequency bands (Debener et al., 2006); e.g., activation in the thalamus but also in the anterior cingulate correlate with alpha activity (Difrancesco et al., 2008).

4.3. Practical relevance of the results

As indicated in the previous paragraph, baseline EEG measures had predictive value concerning the success of theta/beta training and SCP training, respectively. Before we may conclude that children with different EEG patterns may benefit from different NF protocols, our results have to be confirmed in larger samples.

Also, fully standardized recording conditions seem to be an indispensable prerequisite, and indication criteria should not be based solely on EEG measures recorded in a resting condition but also on EEG or ERP parameters reflecting cognitive task processing (see Section 4.1). Moreover, other, non-neurophysiological factors should be taken into account. Drechsler et al. (2007) revealed a significant effect of parental support concerning the outcome of NF training in children with ADHD. Personality factors influenced the success of SCP training embedded in a behavioral treatment program in patients with epilepsy (Kotchoubey et al., 2001). In the linear regression models applied in our study, age and IQ did not turn out as significant predictor variables. However, findings could be different if, e.g., a broader age range than 8 to 12 years was considered, and effects need not be linear.

4.4. Methodological issues

For beta activity, pre- to post-training changes did not depend on the NF training, but were affected by age and IQ. In children with a high IQ, and in older children, respectively, post-training beta activity was lower, particularly over frontal-midline sites.

Although the spectral distribution of the resting EEG is considered as relatively stable and, therefore, can be seen as a trait variable, it is also sensitive to state characteristics (Hegerl et al., 2008). In this respect, the reduction of beta activity in children with high IQ, and in older children, might reflect adaptation to the laboratory setting. 'Habituation' effects are known to be related to intelligence — at least in infants (Kavsek, 2004). Hence, it should be taken into account that such factors could mask potential training effects at the neurophysiological level.

5. Conclusions

Differential EEG patterns for theta/beta and SCP training provide further evidence that distinct neuronal mechanisms may contribute to similar behavioral improvements in children with ADHD. Nevertheless, findings do not allow us to conclude that all trained EEG parameters will lead to distinct changes in the resting EEG. Future studies should address how to optimize NF training for children with ADHD, particularly which treatment protocol (or combination of protocols), and how many training sessions, might be appropriate for an individual child.

Acknowledgments

The authors thank Christa Dahlmann, Martin Deinzer, Claudia Vogel and all student assistants for their valuable support as well as all participating families for their contribution and effort. This study was supported by the German Research Foundation (with a joint grant to H.H., G.H.M, and A.R.; HE 4536/2, MO 726/2, RO 698/4).

References

American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders. 4th Edition (DSM-IV). American Psychiatric Press, Washington, DC.
Banaschewski, T., Brandeis, D., 2007. Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us — a child psychiatric perspective. J. Child Psychol. Psychiatry 48, 415–435.
Barry, R.J., Clarke, A.R., Johnstone, S.J., 2003. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin. Neurophysiol. 114, 171–183.
Birbaumer, N., Elbert, T., Canavan, A.G., Rockstroh, B., 1990. Slow cortical potentials of the cerebral cortex and behavior. Physiol. Rev. 70, 1–41.
Boutron, I., Moher, D., Douglas, G., Altman, G., Schulz, F., Ravaud, P., 2008. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann. Intern. Med. 148, 295–310.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Brown, C.R., Croft, R.J., 2003. Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder predominantly inattentive type. Int. J. Psychophysiol. 47, 129–137.
Debener, S., Ullsperger, M., Siegel, M., Engel, A.K., 2006. Single-trial EEG-fMRI reveals the dynamics of cognitive function. Trends Cogn. Science 10, 558–563.
Difrancesco, M.W., Holland, S.K., Szaflarski, J.P., 2008. Simultaneous EEG/functional magnetic resonance imaging at 4 Tesla: correlates of brain activity to spontaneous alpha rhythm during relaxation. J. Clin. Neurophysiol. 25, 255–264.
Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H.C., Drechsler, R., 2008. Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? J. Neural Transm. 115, 1445–1456.
Döpfner, M., Berner, W., Flechtner, H., Lehmkuhl, G., Steinhausen, H.C., 1999. Psychopathologisches Befund-System für Kinder und Jugendliche (CASCAP-D). Hogrefe, Göttingen.
Döpfner, M., Lehmkuhl, G., 2000. DISYPS-KJ – Diagnostik-System für psychische Störungen im Kindes- und Jugendalter. Hans Huber, Bern.
Doppelmayr, M., Weber, E., Hoedlmoser, K., Klimesch, W., 2009. Effects of SMR feedback on the EEG amplitude. Human Cogn. Neurophysiol. 2, 21–32.
Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H.C., Brandeis, D., 2007. Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). Behav. Brain Funct. 3, 35.
Egner, T., Gruzelier, J.H., 2004. EEG biofeedback of low beta band components: frequency-specific effects on variables of attention and event-related brain potentials. Clin. Neurophysiol. 115, 131–139.
Egner, T., Zech, T.F., Gruzelier, J.H., 2004. The effects of neurofeedback training on the spectral topography of the electroencephalogram. Clin. Neurophysiol. 115, 2452–2460.
El-Sayed, E., Larsson, J.O., Persson, H.E., Rydelius, P.A., 2002. Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. J. Am. Acad. Child Adolesc. Psychiatry 41, 811–819.
Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J.H., Kaiser, J., 2003. Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. Appl. Psychophysiol. Biofeedback 28, 1–12.
Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., Studer, P., Rothenberger, A., Moll, G.H., Heinrich, H., 2009. Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. J. Child Psychol. Psychiatry 50, 780–789.
Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalogr. Clin. Neurophysiol. 55, 468–484.
Heal, L.W., Rusch, F.R., 1995. Predicting employment for students who leave special education high school programs. Except. Child. 61, 472–487.
Hegerl, U., Stein, M., Mulert, C., Mergl, R., Olbrich, S., Dichgans, E., Rujescu, D., Pogarell, O., 2008. EEG-vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. Eur. Arch. Psychiatry Clin. Neurosci. 258, 137–143.
Heinrich, H., Gevensleben, H., Freisleder, F.J., Moll, G.H., Rothenberger, A., 2004. Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. Biol. Psychiatry 55 (7), 772–775.
Heinrich, H., Gevensleben, H., Strehl, U., 2007. Annotation: neurofeedback — train your brain to train behaviour. J. Child Psychol. Psychiatry 48, 3–16.
Kavsek, M.J., 2004. Predicting later IQ from infant visual habitation and dishabituation: a meta-analysis. J. Appl. Dev. Psychol. 25, 369–393.
Kotchoubey, B., Schleichert, H., Lutzenberger, W., Birbaumer, N., 1997. A new method for self-regulation of slow cortical potentials in a timed paradigm. Appl. Psychophysiol. Biofeedback 22, 77–93.
Kotchoubey, B., Strehl, U., Uhlmann, C., Holzapfel, S., Konig, M., Froscher, W., Blankenhorn, V., Birbaumer, N., 2001. Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. Epilepsia 42, 406–416.
Leins, U., Hinterberger, T., Kaller, S., Schober, F., Weber, C., Strehl, U., 2006. Neurofeedback for children with ADHD: a comparison of SCP- and theta/beta-protocols. Prax. Kinderpsychol. Kinderpsychiatr. 55, 384–407.
Monastra, V.J., Monastra, D.M., George, S., 2002. The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl. Psychophysiol. Biofeedback 27, 231–249.
Rothenberger, A., 2009. Brain oscillations forever — neurophysiology in future research of child psychiatric problems. J. Child Psychol. Psychiatry 50, 79–86.
Semlitsch, H.V., Anderer, P., Schuster, P., Presslich, O., 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. Psychophysiology 23, 695–703.
Sergeant, J.A., Oosterlaan, J., Van der Meere, J.J., 1999. Information processing and energetic factors in attention-deficit/hyperactivity disorder. In: Quay, H.C., Hogan, A. (Eds.), Handbook of Disruptive Behavior Disorders. Plenum Press, New York, pp. 75–104.
Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., Birbaumer, N., 2006. Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. Pediatrics 118, e1530–e1540.
Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., Gruzelier, J., 2003. The effect of training distinct neurofeedback protocols on aspects of cognitive performance. Int. J. Psychophysiol. 47, 75–85.

4.3.2 Originalpublikation 4: Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial

Die EPs wurden während des Attention Network Tests abgeleitet, der es erlaubt, drei verschiedene Aspekte von Aufmerksamkeit (Alertness, Orienting, Conflict) zu untersuchen, denen jeweils weitgehend unabhängige neuronale Schaltkreise zugeschrieben werden (Posner & Petersen, 1990; Fan et al., 2002). Wir erwarteten spezifische, an das jeweilige NF-Protokoll gebundene EP-Veränderungen: Während das SCP-Training von einer Erhöhung der CNV gefolgt sein sollte (Heinrich et al., 2004), vermuteten wir für das Theta/Beta-Training eine Erhöhung der P300 (Egner & Gruzelier, 2004).

Tatsächlich zeigte sich nach dem SCP-Training im Vergleich der EPs zwischen den Testzeitpunkten eine Erhöhung der CNV an der Elektrode Cz in beiden Cue-Bedingungen „Neutral Cue“ und „Spatial Cue“ (siehe Originalpublikation 4: Fig. 3). Dieser spezifische neurophysiologische Effekt stützt die Hypothese, dass das SCP-Training auf die phasische Regulation kortikaler Exzitabilität abzielt und sich u.a. auf die Mobilisierung von Ressourcen während stark ressourcenfordernder Prozesse auswirkt.

In beiden Trainingsgruppen bzw. nach beiden NF-Protokollen wurde eine Reduzierung der P300 beobachtet, vermutlich bedingt durch die wiederholte Testdurchführung.

Die Testperformance (Hits, Reaktionszeiten und ANT-Scores Alerting, Orienting u. Conflict) verbesserte sich in der NF- und in der AST-Gruppe in vergleichbarem Maße, wobei dies vermutlich zu größeren Teilen einen Übungseffekt abbildet. In einer Subgruppe von Kindern, die in der Prä-Testung schlecht abgeschnitten hatte, verbesserten die Kinder der AST-Gruppe ihre Testleistungen in der Post-Testung mehr als die entsprechenden Kinder der NF-Gruppe.

Dies lässt sich dadurch erklären, dass die durchzuführenden Testaufgaben in ihrem Anforderungsprofil eine größere Nähe zum AST-Training aufweisen.

Im Vergleich der beiden NF-Protokolle deutete sich eine größere Abnahme im Conflict-Score für das SCP-Trainings an. Tendenziell schien es dort nach einem SCP-Training besser zu gelingen, punktgenau die geforderten kognitiven Ressourcen zu mobilisieren. Möglicherweise liegt dies daran, dass die neuronale Quelle der CNV im vorderen Cingulum liegt, welches am Konflikt-Monitoring wesentlich beteiligt ist (siehe Albrecht et al., 2008). Bezogen auf das Modell unterschiedlicher Aufmerksamkeitsnetzwerke, das der Konstruktion des verwendeten Aufmerksamkeitstests ANT zugrunde liegt, spricht das dafür, dass ein SCP-Training eher als ein Frequenzband-Training den Schaltkreis der exekutiven Aufmerksamkeit adressiert (Fan et al., 2002). Die exekutive Aufmerksamkeit wird als wesentlich für den Erwerb situationsangemessener Selbststeuerungsfähigkeiten angesehen (Posner & Rothbart, 2007).

Clinical Neurophysiology 122 (2011) 942–950

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial

Susanne Wangler [a], Holger Gevensleben [b], Björn Albrecht [b], Petra Studer [a], Aribert Rothenberger [b], Gunther H. Moll [a], Hartmut Heinrich [a,c,*]

[a] Dept. of Child and Adolescent Mental Health, University of Erlangen-Nürnberg, Schwabachanlage 6+10, D-91054 Erlangen, Germany
[b] Child and Adolescent Psychiatry, University of Göttingen, v.Siebold-Str. 5, D-37075 Göttingen, Germany
[c] Heckscher-Klinikum, Deisenhofener Str. 28, D-81539 München, Germany

See Editorial, pages 856–857

ARTICLE INFO

Article history:
Available online 16 September 2010

Keywords:
Neurofeedback
ADHD
Theta/beta training
SCP training
Event-related potentials
Contingent negative variation (CNV)
Prediction

HIGHLIGHTS

- Neurofeedback training in children with ADHD is accompanied by changes in neural processing (e.g., increase of the contingent negative variation after training of slow cortical potentials).
- The success of the training can be predicted by pre-training EEG and event-related potential measures.
- The findings of the randomized controlled trial further support the specificity of training effects and contribute to a better understanding of the mechanisms underlying a successful neurofeedback training in children with ADHD.

ABSTRACT

Objective: In a randomized controlled trial, we could demonstrate clinical efficacy of neurofeedback (NF) training for children with ADHD (Gevensleben et al., 2009a). The present investigation aimed at learning more about the neuronal mechanisms of NF training.
Methods: Children with ADHD either completed a NF training or a computerized attention skills training (ratio 3:2). NF training consisted of one block of theta/beta training and one block of slow cortical potential (SCP) training, each comprising 18 training units. At three times (pre-training, between the two training blocks and at post-training), event-related potentials (ERP) were recorded during the Attention Network Test. ERP analysis focused on the P3, reflecting inter alia attentional resources for stimulus evaluation, and the contingent negative variation (CNV), primarily related to cognitive preparation.
Results: After NF training, an increase of the CNV in cue trials could be observed, which was specific for the SCP training. A larger pre-training CNV was associated with a larger reduction of ADHD symptomatology for SCP training.
Conclusions: CNV effects reflect neuronal circuits underlying resource allocation during cognitive preparation. These distinct ERP effects are closely related to a successful NF training in children with ADHD. In future studies, neurophysiological recordings could help to optimize and individualize NF training.
Significance: The findings contribute to a better understanding of the mechanisms underlying NF training in children with ADHD.

1. Introduction

EEG and event-related potential (ERP) studies significantly contributed to a better understanding of the pathophysiological background of attention-deficit/hyperactivity disorder (ADHD). In the EEG, children with ADHD typically show increased activity in the

* Corresponding author at: Dept. of Child and Adolescent Mental Health, University of Erlangen-Nürnberg, Schwabachanlage 6+10, D-91054 Erlangen, Germany. Tel.: +49 9131/85 39122; fax: +49 9131/85 39126.
E-mail address: hartmut.heinrich@uk-erlangen.de (H. Heinrich).

1388-2457/$36.00 © 2010 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.clinph.2010.06.036

theta band and reduced activity in the beta band during a resting condition as well as during attention tasks (El-Sayed et al., 2002; Barry et al., 2003, 2009). The theta/beta ratio may be interpreted as neurophysiological equivalent of 'activation' according to the model of Pribram and McGuiness (Pribram and McGuinness, 1975; Barry et al., 2009).

ERP studies focused mainly on late components (latencies >300 ms; for review see Banaschewski and Brandeis, 2007). Reduced P3 amplitudes observed in different paradigms could reflect attentional, as well as response control deficits. The contingent negative variation (CNV) is a slow cortical potential[1] (SCP) elicited, e.g., in cue trials of a continuous performance test reflecting anticipation and/or preparation. The CNV was found to be reduced in children with ADHD (e.g., Sartory et al., 2002; Banaschewski et al., 2003). This is in line with models supposing a dysfunctional regulation of energetical resources in ADHD (Sergeant et al., 1999).

Neurofeedback (NF) aims at acquiring self-control over certain brain activity patterns to improve behavioral self-regulation in daily-life. Related to the above-mentioned EEG and ERP findings, two NF training protocols are typically applied in children with ADHD: theta/beta training and SCP training (Heinrich et al., 2007). Theta/beta training aims at tonic aspects of activation with children learning to reduce activity in the theta band and to increase activity in the beta band. SCP training is related to phasic regulation of cortical excitability. Surface-negative SCPs ("negativities") and surface-positive SCPs ("positivities") have to be generated over the sensorimotor cortex.

For both NF protocols positive behavioral and cognitive effects were described in several studies (theta/beta training: Lubar et al., 1995; Monastra et al., 2002; Fuchs et al., 2003); SCP training: Heinrich et al., 2004; Strehl et al., 2006; Drechsler et al., 2007). Less data are available concerning the neurophysiological effects of these NF protocols. A decrease of the theta/beta ratio in the resting EEG was reported after theta/beta training in a group of children with ADHD with an initially enhanced theta/beta ratio (Monastra et al., 2002). Considering ERPs, Heinrich et al. (2004) observed an increase of the CNV after SCP training in cue trials of a continuous performance test. This CNV increase was interpreted as a neurophysiological equivalent of improved self-regulation capabilities. A correlation between SCP regulation capability and change of the CNV amplitude was found in Doehnert et al. (2008).

Egner and Gruzelier (2001, 2004) obtained an increased target-P3 after a beta (15–18 Hz) training in 'healthy' students probably due to higher general background excitation. Kropotov et al. (2005) described a P3 increase in a go/nogo task for children with ADHD who were considered as good performers in a relative beta training.

In a preliminary study using fMRI, increased activity in the anterior cingulate cortex during a stroop test was reported for children with ADHD, who participated in theta/beta (SMR) training (Levesque et al., 2006).

In order to overcome shortcomings of previous NF studies in ADHD (e.g., small sample sizes, lack of an adequate control group, no randomization), our group conducted a randomized controlled trial including 102 children with ADHD.[2] In Gevensleben et al. (2009a; see also Pine, 2009), we evaluated the clinical efficacy of NF training (consisting of one block of theta/beta training and one block of SCP training) in comparison to a computerized attention skills training (AST). For ethical as well as practical reasons discussed in more detail in Heinrich et al. (2007) and Gevensleben et al. (2009a), we preferred an AST training over a sham (placebo) NF training. For the NF group, larger improvements in parent and teacher ratings were obtained. Behavioral improvements were comparable for both NF protocols. Superiority of NF training effects, which, due to comparable settings and demands for NF and control training, was primarily ascribed to specific factors of the NF treatment were still evident at 6-month follow-up (Gevensleben et al., 2010).

In the resting EEG, a reduction of theta activity after the combined NF training was found. Distinct associations between EEG patterns and improvements at the behavioral level (mainly concerning hyperactivity/impulsivity) further supported the specificity of NF effects. For the theta/beta training block, improvements were related to higher pre-training theta activity, as well as to a larger reduction of theta activity, mainly at parietal-midline sites. For the SCP training block, effects in the alpha band were obtained. Smaller parietal alpha activity and a larger increase of central alpha activity were associated with larger behavioral improvements (Gevensleben et al., 2009b).

In the present investigation, we were interested in theta/beta and SCP training effects on cognitive task processing using ERPs. ERPs were recorded during the Attention Network Test (ANT), which allows to differentiate between three particular aspects of attention: alerting, orienting and conflict (Posner and Petersen, 1990; Fan et al., 2002). Testing took place at three times in the course of the training (before the training started, between the training blocks and after the end of the training). Thus, the two NF protocols, which were conducted in separate training blocks, could be compared at the intraindividual level.

We expected distinct ERP effects after the complete NF training in contrast to the control training. For the SCP training, we hypothesized an increase of the CNV (Heinrich et al., 2004) and, for the theta/beta training, a P3 increase was expected (Egner and Gruzelier, 2001, 2004).

Further, regression models were applied to test if changes in ERP parameters were associated with a reduction of ADHD symptomatology. These analyses also included the relation of ERP measures at pre-training to the behavioral outcome in order to assess their predictive value.

2. Materials and methods

2.1. Subjects

One hundred and two children with ADHD (aged 8–12) started either a NF training or an attention skills training.[3] Subjects were randomly assigned to one of the two study groups (ratio NF: control training = 3:2). Eight children (NF: $n = 5$, AST: $n = 3$) were dropouts. Characteristics of the 94 children completing their training are summarized in Table 1. All patients fulfilled DSM-IV criteria for ADHD (American Psychiatric Association, 1994). Diagnoses were based on a semi-structured clinical interview (CASCAP-D; Döpfner et al. 1999) and confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD (Döpfner and Lehmkuhl, 2000). With mean FBB-HKS total scores of about 1.5 (range 0–3), ADHD symptomatology was moderately pronounced in both training groups. Children with comorbid disorders other than conduct disorder, emotional disorders, tic disorder and dyslexia were excluded from the study. All children were drug-free for at least 6 weeks before starting the training and without concurring psychotherapy.

[1] Slow cortical potentials are changes of cortical electrical activity lasting from several hundred milliseconds to several seconds. They are thought to represent task-dependent short-term mobilizations of cortical processing resources. While negative SCPs reflect increased excitation (e.g., during states of behavioral or cognitive preparation), positive SCPs indicate reduction of cortical excitation of the underlying neural networks (e.g., during behavioral inhibition) according to the threshold regulation model of Birbaumer et al. (1990).

[2] ERP data reported in this paper were recorded in the same trial.

[3] Sample size had been estimated a priori to be large enough to detect a medium effect size of about 0.5 for the primary outcome measure at the behavioral level (total score of the German ADHD rating scale, FBB-HKS) with a power of 0.8 (one-sided, 0.05-level test).

Table 1
Demographic and clinical characteristics of the NF group and the control (AST) group. Concerning these variables, there were no significant differences between NF group and control group. Training results for the German ADHD rating scale (FBB-HKS) are also presented.

	NF group $n = 59$		AST group $n = 35$	
Age (years; month)	9;10 ± 1;3		9;4 ± 1;2	
Sex (boys/girls)	51/8 (86.4%/13.6%)		26/9 (74.3%/25.7%)	
IQ (HAWIK-III, Tewes et al., 2000)	106.1 ± 13.2		104.5 ± 12.9	
FBB-HKS (pre-training/change)				
Total score	1.50 ± 0.45	−0.39 ± 0.37	1.49 ± 0.50	−0.14 ± 0.44
Inattention	1.97 ± 0.51	−0.48 ± 0.47	1.83 ± 0.52	−0.19 ± 0.55
Hyperactivity/ impulsivity	1.14 ± 0.66	−0.31 ± 0.44	1.25 ± 0.68	−0.12 ± 0.42
DSM-IV subtype				
Combined type	39 (66.1%)		27 (77.1%)	
Inattentive type	20 (33.9%)		8 (22.9%)	
Drug-naive	54 (91.5%)		33 (97.1%)	
Associated disorders				
Conduct disorder	10 (16.9%)		7 (20.0%)	
Emotional disorder	3 (5.1%)		3 (8.6%)	
Tic disorder	3 (5.1%)		0 (0.0%)	
Dyslexia	12 (20.3%)		10 (28.6%)	

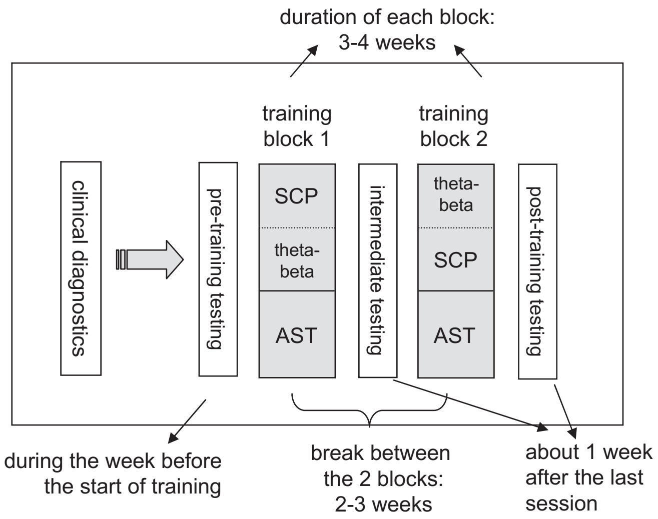


Fig. 1. Schematic illustration of the design of the randomized trial in children with ADHD. The training (neurofeedback, NF; attention skills training, AST) was divided into two blocks. Children of the NF group conducted theta/beta training in one block and SCP training in the other block (balanced order). Behavioral assessments and recordings of event-related potentials were done before the training started, between the two training blocks and after the end of the training.

The study followed the CONSORT guidelines for randomized trials (Boutron et al., 2008). It was approved by the local ethics committees of the participating clinics and conducted according to the declaration of Helsinki. Assent was obtained from the children and written informed consent from their parents.

2.2. Design of the study

The design of the study is illustrated in Fig. 1. Neurofeedback and attention skills training both consisted of 36 units of about 50 min each. These 36 units were divided into two blocks of 18 units. The 18 units of a block were combined to nine (double-) sessions with a short break between the 2 units of a session. The sessions took place two to three times a week. The NF training consisted of one block of 18 units of theta/beta training and one block of 18 units of SCP training (balanced order). For both trainings (NF and AST), there was a break of 2–3 weeks between the treatment blocks. The NF and the AST training were designed as similarly as possible concerning the setting and the demands upon the participants, e.g., in both groups children were instructed by a clinical psychologist to develop strategies for focussing attention and to practice the acquired strategies in daily-life (for further details see Supplementary material).

Behavior ratings and neurophysiological testing were conducted in the week before the training course started (*pre-training*), about 1 week after the last session of the first (*intermediate*) and second training block (*post-training*), respectively.

2.3. Training programs

The neurofeedback system SAM ("Self-regulation and Attention Management"), which was developed by our group for scientific purposes, was used for neurofeedback training.

In theta/beta training, a bar on the left of the screen (representing theta activity) had to be reduced while simultaneously a bar on the right (representing beta activity) had to be increased.

Trials of the theta/beta training lasted for 5 min in the beginning of the training and were extended to 10 min as the training proceeded so that the children had to sustain the alert and focussed but relaxed state for a longer period. Baseline values were determined at the beginning of each session (3 min). In SCP training, the task was to find appropriate strategies to direct a ball upwards (negativity trials) or downwards (positivity trials). Children were instructed to reach an attentive (negativity trials) or relaxed state (positivity trials). Both kinds of trials, which lasted for 8 s (baseline period: 2 s, feedback period: 6 s), were presented in random order.

In both NF protocols, feedback was calculated from Cz (reference: mastoids). Transfer trials, i.e., trials without contingent feedback, were also conducted (about 40% in the beginning of a training block and about 60% at the end of a training block). In each training unit, there were about 25–30 min of pure neuroregulation exercises.

The attention skills training was based on "Skillies" (Auer-Verlag, Donauwörth, Germany), a German learning software which primarily exercises visual and auditive perception, vigilance, sustained attention, and reactivity. In "Skillies", the children had to sail to several islands. On each island, a defined task – each requiring different attention-based skills – had to be solved.

A more detailed description of the training programs is provided in Supplementary material.

2.4. Attention Network Test (ANT)

Fig. 2 shows a schematic illustration of the ANT version used in this study, which was realized in Presentation (Neurobehavioral Systems, Albany, CA, USA). Children were instructed to feed a hungry fish (center fish in a row of five fish) by pressing the button of the mouse that matched the direction the center fish was pointing to. The flanking fish either looked in the same direction (congruent trials) or to the opposite direction (incongruent trials).

The fish appeared either slightly (about 1°) above or below a fixation cross and were preceded by one of three cue stimuli (equal probability). In the SpatialCue condition, an asterisk was presented at the location of the target fish (all cues were valid). In the NeutralCue condition, an asterisk at the center of the screen indicated that the target fish was to about to appear soon. In the NoCue condition, the fish appeared without a cue stimulus.

Starting 1400 ms before the appearance of the target fish, the cue stimuli were presented for 150 ms. In comparison to the standard ANT version (Fan et al., 2002), the interval between cue and

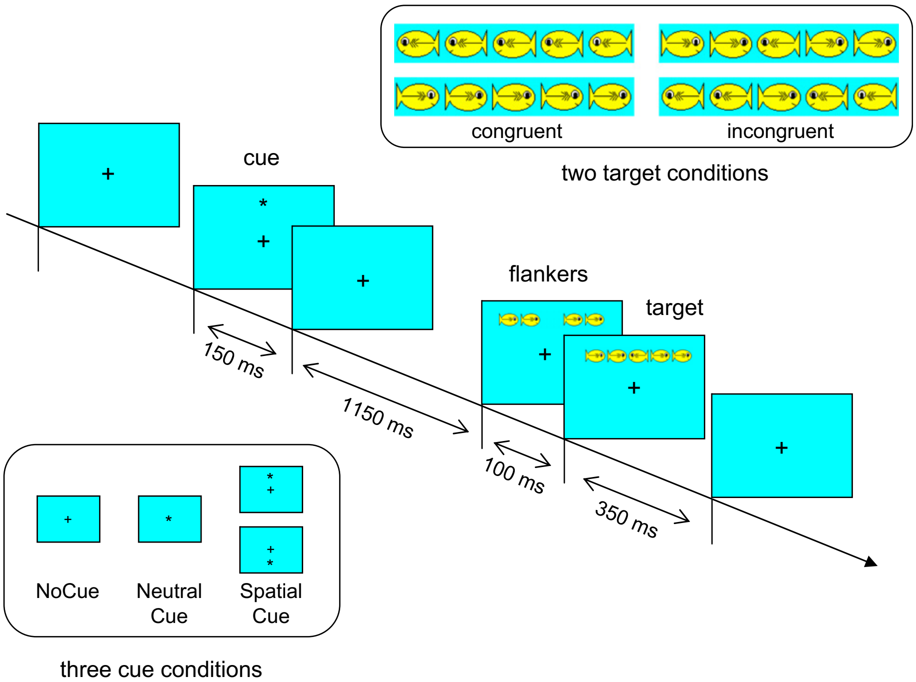


Fig. 2. Schematic illustration of the Attention Network Test (ANT). In each trial, one of three cue conditions (NoCue, NeutralCue, and SpatialCue) preceeded the target fish which either pointed to the left or the right (SOA 1400 ms). The flanker fish (congruent, incongruent) appeared 100 ms before the target fish, which was visible for 350 ms. Each fish subtended 1.6° of visual angle and the contours of adjacent fish were separated by 0.21°. The target fish was presented either about 1° above or below fixation. Viewing distance was about 72 cm. The intertrial interval varied randomly between 3.5 and 5.0 s. Reaction times between 200 and 1500 ms after onset of the target stimulus were considered for analysis.

target stimulus was prolonged to elicit a CNV in the ERPs. Presentation of the flanking fish started 100 ms before the center fish appeared.

The ANT was administered after a 2-min resting-EEG (eyes open) recording (Gevensleben et al. 2009b) and followed by a cued continuous performance test. It consisted of four blocks of 48 trials each. The test (incl. short breaks between the blocks) lasted about 15 min. At each recording, the task was described to the children first, and a practice block of 24 trials was run.

The following performance measures were determined according to Fan et al. (2002): hits, mean reaction time (RT), alerting score (RT for NoCue trials minus RT for NeutralCue trials), orienting score (RT for NeutralCue trials minus RT for SpatialCue trials) and conflict score (RT for incongruent trials minus RT for congruent trials). Only children with a minimum of 55% correct responses were included in the statistical analysis.

2.5. ERP recording and analysis

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

For data processing, the VisionAnalyzer software (Brain Products, Munich, Germany) was used. After downsampling to 256 Hz, brain electrical activity was re-referenced to the mastoids and filtered offline with 0.05–30 Hz, 24 dB/oct Butterworth filters. Ocular artefacts were corrected with the method of Gratton et al. (1983). If the amplitude at any EEG electrode exceeded ±100 µV, a segment −300 to 700 ms was excluded from further analyses.

Averaged event-related responses to cue stimuli and to target stimuli were computed. Recordings were only considered if at least 20 segments without artefacts and correct overt responses were available.

The CNV in NeutralCue and SpatialCue trials was determined as the mean amplitude from 1000 to 1300 ms following cue onset at electrode Cz. Cue-P3 and target-P3 were maximal at Pz. At this electrode, the most positive peak in the time-frame 400–900 ms was determined for cue trials, and in the time-frame 270–650 ms for target trials. Latencies of the target-P3 were also considered.

2.6. Behavioral assessments

The German ADHD rating scale (FBB-HKS) completed by the parents was used to measure training effects at the behavioral level. The severity of each item, which are related to DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorders, was rated from 0 to 3. Outcome measures were the FBB-HKS total score, i.e., the mean value of all items, as well as subscores for inattention and hyperactivity/impulsivity.

2.7. Statistical analysis

To study training effects, ANT performance were analysed in repeated measure ANOVAs with factors GROUP (NF, AST) as between-subject factor and TIME (pre-training, post-training) as within-subject factor. Concerning the ERP measures, an additional factor CUE (NeutralCue, SpatialCue) was introduced for the CNV and the cue-P3, and the factor CONGRUENCY (congruent, incongruent) for the target-P3, respectively. If significant effects containing the factor GROUP were obtained, additional post hoc tests were run for each group separately.

For the comparison of the NF protocols (theta/beta vs. SCP), the difference between the performance and ERP parameters at the end and the start of a training block were calculated. These change measures were subjected to ANOVAs with the within-subject factor PROTOCOL (theta/beta, SCP) and the between-subject factor ORDER representing the order in which the protocols were applied.

To investigate if training effects can be predicted by and/or correlate with ERP measures, block-wise linear regression models were applied (Heal and Rusch, 1995; Gevensleben et al., 2009b). In a first block, age and IQ were considered. In a second block, ERP baseline measures were introduced, and changes (post-training minus pre-training) of ERP parameters were added in the third block of the regression models. Only those ERP measures were used for the regression analysis for which at least a tendency for significance resulted for the Pearson correlation with the behavioral outcome measure. Outcome measures were the change of the FBB-HKS total score as well as the change of the subscales inattention and hyperactivity/impulsivity. Corresponding regression analyses were computed for the NF protocols separately. Change values refer to differences between the end and the start of a training block.

If comparable relations to the clinical outcome were found for the ERP measures as for the resting-EEG measures reported in Gevensleben et al. (2009b), it was studied if the respective ERP and EEG measures were related (by calculating Pearson's correlation coefficients) and whether prediction could be improved by considering both ERP and EEG measures.

Significance was assumed if $p < 0.05$. For the ANOVAs, effect sizes in terms of partial eta square (part. η^2) were computed and interpreted following the notion that part. $\eta^2 > 0.01$ indicates small, part. $\eta^2 > 0.06$ medium, and part. $\eta^2 > 0.14$ large effects (Cohen, 1988).

3. Results

3.1. Performance measures

3.1.1. Neurofeedback vs. control training

From the 94 children with ADHD completing their training, nine children had to be excluded either due to insufficient test performance, i.e., less than 55% correct responses ($n = 6$) or due to technical reasons ($n = 4$). Analyses of performance measures comprised 56 (of 59) children in the NF group and 28 (of 35) children in the AST group.

For all the measures, (highly) significant TIME effects were obtained but no significant GROUP × TIME interactions (see Table 2). Hits increased, mean reaction time, alertness, orienting and conflict scores decreased. Effects were not larger for the NF group but rather tended to be higher in the AST group (e.g., increase of hits). From our clinical impression, there were some children in the AST group who had basic problems in solving tasks at the computer but improved their basic skills during the course of their training. So, we ran some post hoc analysis considering 'poor performers' (defined as children with 55–75% hits at pre-training) separately. Considering this subgroup of children (NF group: $n = 8$; AST group: $n = 6$), there was a larger increase of hits ($F(1,12) = 5.04$, $p < 0.05$, part. $\eta^2 = 0.30$) in the AST group (pre-training: 123.5 ± 11.5, post-training: 163.2 ± 13.0) compared to the NF group (pre-training: 132.0 ± 10.6; post-training: 148.0 ± 15.9), partly at the cost of (non-significantly) slower mean reaction times (AST: pre-training: 482.5 ± 57.0 ms, post-training: 532.3 ± 139.1 ms; NF: pre-training: 491.8 ± 113.6 ms, post-training: 482.3 ± 124.9 ms).

3.1.2. Theta/beta vs. SCP training

Comparing theta/beta and SCP training, a trend for the conflict score was obtained ($F(1,51) = 3.2$, $p < 0.1$, part. $\eta^2 = 0.06$) indicating a larger decrease for the SCP training (change: −14.4 ± 24.1 ms) compared to the theta/beta training (−4.8 ± 29.4 ms).

For the number of hits, the orienting and conflict score, a significant ORDER × PROTOCOL interaction was observed ($F(1,51) > 6.6$. $p < 0.02$, part. $\eta^2 > 0.09$). Changes in performance measures occurred mainly from the first to the second testing but only to a smaller amount from the second to third testing.

3.2. Event-related potential measures

3.2.1. Neurofeedback vs. control training

At least 20 trials with correct responses and without artefacts for the different task conditions were available in 43 children of the NF group and 21 children of the AST group. Those children who could not be included in the ERP analysis were not characterized by different clinical (FBB-HKS) parameters (neither at pre-training nor at post-training); t-test: $|t(92)| < 1.3$; $p > 0.18$) but were younger than the children with sufficient test performance and signal quality (9;1 ± 0;11 years vs. 9;11 ± 1;2 years, t-test: $t(92) = -3.5$; $p = 0.001$).

For the CNV at electrode Cz, the repeated measure ANOVA revealed a significant GROUP × TIME effect ($F(1,62) = 4.2$, $p < 0.05$, part. $\eta^2 = 0.07$) and a trend for the GROUP × TIME × CUE interaction ($F(1,62) = 3.0$, $p < 0.1$, part. $\eta^2 = 0.04$; see Table 3). Considering the two groups separately, a highly significant TIME effect was obtained for the NF group ($F(1,42) = 13.0$, $p < 0.001$, part. $\eta^2 = 0.24$) indicating an increase of the CNV from pre- to post-training (see also Fig. 3). For the AST group, the TIME effect was not significant ($F(1,21) = 0.1$, n.s.) but a significant CUE × TIME interaction was obtained ($F(1,21) = 5.3$, $p < 0.05$, part. $\eta^2 = 0.20$) indicating a differential behavior of the CNV for NeutralCue vs. SpatialCue trials from pre- to post-training.

The CNV was larger (more negative) in SpatialCue vs. NeutralCue trials (factor CUE: $F(1,62) = 25.3$, $p < 0.001$, part. $\eta^2 = 0.30$).

For the cue-P3 at electrode Pz, a significant GROUP - CUE × TIME interaction ($F(1,62) = 5.9$, $p < 0.05$, part. $\eta^2 = 0.09$) resulted. Analyzing NF and AST group separately, revealed a significant CUE × TIME interaction for the NF group ($F(1,42) = 9.7$, $p < 0.01$, part. $\eta^2 = 0.18$): whereas the P3 amplitude slightly increased in NeutralCue trials, it rather decreased in SpatialCue trials.

Table 2
Performance data.

	NF group ($n = 56$)		AST group ($n = 28$)		Repeated measure ANOVAs
	Pre	Post	Pre	Post	Significant effects
Hits	168.7 ± 19.8	175.12 ± 15.9	167.7 ± 19.9	179.2 ± 12.7	TIME: $F(1,82) = 20.6^{**}$, part. $\eta 2 = 0.20$
Mean RT (ms)	561.8 ± 117.9	542.2 ± 121.1	604.1 ± 135.6	571.4 ± 123.0	TIME: $F(1,82) = 6.8^{*}$, part. $\eta^2 = 0.08$
Alerting (ms)	35.1 ± 31.8	24.4 ± 31.7	41.8 ± 36.4	25.9 ± 28.6	TIME: $F(1,82) = 9.0^{*}$, part. $\eta^2 = 0.10$
Orienting (ms)	39.9 ± 27.7	19.1 ± 25.3	31.1 ± 31.4	19.6 ± 30.6	TIME: $F(1,82) = 13.0^{**}$, part. $\eta^2 = 0.14$
Conflict (ms)	76.6 ± 30.8	57.5 ± 28.3	79.8 ± 32.1	51.7 ± 29.8	TIME: $F(1,82) = 45.9^{**}$, part. $\eta^2 = 0.25$

* $p < 0.01$.
** $p < 0.001$.

Table 3
Neurophysiological (event-related potentials) data.

	NF group ($n = 43$)		AST group ($n = 21$)		Repeated measure ANOVAs
	Pre	Post	Pre	Post	Significant effects
CNV (Cz, μV)					
NeutralCue	1.22 ± 3.00	−0.38 ± 2.80	0.93 ± 3.76	0.10 ± 3.43	GROUP × TIME: $F(1,62) = 4.2^{*}$, part. $\eta^2 = 0.07$
SpatialCue	−0.55 ± 3.08	−1.74 ± 3.32	−1.25 ± 3.25	0.22 ± 3.22	GROUP × CUE × TIME: $F(1,62) = 3.0^{+}$, part. $\eta^2 = 0.04$
					CUE: $F(1,62) = 25.3^{***}$, part. $\eta^2 = 0.30$
					CUE × TIME: $F(1,62) = 6.3^{*}$, part. $\eta^2 = 0.09$
Cue-P3 (Pz, μV)					
NeutralCue	5.59 ± 3.63	6.63 ± 4.24	5.58 ± 3.04	4.27 ± 2.74	GROUP × CUE × TIME: $F(1,62) = 5.9^{*}$, part. $\eta^2 = 0.09$
SpatialCue	8.58 ± 3.95	7.43 ± 3.17	7.39 ± 3.20	6.88 ± 3.84	CUE: $F(1,62) = 29.5^{***}$, part. $\eta^2 = 0.32$
Target-P3 (Pz)					
Amplitude (μV)					TIME: $F(1,62) = 25.4^{***}$, part. $\eta^2 = 0.29$
Congruent	22.0 ± 6.8				
Incongruent	22.7 ± 6.4				
Latency (ms)					TIME: $F(1,62) = 25.0^{***}$, part. $\eta^2 = 0.29$
Congruent	531.9 ± 80.9	489.2 ± 88.9	546.1 ± 40.8	507.6 ± 79.7	CONGRUENCY: $F(1,62) = 7.2^{**}$, part. $\eta^2 = 0.10$
Incongruent	539.6 ± 62.4	500.8 ± 67.1	568.1 ± 42.5	530.7 ± 70.5	

$^{+}$ $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

P3 amplitudes were larger in SpatialCue vs. NeutralCue trials (factor CUE: $F(1,62) = 29.5$, $p < 0.001$, part. $\eta^2 = 0.32$).

For the target-P3 at electrode Pz, no group-specific effect was found. Latencies were shorter in congruent vs. incongruent trials (factor CONGRUENCY: $F(1,62) = 7.2$, $p < 0.01$, part. $\eta^2 = 0.10$). They decreased from pre- to post-training (factor TIME: $F(1,62) = 25.0$, $p < 0.001$, part. $\eta^2 = 0.29$). Target-P3 amplitudes also decreased from pre- to post-training (factor TIME: $F(1,62) = 25.4$, $p < 0.001$, part. $\eta^2 = 0.29$).

Post-hoc, we investigated if the decreases in P3 amplitude and latency were moderated by other factors and tested age and IQ as possible covariates. IQ was associated with a decrease of the P3 amplitude ($F(1,61) = 4.6$, $p < 0.05$, part. $\eta^2 = 0.07$).

3.2.2. Theta/beta vs. SCP training

The CNV increase in the NF group was due the SCP training block (CNV changes NeutralCue: −1.6 ± 3.2 μV; SpatialCue: −1.8 ± 3.5 μV) as indicated by a significant effect for the factor PROTOCOL ($F(1,37) = 4.3$, $p < 0.05$, part. $\eta^2 = 0.10$). After the theta/beta training block, CNV amplitudes had not actually changed (NeutralCue: −0.1 ± 4.0 μV; SpatialCue: 0.3 ± 3.9 μV).

Neither for the cue-P3 nor for the target-P3, any of the effects containing the factors ORDER and/or PROTOCOL turned out to be significant.

Relations between ERP measures, resting-EEG measures and behavioral outcome.

For the SCP training block, the CNV measured at baseline (pre-training, $n = 44$) in spatial cue trials at Cz turned out as a significant predictor variable for the improvement of the FBB-HKS total score (accounting for about 20% of the variance; $R^2 = 0.214$, $\beta = 0.463$, $p < 0.005$; see Fig. 4) as well as the inattention ($R^2 = 0.162$, $\beta = 0.402$, $p < 0.005$) and the hyperactivity/impulsivity subscale ($R^2 = 0.120$, $\beta = 0.347$, $p < 0.01$). This ERP parameter was also associated with the success of the complete NF training (FBB-HKS total score: $R^2 = 0.085$, $\beta = 0.292$, $p < 0.05$, $n = 50$).

For the SCP training block, pre-training alpha activity in the resting-EEG (at left parietal sites) had also been found to be associated with behavioral improvements (reduction of the FBB-HKS total score and the hyperactivity/impulsivity subscale, respectively) (Gevensleben et al., 2009b). But pre-training CNV amplitude and alpha activity were not significantly correlated ($r = 0.175$; n.s.). Calculating regression models for both variables, prediction of the behaviorial outcome was improved. Concerning the improvement of the FBB-HKS total score induced by the SCP training, nearly 30% of the variance ($R^2 = 0.286$) could be explained by the predictor variables CNV ($\beta = 0.409$, $p < 0.005$) and alpha activity ($\beta = 0.262$, $p < 0.1$). For the change of the FBB-HKS hyperactivity/impulsivity subscale, comparable results were obtained ($R^2 = 0.280$; CNV: $\beta = 0.316$, $p < 0.05$; alpha activity ($\beta = 0.359$, $p < 0.05$).

For the theta/beta training block, none of the parameters under consideration was associated with any of the FBB-HKS outcome measures. For the AST group, a significant predictor variable could not be found. Age and IQ did not turn out as a significant predictor variable in any model.

4. Discussion

In order to learn more about the mechanisms underlying NF training in children with ADHD, we studied the impact of two distinct NF protocols (theta/beta and SCP training) on the ERP components P3 and CNV (elicited in the Attention Network Test). Further, we searched for possible associations between ERP measures and behavioral outcome measures. Effects were evaluated in comparison to a computerized attention skills training.

As a main result, an increase of the CNV in the ANT was observed after NF training. This effect could be ascribed solely to the SCP training, i.e., it was specific for the SCP training. Children with a higher baseline CNV improved more in their parental ratings of ADHD symptomatology after SCP training and the complete NF treatment, respectively. Thus, the baseline CNV emerged as a relevant predictor variable for treatment outcome.

In both groups (NF and AST), an improved test performance and a reduced target-P3 component were found after training, probably mainly reflecting adaptation to the attention test. In the NF group, the cue-P3 developed differentially in NeutralCue and SpatialCue trials from pre- to post-training. But this effect was not specific for the theta/beta protocol.

Nearly 1/3 of the children could not be included in the ERP analysis due to insufficient test performance and insufficient signal quality, respectively. These "dropouts" were characterized by younger age but not by different clinical attributes. Therefore, generality of the neurophysiological findings should not be affected by the dropouts.

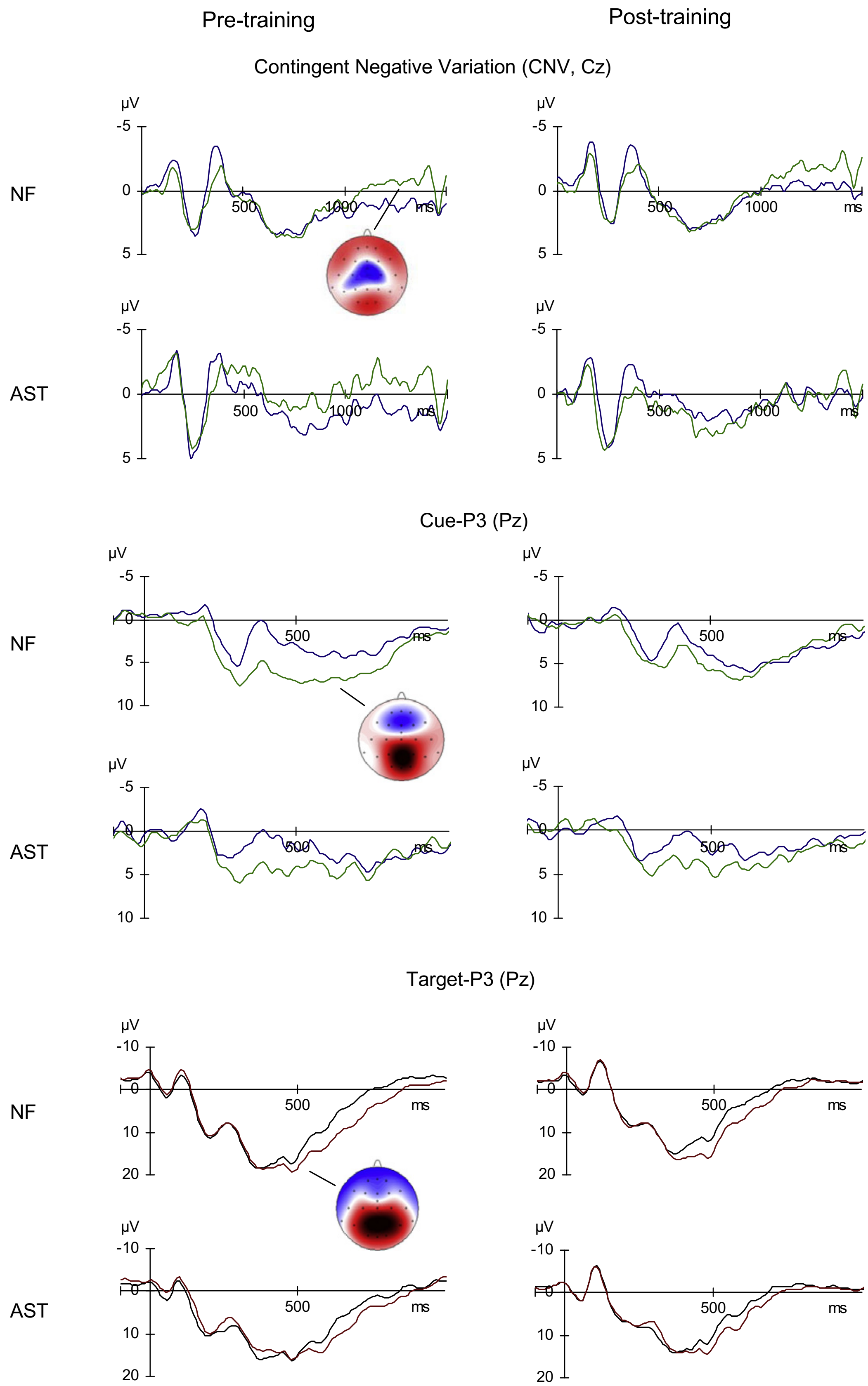


Fig. 3. Grand averages ERPs for NF and AST group at pre-training and post-training. Top: NeutralCue (blue) and SpatialCue (green) ERPs recorded at electrode Cz. t = 0 ms represents the onset of the cue. The CNV (mean amplitude) was measured in the interval [1000 ms; 1300 ms]. Middle: NeutralCue (blue) and SpatialCue (green) ERPs recorded at electrode Pz. *t* = 0 ms represents the onset of the cue. The cue-P3 was determined as the maximum positive peak in the interval [400 ms; 900 ms]. Bottom: target ERPs to congruent (black) and incongruent (red) stimuli, recorded at electrode Pz. *t* = 0 ms represents the onset of the target stimulus. The target-P3 was determined as the maximum positive peak in the interval [270 ms; 650 ms]. Spline-interpolated maps illustrate the topography of the components. Red (blue) colors indicate positive (negative) amplitude values.

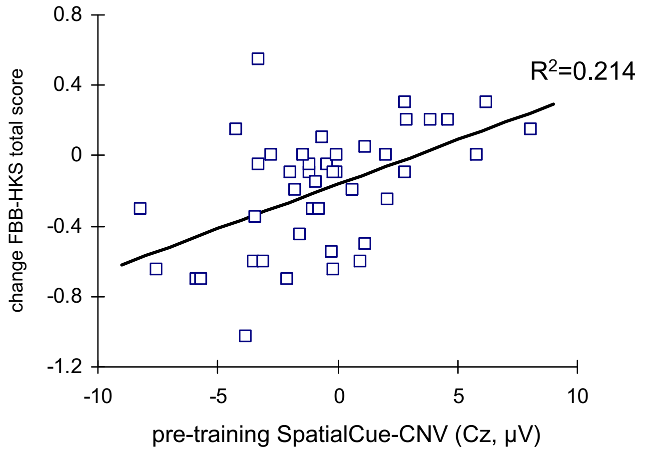


Fig. 4. SCP training block. Change of the FBB-HKS total score vs. CNV amplitude at electrode Cz in SpatialCue trials of the Attention Network Test (pre-training). The linear regression line is also depicted.

4.1. SCP training/CNV

The CNV increase in the NF group reflected a large effect (partial η^2 of 0.24), comparable to the behavioral improvements with respect to ADHD symptomatology (Gevensleben et al. 2009a). An increase of the CNV (in a cued continuous performance test) following SCP treatment had already been observed in our previous study comprising only a small sample (Heinrich et al., 2004). Though Doehnert et al. (2008) could not directly replicate this finding, they reported a correlation between SCP regulation capability and change of the CNV amplitude. Thus, SCP training is clearly associated with CNV effects in attention tests. In the attentional tasks considered so far, the cue-target interval was about 1.5 s. In future studies, longer intervals could be considered to differentiate between the early and late part of the CNV which are related to different neuronal networks (Lütcke et al., 2009).

In our opinion, the CNV increase observed after SCP training is not related to one of the attention networks supposed to be differentiated using the ANT. It supports the notion that SCP training targets phasic regulation of cortical excitability affecting, i.e., resource allocation during effort-demanding processes. Thus, SCP training could improve regulation of energetical resources which is supposed to be deficient in children with ADHD (Sergeant et al., 1999). A better synchronization of certain oscillatory neuronal networks may account for this phenomenon (Rothenberger, 2009).

Children with a higher baseline CNV, i.e., being initially able to recruit more resources, improved more in their parental behavior ratings. They seem to accomplish the transfer into daily-life better than children, who have to build up these resources first. One might compare this to an athlete in sports, who, in parallel, has to build up muscles for a powerful performance and to work on his technique to utilize his muscle power. The more muscle power he already has, the more time he can spend on improving his technique.

In this respect, the baseline CNV should be regarded as an indicator for the number of SCP training units rather than a general predictor for the success. But this issue has to be investigated systematically in future studies.

In the regression analyses, a better prediction of the clinical outcome related to SCP training could be achieved by considering alpha activity in the resting-EEG at pre-training as a further predictor variable besides the pre-training CNV. Thus, both pre-training measures appear to be related to different aspects of the SCP training. Interestingly, the associations between EEG measures in the alpha band and the behavioral outcome were primarily related to hyperactivity/impulsivity (Gevensleben et al., 2009b) whereas the pre-training CNV predicted the outcome in both ADHD symptom domains significantly. In this context, future studies should address the role of negativity and positivity trials of a SCP training, which aim at increasing and decreasing of cortical excitability, respectively.

4.2. Theta/beta training/P3

Based on the findings of Egner and Gruzelier (2001, 2004), we expected an increase of the P3 following theta/beta training. However, irrespective of the training, a decrease of the target-P3 was observed. As indicated by a larger decrease for more intelligent children, the effect may mainly reflect adaption to the task, which was conducted three times by each child. The cue-P3 effect observed for the complete NF training (not specific for the theta/beta training block) may indicate that more attentional resources were allocated to process more salient stimuli.

Though no specific ERP effect could be found for theta/beta training, it has to be kept in mind that we could demonstrate associations between theta activity in the resting EEG (pre-training, change from pre- to post-training) and improvements in the ADHD rating scale for theta/beta training (Gevensleben et al., 2009b).

When considering pre- to post-training effects, the number of training units also has to be taken into account. In this respect, the number of 18 units for a single NF protocol might have been too small to obtain specific ERP effects for theta/beta training in children with ADHD.

4.3. Training effects on test performance

Due to the study design, it cannot be differentiated to what extent the improvements in the ANT at the performance level observed in both groups (NF and AST) reflect training effects or are just due to repeated test execution.

The use of a computerized attention skills training, which is directly related to a cognitive task like the ANT, surely has raised the bar to demonstrate improvements at the performance level for NF training. So, it is not surprising that, in a smaller subgroup of 'poor performers' (between 55% and 75% hits at pre-training testing), children of the AST improved more than those of the NF group.

Distinct effects for the NF protocols – a trend for a larger reduction of the conflict score after SCP training was obtained – may partly be masked by large standard deviations of the ANT measures. Large standard deviations for these measures are also reported in other studies using the ANT to study attentional functions in children with ADHD (Konrad et al., 2006; Adólfsdóttir et al., 2008; Johnson et al., 2008) and may contribute to the mixed results reported there.

5. Conclusion

Successful NF treatment in children with ADHD is accompanied by specific neurophysiological effects like an enhancement of the CNV following SCP training – or as described in Gevensleben et al. (2009b) – effects in the resting EEG. Further, distinct neurophysiological baseline values predict the clinical outcome. Thus, these findings contribute significantly to a better understanding of the mechanisms underlying this clinically effective treatment and also indicate that NF training could be optimized and individualized based on a subject's neurophysiological profile.

Acknowledgments

The authors thank their clinical colleagues, technical assistants and the student assistants for their valuable support as well as all participating families for their contribution and effort.

This study was supported by the German Research Foundation (with a joint grant to H. Heinrich, G.H. Moll, and A. Rothenberger; HE 4536/2, MO 726/2, RO 698/4). A. Rothenberger also serves on advisory boards and speakers' bureaus of Eli Lilly, Shire and Medice and received educational grants from Eli Lilly and Shire. S. Wangler, H. Gevensleben, B. Albrecht and P. Studer reported no biomedical financial interests or potential conflicts of interest.

Trial registry: ISRCTN87071503 (http://www.controlled-trials.com/ISRCTN87071503)-Comparison of neurofeedback and computerized attention skills training in children with attention-deficit/hyperactivity disorder (ADHD).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2010.06.036.

References

Adólfsdóttir S, Sørensen L, Lundervold AJ. The attention network test: a characteristic pattern of deficits in children with ADHD. Behav Brain Funct 2008;4:9.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. (DSM-IV). Washington, DC: American Psychiatric Press; 1994.

Banaschewski T, Brandeis D. Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective. J Child Psychol Psychiatry 2007;48:415–35.

Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A. Association of ADHD and conduct disorder—brain electrical evidence for the existence of a distinct subtype. J Child Psychol Psychiatry 2003;44:356–76.

Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 2003;114:171–83.

Barry RJ, Clarke AR, Johnstone SJ, McCarthy R, Selikowitz M. Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. Biol Psychiatry 2009;66:398–401.

Birbaumer N, Elbert T, Canavan AG, Rockstroh B. Slow cortical potentials of the cerebral cortex and behavior. Physiol Rev 1990;70:1–41.

Boutron I, Moher D, Douglas G, Altman G, Schulz F, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation an elaboration. Ann Intern Med 2008;148:295–310.

Cohen JD. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, New York: Erlbaum; 1988.

Doehnert M, Brandeis D, Straub M, Steinhausen H-C, Drechsler R. Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? J Neural Transm 2008;115:1445–56.

Döpfner M, Lehmkuhl G. DISYPS-KJ – Diagnostik-System für psychische Störungen im Kindes- und Jugendalter. Bern: Hans Huber; 2000.

Döpfner M, Berner W, Flechtner H, Lehmkuhl G, Steinhausen HC. Psychopathologisches Befundsystem für Kinder und Jugendliche (CASCAP-D). Göttingen: Hogrefe; 1999.

Drechsler R, Straub M, Doehnert M, Heinrich H, Steinhausen H-C, Brandeis D. Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). Behav Brain Funct 2007;3:35.

Egner T, Gruzelier JH. Learned self-regulation of EEG frequency components affects attention and event-related brain potentials in humans. Neuroreport 2001;12:4155–9.

Egner T, Gruzelier JH. EEG biofeedback of low beta band components: frequency-specific effects on variables of attention and event-related brain potentials. Clin Neurophysiol 2004;115:131–9.

El-Sayed E, Larsson JO, Persson HE, Rydelius PA. Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. J Am Acad Child Adolesc Psychiatry 2002;41:811–9.

Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci 2002;14:340–7.

Fuchs T, Birbaumer N, Lutzenberger W, Gruzelier JH, Kaiser J. Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl Psychophysiol Biofeedback 2003;28:1–12.

Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O, Studer P, Rothenberger A, Moll GH, Heinrich H. Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. J Child Psychol Psychiatry 2009a;50:780–9.

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P, Wangler S, Rothenberger A, Moll GH, Heinrich H. Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. Int J Psychophysiol 2009b;74:149–57.

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P, et al. Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial. Eur Child Adolesc Psychiatry 2010;19:715–24.

Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 1983;55:468–84.

Heal LW, Rusch FR. Predicting employment for students who leave special education high school programs. Except Child 1995;61:472–87.

Heinrich H, Gevensleben H, Freisleder FJ, Moll GH, Rothenberger A. Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. Biol Psychiatry 2004;55:772–5.

Heinrich H, Gevensleben H, Strehl U. Annotation: neurofeedback – train your brain to train behaviour. J Child Psychol Psychiatry 2007;48:3–16.

Johnson KA, Robertson IA, Barry E, Mulligan A, Daibhis A, Daly M. Impaired conflict resolution and alerting in children with ADHD: evidence from the Attention Network Task (ANT). J Child Psychol Psychiatry 2008;49: 1339–47.

Konrad K, Neufang S, Hanisch C, Fink GR, Herpertz-Dahlmann B. Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. Biol Psychiatry 2006;59:643–51.

Kropotov JD, Grin-Yatsenko VA, Ponomarev VA, Chutko LS, Yakovenko EA, Nikishena IS. ERPs correlates of EEG relative beta training in ADHD children. Int J Psychophysiol 2005;55:23–34.

Levesque J, Beauregard M, Mensour B. Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. Neurosci Lett 2006;394:216–21.

Lubar JF, Swartwood MO, Swartwood JN, O'Donnell PH. Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. Biofeedback Self Regul 1995;20:83–99.

Lütcke H, Gevensleben H, Albrecht B, Frahm J. Brain networks involved in early versus late response anticipation and their relation to conflict processing. J Cogn Neurosci 2009;21:2172–84.

Monastra V, Monastra D, George S. The effects of stimulant therapy, EEG-biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback 2002;27: 231–49.

Pine DS. Editorial: evaluating new and old treatments for ADHD. J Child Psychol Psychiatry 2009;50:767–8.

Posner MI, Petersen SE. The attention system of human brain. Annu Rev Neurosci 1990;13:25–42.

Pribram KH, McGuinness D. Arousal, activation and effort in the control of attention. Psychol Rev 1975;82:116–49.

Rothenberger A. Brain oscillations forever—neurophysiology in future research of child psychiatric problems. J Child Psychol Psychiatry 2009;50:79–86.

Sartory G, Heine A, Müller BW, Elvermann-Hallner A. Event- and motor-related potentials during the continuous performance task in attention-deficit/hyperactivity disorder. J Psychophysiol 2002;16:97–106.

Sergeant JA, Oosterlaan J, Van der Meere JJ. Information processing and energetic factors in attention-deficit/hyperactivity disorder. In: Quay HC, Hogan A, editors. Handbook of disruptive behavior disorders. New York: Plenum Press; 1999. p. 75–104.

Strehl U, Leins U, Goth G, Klinger C, Hinterberger T, Birbaumer N. Self-regulation of slow cortical potentials: a new treatment for children with attention deficit/hyperactivity disorder. Pediatrics 2006;118:e1530–40.

Tewes U, Rossmann P, Schallberger U. Hamburg-Wechsler-Intelligenztest für Kinder III (HAWIK-III). Hogrefe: Göttingen; 2000.

4.4 Prädiktion

Das Alter und der IQ hatten ebenso keinen (linearen) Einfluss auf den Erfolg eines Trainings wie die Ausprägung der ADHS-Symptomatik zu Trainingsbeginn, der ADHS-Subtyp oder das Vorliegen einer bestimmten Komorbidität. Die Untersuchung des Einflusses unterschiedlicher Persönlichkeitseigenschaften (Selbstwirksamkeitsüberzeugung, Stressverarbeitung, Introversion vs. Extraversion u.a.) sowie der Motivation der Kinder steht noch aus.

Wir führten blockweise Regressionsanalysen (Heal & Rusch, 1995) durch, um mögliche Prädiktoren auf neurophysiologischer Ebene zu finden (getrennt für EEG und EPs). Baseline-Werte wurden hierbei vor den Variablen eingeführt, die die Veränderung vom Beginn zum Ende des Trainings bzw. eines Trainingsblocks abbildeten. Hinweise auf einen Zusammenhang des Trainingserfolgs mit neurophysiologischen Parametern ergaben sich jeweils spezifisch für die NF-Trainingsprotokolle (siehe Originalpublikation 3, table2).

Kinder, die vor Trainingsbeginn eine höhere Theta-Aktivität im Spontan-EEG aufwiesen und bei denen nach dem Theta/Beta-Training die Theta-Aktivität stärker abgenommen hatte, verbesserten sich deutlicher im FBB-HKS Gesamtwert (Originalpublikation 3, Fig. 5). Beide Parameter zusammen trugen zu 21.6% Varianzaufklärung bei.

Für das SCP-Training gab es EEG-basierte Prädiktorvariablen für das Alpha-Band (Varianzaufklärung R^2 = 41.5%, Originalpublikation 3, Fig. 6). Außerdem zeigte sich, dass Kinder mit stärker ausgeprägter CNV im Attention Network Test vor Trainingsbeginn eine größere Reduzierung der ADHS-Symptomatik (FBB-HKS Gesamtwert) erreichten, nicht nur bezogen auf den SCP-Trainingsblock (R^2 = 0.214), sondern auch in Bezug auf das komplette NF-Training (R^2 = 0.085, Originalpublikation 4, Fig. 4). Kinder, die von vornherein mehr Ressourcen rekrutieren können, scheinen den Transfer in den Alltag besser bzw. schneller bewerkstelligen zu können als Kinder, die diese Ressourcen erst aufbauen müssen. Dies ist vergleichbar mit einem Sportler, der einerseits Muskeltraining betreiben muss, andererseits an seiner Technik arbeitet. Je mehr Muskelkraft er bereits mitbringt, desto mehr kann er sich auf die Verfeinerung seiner Technik konzentrieren.

4.5 Bewertung und Ausblick

4.5.1 Einordnung der Ergebnisse

Unsere Studie stellt die bislang größte und methodisch strengste Überprüfung der Wirksamkeit eines NF-Trainings bei Kindern mit ADHS dar. Als wesentlicher und klinisch relevanter Punkt ist festzuhalten, dass sich das Training - wenngleich in seinem Setting sehr wissenschaftlich gehalten und nicht auf Maximierung der Wirksamkeit ausgelegt – als wirksam und dem Kontrolltraining überlegen erwiesen hat. Die Verbesserungen auf Verhaltensebene erwiesen sich als stabil und ließen sich auch 6 Monate nach Abschluss des Trainings in der Katamnese-Erhebung aufzeigen.

Das Kontrolltraining war möglichst vergleichbar konzipiert. Bzgl. unspezifischer Wirkfaktoren (z.B. Erwartungshaltung oder Therapiezufriedenheit der Eltern) unterschieden sich NF- und AST-Gruppe nicht. Die Überlegenheit des NF kann damit auf spezifische Wirkfaktoren des Trainings zurückgeführt werden. Die Ergebnisse lassen den Schluss zu, dass NF einen klinisch wirksamen Therapiebaustein zur Behandlung von Kindern mit ADHS darstellt.

Die Spezifität der Trainingseffekte wird auch durch die Ergebnisse auf neurophysiologischer Ebene gestützt. Dort führte das NF-Training zu einer Reduzierung der Theta-Aktivität im Spontan-EEG, die in der Kontrollgruppe nicht beobachtet werden konnte. Im Spontan-EEG konnten zwar zwischen Theta/Beta- und SCP-Training keine differierenden Prä-Post-Effekte gefunden werden; es zeigten sich jedoch spezifische Assoziationen zwischen EEG-Parametern und Verbesserungen auf klinischer Ebene. Darüber hinaus ergab sich nach dem SCP-Block des NF-Trainings eine Erhöhung der CNV, die weder nach dem Theta/Beta-Block noch nach dem AST-Training auftrat. Ein Einfluss des SCP-Trainings auf die CNV stellt damit den robustesten und am häufigsten replizierten Befund zum SCP-Training dar (Heinrich et al., 2004; Doehnert et al., 2008).

Die Analyse des Zusammenhangs der NF-Regulationsleistung im Training und der Effekte auf Verhaltens- bzw. neurophysiologischer Ebene steht noch aus. Diese Auswertung könnte Informationen darüber liefern, inwiefern eine stabile Regulationsleistung und Trainingserfolg zusammenhängen, sowie Hinweise auf weitere Variablen geben, die den Trainingserfolg beeinflussen.

4.5.2 Anmerkungen zu Placebo-Kontrollbedingungen in der Neurofeedback-Forschung

Die Anforderungen an Evaluationsstudien zur Einschätzung der Wirksamkeit von psychotherapeutischen Interventionen im Bereich Kinder- und Jugendpsychotherapie orientieren sich an den von Chambless & Hollon (1998) entwickelten Richtlinien, die im Bemühen um evidenzbasierte Effektivitätsforschung formuliert wurden (APA, 1995). Wesentliche Forderungen umfassen u. a. eine angemessene Kontrollgruppe, ausreichende Stichprobengröße (Teststärke), valide diagnostische und Effektivitätsmaße sowie Replizierbarkeit der therapeutischen Interventionen und Erfassung langfristiger Effekte (Hibbs, 2001). Über die Frage der klinischen Wirksamkeit hinaus stellt sich gerade beim

Neurofeedback die Frage nach spezifischen und unspezifischen Wirkfaktoren (Kirsch, 2005; Heinrich et al., 2007).

Mit zunehmender Anzahl an Evaluationsstudien und Wirksamkeitsnachweisen auf dem Gebiet Neurofeedback bei ADHS wurde von verschiedenen Autoren die Forderung gestellt, spezifische Wirkfaktoren im Rahmen placebokontrollierter Studien (z.B. Loo & Barkley, 2005; Lansbergen et al., 2010) nachzuweisen. Placebo-Kontrollgruppen werden in der Psychotherapieforschung jedoch als problembehaftet und weitgehend unangemessen angesehen (Herbert & Gaudiano, 2005), nicht zuletzt, da sie von der falschen Annahme ausgehen, man könne bei psychotherapeutischen Interventionen unspezifische von spezifischen Faktoren trennen (Omer & London, 1989).Im Unterschied zu medikamentösen Behandlungen erfordert Neurofeedback ebenso wie andere psychotherapeutische Methoden die aktive Mitarbeit des Patienten. Eine wesentliche Wirkvariable psychotherapeutischer Interventionen ist dabei die Wirksamkeitserwartung (Goldstein & Shipman, 1961), die wiederum weitere unspezifische, aber unerlässliche Wirkfaktoren (z. B. Mitarbeitsbereitschaft) beeinflusst.

Die Annahme, möglicherweise ein Placebotraining zu absolvieren, geht mit einer Reduzierung der (Selbst-) Wirksamkeitserwartung einher, insbesondere beim Neurofeedback-Training, bei dem es den Kindern eher schwer fällt, die Kontrolle über die zu regulierenden EEG-Parameter zu gewinnen. Somit kann die Wirksamkeit der Methode deutlich beeinträchtigt werden. In bisherigen Versuchen placebokontrollierter Neurofeedback-Studien nahm der weitaus überwiegende Teil der Teilnehmer an, ein Placebotraining zu absolvieren, unabhängig von der wahren Gruppenzugehörigkeit (Lansbergen et al., 2010; Logemann et al., 2010).

Es bedarf unseres Erachtens kreativerer Methoden, die spezifischen Effekte eines Neurofeedback-Trainings aufzudecken. Dies kann dadurch geschehen, dass einzelne potentielle Wirkvariablen in systematischer Weise kontrolliert und variiert werden. So kann z. B. die Wirksamkeitserwartung des Patienten durch geeignete Instruktionen systematisch variiert oder durch geeignete Fragebögen erfasst werden, um den Einfluss auf den Therapieerfolg abzuschätzen (vgl. Chatoor u. Krupnik, 2001; Gevensleben et al., 2009a). Eine weitere Möglichkeit zur Analyse der Wirkmechanismen besteht beim Neurofeedback im Vergleich unterschiedlicher Trainingsprotokolle (z. B. Theta/Beta- vs. SCP-Training), für die auf neurophysiologischer Ebene differentielle Effekte gewonnen werden können (Gevensleben et al., 2009b; Wangler et al., 2011).

4.5.3. „Wirkmodell“

Die Anwendung von Neurofeedback bei Kindern mit ADHS beruht ursprünglich auf Annahmen zu bestimmten Defiziten in EEG- und EP-Parametern (erhöhter Theta/Beta-Quotient, verminderte CNV), die durch das Training behoben werden sollen. Unsere bisherigen Befunde sprechen nicht dafür, dass die positive Wirkung alleine auf der Korrektur eines vorliegenden neurophysiologischen Defizits beruht. Gegen dieses ‚mechanistische' Modell spricht beispielsweise der für das (relativ kurze) SCP-Training gewonnene Befund, dass Kinder mit einer höheren CNV vor Trainingsbeginn stärker vom SCP-Training (bzw. vom NF-Training insgesamt) profitierten. Eine Zunahme der CNV alleine genügt nicht, um Effekte auf Verhaltensebene erreichen zu können, auch wenn verbessertes Konflikt-Monitoring und gezieltere Ressourcenaktivierung wichtige Faktoren für eine bessere Selbststeuerung sind. Vielmehr gehen wir davon aus (wie im Abschnitt „Prädiktion“ bereits ausgeführt), dass es wichtig ist einzuüben, wann und wie die im Training erworbenen Fähigkeiten im Alltag anzuwenden und mit „Cues“ zu verknüpfen sind. Neben neurophysiologischen Faktoren spielen vermutlich psychologische und motivationale Aspekte (u. a. Kontrollüberzeugungen, Selbstwirksamkeitserwartungen, Leistungsmotivation) eine wichtige Rolle beim Erfolg eines NF-Trainings. Studien dazu stehen noch aus.

Beim Theta/Beta-Training, bei dem die Kinder einen aufmerksamen, fokussierten, aber dennoch gelassenen Zustand (tonische Aktivierung) erlernen sollen, kann spekuliert werden, ob die Neuromodulation per se eine breitere neuronale Ausgangsbasisfür den therapeutischen Erfolg schafft. Höhere Theta-Ausgangswerte und größere Theta-Reduzierung nach dem Theta/Beta-Training waren in unserer Studie mit einer stärkeren Abnahme der ADHS-Symptomatik assoziiert. Allerdings sollte das Ruhe-EEG nicht ausschließlich als Trait-, sondern auch als State-Variable betrachtet werden, in der sich neben individuell stabilen Mustern auch Aspekte der aktuellen situativen Gegebenheiten (Aktivierungsstatus/Müdigkeit, emotionale Verfassung etc.) widerspiegeln (Hegerl et al., 2008). Somit kann sich auch in EEG-Untersuchungssituationen eine Transferleistung abbilden.

Schließlich sollte bedacht werden, dass keinesfalls dysfunktionale neuronale Regelkreise vorliegen müssen, um positive Neurofeedback-Effekte erzielen zu können. Beispielsweise versuchen Sportler (Landers, 1991) oder Künstler (Egner & Gruzelier, 2003) ihre Leistungen mittels NF zu verbessern. Bei diesen „Peak Performance“-Anwendungen ist eher von einer weiteren Stärkung bzw. Förderung (bereits adäquat funktionierender) neuronaler Regelkreise („Optimierung“) auszugehen.

4.5.4 Optimierung des Trainings

Die Responder-Rate von knapp über 50% in der NF-Gruppe mag – wie bereits ausgeführt – teilweise dem akademischen Setting der Studie geschuldet sein. Wir verzichteten auch auf begleitende Interventionen, wie etwa den engeren Einbezug der Eltern oder die Kombination mit allgemeinen Lernstrategien, um eine Konfundierung des Neurofeedback-Effekts mit diesen Variablen zu verhindern. Gerade der Einbezug bzw. die Unterstützung der Eltern könnte jedoch eine moderierende Variable bezüglich der Wirksamkeit eines NF-Trainings darstellen (Drechsler et al., 2007). Die Effektivität kognitiv-verhaltenstherapeutischer Interventionen steigt offensichtlich generell mit dem Einbezug der Eltern (Dowell & Ogles, 2010). Auch wenn nach unserer Einschätzung ein Neurofeedback-Training als alleinige Intervention bei der Mehrzahl der Kinder mit ADHS nicht ausreichen wird, so kann doch davon ausgegangen werden, dass die Wirksamkeit durch ein optimiertes Setting noch erhöht werden kann.

Dies sollte in zukünftigen Studien anhand größerer Stichproben systematisch untersucht werden. Zu klärende Fragen sind hierbei, welchem Kind welches Trainingsprotokoll (oder Kombination von Trainingsprotokollen) in welchem Umfang, kombiniert mit welchen weiteren Interventionsstrategien angeboten werden sollte. Hierbei sollten auch neurophysiologische Parameter (EEG, EPs) berücksichtigt werden. Im Sinne einer multimodalen Behandlung sollten mögliche Kombinationen mit etablierten verhaltenstherapeutischen oder medikamentösen Behandlungsansätzen („Relapse Prevention“) getestet werden.

Aber auch methodische Erweiterungen sind möglich (Rothenberger 2009), wie z.B. ein sog. tomografisches (Loreta) NF-Training, bei dem die Aktivierung und / oder Deaktivierung eines bestimmten Hirnareals gezielt trainiert wird. Mit diesem Ansatz könnte möglicherweise ein spezifischeres Training verbunden mit größeren klinischen Verbesserungen durchgeführt werden. Erste Ergebnisse einer Studie, bei der die Kinder die Regulation ihrer hirnelektrischen Aktivität im anterioren Cingulum trainieren, sind ermutigend (Liechti et al., 2009).

Die vorgestellte Studie leistet einen wichtigen Beitrag zur Evaluation von Neurofeedback bei Kindern mit ADHS. NF könnte ein wichtiger Therapiebaustein in der Behandlung von Kindern mit ADHS werden, wobei künftige Studien darauf abzielen sollten, in welcher Form ein Training optimiert bzw. in ein multimodales Behandlungssetting integriert/implementiert werden kann.

5. Zusammenfassung

Im Rahmen einer multizentrischen, randomisierten, kontrollierten Studie evaluierten wir die klinische Wirksamkeit eines Neurofeedback-Trainings (NF) bei Kindern mit einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) und untersuchten die einem erfolgreichen Training zugrunde liegenden neurophysiologischen Wirkmechanismen. Als Vergleichstraining diente ein computergestütztes Aufmerksamkeitstraining, das dem Setting des Neurofeedback-Trainings in den wesentlichen Anforderungen und Rahmenbedingungen angeglichen war.

Auf Verhaltensebene (Eltern- und Lehrerbeurteilung) zeigte sich das NF-Training nach Trainingsende dem Kontrolltraining sowohl hinsichtlich der ADHS-Kernsymptomatik als auch in assoziierten Bereichen überlegen. Für das Hauptzielkriterium (Verbesserung im FBB-HKS

Gesamtwert) ergab sich eine mittlere Effektstärke (von 0.6). Sechs Monate nach Trainingsende (follow-up) konnte das gleiche Ergebnismuster gefunden werden.

Auf neurophysiologischer Ebene (EEG; ereignisbezogene Potentiale, EPs) konnten für die beiden Neurofeedback-Protokolle Theta/Beta-Training und Training langsamer kortikaler Potentiale spezifische Effekte aufgezeigt werden. So war für das Theta/Beta-Training beispielsweise die Abnahme der Theta-Aktivität mit einer Reduzierung der ADHS-Symptomatik assoziiert. Für das SCP-Training wurde u.a. im Attention Network Test eine Erhöhung der kontingenten negativen Variation beobachtet, die die mobilisierten Ressourcen bei Vorbereitungsprozessen widerspiegelt. EEG- und EP-basierte Prädiktorvariablen konnten ermittelt werden.

Insgesamt sprechen die Ergebnisse für die Annahme, dass Neurofeedback einen effektiven Baustein in der Behandlung von Aufmerksamkeitsdefizit- und Hyperaktivitätsstörungen darstellen und die Entwicklungsplastizität des kindlichen Gehirns günstig beeinflussen kann.

6. Literatur

American Psychiatric Association (APA) (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington: American Psychiatric Association.

Kassenärztliche Bundesvereinigung, KBV (2008). *Qualitätsgesicherte Versorgung von Kindern und Jugendlichen mit ADHS/ADS. Ein Konzept der Vertragswerkstatt.* Berlin: KBV.

Abikoff, H. (1991). Cognitive training in ADHD children: less to it than meets the eye. *Journal of Learning Disabiitiesl, 24*(4), 205-209.

Adler, L. D., & Nierenberg, A. A. (2010). Review of medication adherence in children and adults with ADHD. *Postgraduate Medicin, 122*(1), 184-191.

Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., et al. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: evidence for an endophenotype. *Biological Psychiatry, 64*(7), 615-625.

Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Heise, A., Hasselhorn, M., et al. (2010). Action monitoring in children with or without a family history of ADHD--effects of gender on an endophenotype parameter. *Neuropsychologia, 48*(4), 1171-1177.

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clinical EEG and Neuroscience, 40*(3), 180-189.

Atzori, P., Usala, T., Carucci, S., Danjou, F., & Zuddas, A. (2009). Predictive factors for persistent use and compliance of immediate-release methylphenidate: a 36-month naturalistic study. *Journal of Child and Adolescent Psychopharmacology, 19*(6), 673-681.

Banaschewski, T. (2010). Genetik. In Steinhausen, H.-C., Rothenberger, A. & Döpfner, M. (Ed.), *Handbuch ADHS. Grundlagen, Klinik, Therapie und Verlauf der Aufmerksamkeitsdefizit-Hyperaktivitätsstörung*. Stuttgart: Kohlhammer.

Banaschewski, T., & Brandeis, D. (2007). Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us - a child psychiatric perspective. *Journal of Child Psychology and Psychiatry, 48*(5), 415-435.

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., et al. (2006). Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. *European Child and Adolescent Psychiatry, 15*(8), 476-495.

Banaschewski, T., Roessner, V., Dittmann, R. W., Santosh, P. J., & Rothenberger, A. (2004). Non-stimulant medications in the treatment of ADHD. *European Child and Adolescent Psychiatry, 13 Suppl 1*, I102-116.

Banaschewski, T., Buitelaar, J., Coghill, D. R., Sergeant, J. A., Sonuga-Barke, E., Zuddas, A., et al. (2009). The MTA at 8. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(11), 1120-1121.

Barkley, R. A. (1997). *ADHD and the Nature of Self-Control.* New York: Guilford Press.

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2004). Young adult follow-up of hyperactive children: antisocial activities and drug use. *Journal of Child Psychology and Psychiatry, 45*(2), 195-211.

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2006). Young adult outcome of hyperactive children: adaptive functioning in major life activities. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(2), 192-202.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003a). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology, 114*(2), 171-183.

Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003b). A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clinical Neurophysiology, 114*(2), 184-198.

Beck, M. (1998). Therapiebaukasten oder Trainingsprogramm? In D. G. f. Verhaltenstherapie (Ed.), *Evaluation als Maßnahme der Qualitätssicherung. Pädagogisch-psychologische Interventionen auf dem Prüfstand* (pp. 161 - 172). Tübingen.

Berger, I., Dor, T., Nevo, Y., & Goldzweig, G. (2008). Attitudes toward attention-deficit hyperactivity disorder (ADHD) treatment: parents' and children's perspectives. *Journal of Child Neurology, 23*(9), 1036-1042.

Biederman, J. (2005). Attention-deficit/hyperactivity disorder: a selective overview. *Biological Psychiatry, 57*(11), 1215-1220.

Biederman, J., & Spencer, T. J. (2008). Psychopharmacological interventions. *Child and Adolescent Psychiatric Clinics of North America, 17*(2), 439-458.

Birbaumer, N., Elbert, T., Canavan, A. G., & Rockstroh, B. (1990). Slow potentials of the cerebral cortex and behavior. *Physiological Review, 70*(1), 1-41.

Bodenmann, G., Cina, A., Ledermann, T., & Sanders, M. R. (2008). The efficacy of the Triple P-Positive Parenting Program in improving parenting and child behavior: a comparison with two other treatment conditions. *Behaviour Research and Therapy, 46*(4), 411-427.

Bor, W., Sanders, M. R., & Markie-Dadds, C. (2002). The effects of the Triple P-Positive Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. *Journal of Abnormal Child Psychology, 30*(6), 571-587.

Boutron, I., Moher, D., Altman, D. G., Schulz, K. F., & Ravaud, P. (2008). Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Annals of Internal Medicine, 148*(4), 295-309.

Brandeis, D. (2010). Neurofeedback training in ADHD: More news on specificity. *Clinical Neurophysiology*.

Brookes, K., Xu, X., Chen, W., Zhou, K., Neale, B., Lowe, N., et al. (2006). The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. *Molecular Psychiatry, 11*(10), 934-953.

Castellanos, F. X., Sonuga-Barke, E. J., Milham, M. P., & Tannock, R. (2006). Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Science, 10*(3), 117-123.

Castellanos, F. X., Sonuga-Barke, E. J., Scheres, A., Di Martino, A., Hyde, C., & Walters, J. R. (2005). Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry, 57*(11), 1416-1423.

Chan, R. C., Shum, D., Toulopoulou, T., & Chen, E. Y. (2008). Assessment of executive functions: review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology, 23*(2), 201-216.

Charach, A., Ickowicz, A., & Schachar, R. (2004). Stimulant treatment over five years: adherence, effectiveness, and adverse effects. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(5), 559-567.

Chatoor, I., & Krupnick, J. (2001). The role of non-specific factors in treatment outcome of psychotherapy studies. *European Child and Adolescent Psychiatry, 10 Suppl 1*, I19-25.

Chronis, A. M., Jones, H. A., & Raggi, V. L. (2006). Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. *Clinical Psychology Review, 26*(4), 486-502.

Coghill, D. (2010). Neurofeedback training improves ADHD symptoms more than attention skills training. *Evidence Based Mental Health, 13*(1), 21.

Corkum, P., Rimer, P., & Schachar, R. (1999). Parental knowledge of attention-deficit hyperactivity disorder and opinions of treatment options: impact on enrollment and adherence to a 12-month treatment trial. *Canadian Journal of Psychiatry, 44*(10), 1043-1048.

Crosbie, J., Perusse, D., Barr, C. L., & Schachar, R. J. (2008). Validating psychiatric endophenotypes: inhibitory control and attention deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews, 32*(1), 40-55.

Deutsche Gesellschaft für Kinder- und Jugend Psychotherapie und Psychiatrie (Ed.). (2007). (Vol. 3. überarbeitete Auflage). Köln: Deutscher Ärzte Verlag.

Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H. C., & Drechsler, R. (2008). Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? *Journal of Neural Transmission, 115*(10), 1445-1456.

Döpfner, M. , Fröhlich, J. & Lehmkuhl, G. (2009). *Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS). Leitfaden Kinder- und Jugendpsychiatrie, Band 1, 2. Auflage.* Göttingen: Hogrefe.

Döpfner, M., Rothenberger, A. & Steinhausen, H.C. (2010). Integrative ätiologische Modelle. In H.-C. Steinhausen, Rothenberger, A. & Döpfner, M. (Ed.), Handbuch ADHS. Stuttgart: Kohlhammer.

Döpfner, M., Schürmann, S. & Frölich, J. (2007). *Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten (THOP)*. Weinheim: Beltz.

Döpfner, M. L., G. (2000). *DISYPS-KJ - Diagnostik-System für psychische Störungen im Kindes- und Jugendalter*. Bern: Hans Huber.

dosReis, S., & Myers, M. A. (2008). Parental attitudes and involvement in psychopharmacological treatment for ADHD: a conceptual model. *International Review of Psychiatry, 20*(2), 135-141.

Dowell, K. A., & Ogles, B. M. (2010). The effects of parent participation on child psychotherapy outcome: a meta-analytic review. *Journal of Clinical Child and Adolescent Psychology, 39*(2), 151-162.

Doyle, A. E. (2006). Executive functions in attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry, 67 Suppl 8*, 21-26.

Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H. C., & Brandeis, D. (2007). 1Controlled evaluation of a neurofeedback training of slow cortical potentials in children with Attention Deficit/Hyperactivity Disorder (ADHD). *Behavioral and Brain Functions, 3*, 35.

Egner, T., & Gruzelier, J. H. (2003). Ecological validity of neurofeedback: modulation of slow wave EEG enhances musical performance. *Neuroreport, 14*(9), 1221-1224.

Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology, 115*(1), 131-139.

El-Sayed, E., Larsson, J. O., Persson, H. E., & Rydelius, P. A. (2002). Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(7), 811-819.

Engert, V., & Pruessner, J. C. (2008). Dopaminergic and noradrenergic contributions to functionality in ADHD: the role of methylphenidate. *Current Neuropharmacology, 6*(4), 322-328.

Falkenstein, M., Hoormann, J., Hohnsbein, J., & Kleinsorge, T. (2003). Short-term mobilization of processing resources is revealed in the event-related potential. *Psychophysiology, 40*(6), 914-923.

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience, 14*(3), 340-347.

Faraone, S. V., Biederman, J., Morley, C. P., & Spencer, T. J. (2008). Effect of stimulants on height and weight: a review of the literature. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(9), 994-1009.

Faraone, S. V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child and Adolescent Psychiatry, 19*(4), 353-364.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., et al. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1313-1323.

Faraone, S. V., Sergeant, J., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry, 2*(2), 104-113.

Frazier, T. W., Demaree, H. A., & Youngstrom, E. A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18*(3), 543-555.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. *Applied Psychophysiology and Biofeedback, 28*(1), 1-12.

Garnock-Jones, K. P., & Keating, G. M. (2009). Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatric Drugs, 11*(3), 203-226.

Gau, S. S., Chen, S. J., Chou, W. J., Cheng, H., Tang, C. S., Chang, H. L., et al. (2008). National survey of adherence, efficacy, and side effects of methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. *Journal of Clinical Psychiatry, 69*(1), 131-140.

Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen (2009). *Sondergutachten zur Koordination und Integration der Gesundheitsversorgung in einer Gesellschaft des längeren Lebens.* http://infomed.mds-ev.de/sindbad.nsf/de28b7f694cc5f7fc12571e700442bed/2045f9b546ccd0cec12575e500426101/$FILE/SVR_GA_2009.pdf (April 2011).

Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., et al. (2009a). Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. *Journal of Child Psychology and Psychiatry, 50*(7), 780-789.

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., et al. (2009b). Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. *International Journal of Psychophysiology, 74*(2), 149-157.

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., et al. (2010a). Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial. *European Child and Adolescent Psychiatry, 19*(9), 715-724.

Gevensleben, H., Moll, G. H., & Heinrich, H. (2010b). [Neurofeedback training in children with ADHD: behavioral and neurophysiological effects]. *Zeitschrift für Kinder- und Jugendpsychiatrie und*

Psychotherapie, 38(6), 409-419.

Gillberg, C., Gillberg, I. C., Rasmussen, P., Kadesjo, B., Soderstrom, H., Rastam, M., et al. (2004). Co-existing disorders in ADHD -- implications for diagnosis and intervention. *European Child and Adolescent Psychiatry, 13 Suppl 1*, I80-92.

Goldstein, A. P., & Shipman, W. G. (1961). Patient expectancies, symptom reduction and aspects of the initial psychotherapeutic interview. *Journal of Clinical Psychology, 17*, 129-133.

Hack, S., & Chow, B. (2001). Pediatric psychotropic medication compliance: a literature review and research-based suggestions for improving treatment compliance. *Journal of Child and Adolescent Psychopharmacology, 11*(1), 59-67.

Halperin, J. M., & Healey, D. M. (2010). The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? *Neuroscience and Biobehavioral Reviews, 35*(3), 621-634.

Hanisch, C., Freund-Braier, I., Hautmann, C., Janen, N., Pluck, J., Brix, G., et al. (2010). Detecting effects of the indicated prevention Programme for Externalizing Problem behaviour (PEP) on child symptoms, parenting, and parental quality of life in a randomized controlled trial. *Behavioural and Cognitive Psychotherapy, 38*(1), 95-112.

Hautmann, C., Hanisch, C., Mayer, I., Pluck, J., & Dopfner, M. (2008). Effectiveness of the prevention program for externalizing problem behaviour (PEP) in children with symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder--generalization to the real world. *Journal of Neural Transmission, 115*(2), 363-370.

Hegerl, U., Stein, M., Mulert, C., Mergl, R., Olbrich, S., Dichgans, E., et al. (2008). EEG-vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. *European Archives of Psychiatry and Clinical Neuroscience, 258*(3), 137-143.

Heinrich, H. (2010). Neurofeedback. In H.-C. Steinhausen, Rothenberger, A. & Döpfner, M. (Ed.), *Handbuch ADHS: Grundlagen, Klinik, Therapie und Verlauf der Aufmerksamkeitsdefizit-Hyperaktivitätsstörung*. Göttingen: Hogrefe.

Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry, 55*(7), 772-775.

Heinrich, H., Gevensleben, H., & Strehl, U. (2007). Annotation: neurofeedback - train your brain to train behaviour. *Journal of Child Psychology and Psychiatry, 48*(1), 3-16.

Herbert, J. D., & Gaudiano, B. A. (2005). Moving from empirically supported treatment lists to practice guidelines in psychotherapy: the role of the placebo concept. *Journal of Clinical Psychology, 61*(7), 893-908.

Hibbs, E. D. (2001). Evaluating empirically based psychotherapy research for children and adolescents. *European Child and Adolescent Psychiatry, 10 Suppl 1*, I3-11.

Holtmann, M., Stadler, C., Leins, U., Strehl, U., Birbaumer, N., & Poustka, F. (2004). [Neurofeedback for the treatment of attention-deficit/hyperactivity disorder (ADHD) in childhood and adolescence]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 32*(3), 187-200.

Hudziak, J. J., & Faraone, S. V. (2010). The new genetics in child psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(8), 729-735.

Huss, M., Holling, H., Kurth, B. M., & Schlack, R. (2008). How often are German children and adolescents diagnosed with ADHD? Prevalence based on the judgment of health care professionals: results of the German health and examination survey (KiGGS). *European Child and Adolescent Psychiatry, 17 Suppl 1*, 52-58.

Jacobs, K. P., Franz. (2008). *Training für Kinder mit Aufmerksamkeitsstörung. Das neuropsychologische Gruppenprogramm ATTENTIONER*. Göttingen.

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., et al. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *American Journal of Psychiatry, 163*(4), 716-723.

Kirsch, I. (2005). Placebo psychotherapy: synonym or oxymoron? *Journal of Clinical Psychology, 61*(7), 791-803.

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., et al. (2005). Computerized training of working memory in children with ADHD--a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*(2), 177-186.

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Training of working memory in children with ADHD. *Journal of Clinical and Experimental Neuropsychology, 24*(6), 781-791.

Krowatschek, D., Albrecht, S. & Krowatschek, G. (2004). *Das Marburger Konzentrationstraining (MKT) für Schulkinder.* Dortmund: Verlag Modernes Lernen.

Landers, D. M., Petruzzello, S. J., Salazar, W., Crews, D. J., Kubitz, K. A., Gannon, T. L., et al. (1991). The influence of electrocortical biofeedback on performance in pre-elite archers. *Medicin and Science in Sports and Exercises, 23*(1), 123-129.

Lansbergen, M. M., van Dongen-Boomsma, M., Buitelaar, J. K., & Slaats-Willemse, D. (2010). ADHD and EEG-neurofeedback: a double-blind randomized placebo-controlled feasibility study. *Journal of Neural Transmission*.

Lauth, G. W., Naumann, K., Roggenkamper, A., & Heine, A. (1996). [Behavior medicine indications and evaluation of cognitive-behavioral therapy with attention-deficit/hyperkinetic children]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 24*(3), 164-175.

Lauth, G. W., Schlottke, P. F. (2009). *Training mit aufmerksamkeitsgestörten Kindern* (Vol. 6. Auflage). Weinheim: Beltz Psychologie Verlags Union.

Leins, U., Hinterberger, T., Kaller, S., Schober, F., Weber, C., & Strehl, U. (2006). [Neurofeedback for children with ADHD: a comparison of SCP- and theta/beta-protocols]. *Praxis der Kinderpsychologie und Kinderpsychiatrie, 55*(5), 384-407.

Levesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neuroscience Letters, 394*(3), 216-221.

Liechti, M., Maurizio, S., Heinrich, H., Thalmann, G., Meier, L., Schwitter, Y., Hartmann, M., Walitza, S., Steinhausen, H.-C., Jäncke, L., Drechsler, R. & Brandeis, D. (2010). *Preliminary tomopgraphic neurofeedback results from children with ADHD.* Paper presented at the 18. Deutsches EEG/EP Mapping Meeting, Giessen.

Logemann, H. N., Lansbergen, M. M., Van Os, T. W., Bocker, K. B., & Kenemans, J. L. (2010). The effectiveness of EEG-feedback on attention, impulsivity and EEG: a sham feedback controlled study. *Neuroscience Letters, 479*(1), 49-53.

Loo, S. K., & Barkley, R. A. (2005). Clinical utility of EEG in attention deficit hyperactivity disorder. *Applied Neuropsychology, 12*(2), 64-76.

Luman, M., Oosterlaan, J., & Sergeant, J. A. (2005). The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. *Clinical Psychology Review, 25*(2), 183-213.

Lütcke, H., Gevensleben, H., Albrecht, B., & Frahm, J. (2009). Brain networks involved in early versus late response anticipation and their relation to conflict processing. *Journal of Cognitive Neuroscience, 21*(11), 2172-2184.

Madras, B. K., Miller, G. M., & Fischman, A. J. (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1397-1409.

Margraf, J., Ehlers, A., Roth, W. T., Clark, D. B., Sheikh, J., Agras, W. S., et al. (1991). How "blind" are double-blind studies? *Journal of Consulting and Clinical Psychology, 59*(1), 184-187.

Moll, G. H., Heinrich, H., Gevensleben, H., & Rothenberger, A. (2006). Tic distribution and inhibitory processes in the sensorimotor circuit during adolescence: a cross-sectional TMS study. *Neuroscience Letters, 403*(1-2), 96-99.

Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 27*(4), 231-249.

Morin, C. M., Colecchi, C., Brink, D., Astruc, M., Mercer, J., & Remsberg, S. (1995). How "blind" are double-blind placebo-controlled trials of benzodiazepine hypnotics? *Sleep, 18*(4), 240-245.

MTA Cooperative Group (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. *Archives of General Psychiatry, 56*(12), 1073-1086.

MTA Cooperative Group (2004). National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics, 113*(4), 754-761.

Olfson, M., Gameroff, M. J., Marcus, S. C., & Jensen, P. S. (2003). National trends in the treatment of attention deficit hyperactivity disorder. *American Journal of Psychiatry, 160*(6), 1071-1077.

Omer, H., & London, P. (1989). Signal and noise in psychotherapy. The role and control of non-specific factors. *British Journal of Psychiatry, 155*, 239-245.

Pelham, W. E., Jr., & Fabiano, G. A. (2008). Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology, 37*(1), 184-214.

Pelham, W. E., Jr., Wheeler, T., & Chronis, A. (1998). Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology, 27*(2), 190-205.

Perry, G. M., Sagvolden, T., & Faraone, S. V. (2010). Intraindividual variability (IIV) in an animal model of ADHD - the Spontaneously Hypertensive Rat. *Behavioral and Brain Functions, 6*, 56.

Pine, D. S. (2009). Editorial: Evaluating new and old treatments for ADHD. *Journal of Child Psychology and Psychiatry, 50*(7), 767-768.

Plück, J., Wieczorrek, E., Wolff Metternich, T., Döpfner, M. (2006). *Präventionsprogramm für Expansives Problemverhalten (PEP)*

Ein Manual für Eltern- und Erziehergruppen. Göttingen: Hogrefe.

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry, 164*(6), 942-948.

Polderman, T. J., Boomsma, D. I., Bartels, M., Verhulst, F. C., & Huizink, A. C. (2010). A systematic review of prospective studies on attention problems and academic achievement. *Acta Psychiatrica Scandinavica, 122*(4), 271-284.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25-42.

Posner, M. I., & Rothbart, M. K. (2007). Research on attention networks as a model for the integration of psychological science. *Annual Review of Psychology, 58*, 1-23.

Prins, P. J., Dovis, S., Ponsioen, A., Ten Brink, E., & van der Oord, S. (2010). Does Computerized Working Memory Training with Game Elements Enhance Motivation and Training Efficacy in Children with ADHD? *Cyberpsychology, Behavior and Social Networking,* 14, 115-122.

Rockstroh, B., Elbert, T., Lutzenberger, W., & Birbaumer, N. (1990). Biofeedback: Evaluation and Therapy in Children with Attentional Dysfunctions. In A. Rothenberger (Ed.), *Brain and Behavior in Child Psychiatry* (Vol. 9, pp. 345-357). Berlin: Springer.

Rockstroh, B., Muller, M., Wagner, M., Cohen, R., & Elbert, T. (1993). "Probing" the nature of the CNV. *Electroencephalography and Clinical Neurophysiology, 87*(4), 235-241.

Rösler, M., Casas, M., Konofal, E., & Buitelaar, J. (2010). Attention deficit hyperactivity disorder in adults. *World Journal of Biological Psychiatry, 11*(5), 684-698.

Rothenberger, A. (2009). Brain oscillations forever--neurophysiology in future research of child psychiatric problems. *Journal of Child Psychology and Psychiatry, 50*(1-2), 79-86.

Rusch, F. R., Wilson, P. G., Hughes, C., & Heal, L. W. (1995). Interaction of persons with severe mental retardation and their nondisabled co-workers in integrated work settings. *Behavior Modification, 19*(1), 59-77.

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Science, 28*(3), 397-419; discussion 419-368.

Sanders, M. R. (1999). Triple P-Positive Parenting Program: towards an empirically validated multilevel parenting and family support strategy for the prevention of behavior and emotional problems in children. *Clinical Child and Family Psychology Review, 2*(2), 71-90.

Schlander, M., Trott, G. E., & Schwarz, O. (2010). The health economics of attention deficit hyperactivity disorder in Germany. Part 1: Health care utilization and cost of illness. *Nervenarzt, 81*(3), 289-300.

Sergeant, J. (2000). The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews, 24*(1), 7-12.

Sergeant, J. A. (2005). Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. *Biological Psychiatry, 57*(11), 1248-1255.

Sobanski, E., & Alm, B. (2004). Attention deficit hyperactivity disorder in adults. An overview. *Nervenarzt, 75*(7), 697-715.

Solanto, M. V. (2002). Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behavioural Brain Research, 130*(1-2), 65-71.

Sonuga-Barke, E. J. (2002). *Psychological heterogeneity in AD/HD - a dual pathway model of behaviour and cognition. Behavioural Brain Research,* 130, 29-36.

Sonuga-Barke, E. J. (2005). *Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways*. Biological Psychiatry, 57, 1231-1238.

Sonuga-Barke, E. J., & Sergeant, J. (2005). The neuroscience of ADHD: multidisciplinary perspectives on a complex developmental disorder, *Developmental Science*, 8, 103-104.

Sowell, E. R., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., & Peterson, B. S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet, 362*, 1699-1707.

Steinhausen, H.-C., Rothenberger, A. & Döpfner, M. (Ed.). (2010). *Handbuch ADHS. Grundlagen, Klinik, Therapie und Verlauf der Aufmerksamkeitsdefizit-Hyperaktivitätsstörung*. Stuttgart: Kohlhammer.

Stiefel, G., & Besag, F. M. (2010). Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder. *Drug Safety, 33*(10), 821-842.

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Birbaumer, N. (2006). Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. *Pediatrics,* 118, 1530-1540.

Swanson, J., Arnold, L. E., Kraemer, H., Hechtman, L., Molina, B., Hinshaw, S., et al. (2008). Evidence, interpretation, and qualification from multiple reports of long-term outcomes in the Multimodal Treatment study of Children with ADHD (MTA): part I: executive summary. *Journal of Attention Disorders, 12*, 4-14.

Swanson, J. M., Elliott, G. R., Greenhill, L. L., Wigal, T., Arnold, L. E., Vitiello, B., et al. (2007). Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*, 1015-1027.

Taylor, E., Dopfner, M., Sergeant, J., Asherson, P., Banaschewski, T., Buitelaar, J., et al. (2004). European clinical guidelines for hyperkinetic disorder -- first upgrade. *European Child and Adolescent Psychiatry, 13 Suppl 1*, I7-30.

Uebel, H., Albrecht, B., Asherson, P., Borger, N. A., Butler, L., Chen, W., et al. (2010). Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry, 51*(2), 210-218.

Van der Oord, S., Prins, P. J., Oosterlaan, J., & Emmelkamp, P. M. (2008). Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. *Clinical Psychology Review, 28*, 783-800.

Vloet, T. D., Marx, I., Kahraman-Lanzerath, B., Zepf, F. D., Herpertz-Dahlmann, B., & Konrad, K. (2010). Neurocognitive performance in children with ADHD and OCD. *Journal of Abnormal Child Psychology, 38*, 961-969.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L., et al. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *Journal of Neuroscience, 21*, RC121.

Volkow, N. D., Wang, G. J., Kollins, S. H., Wigal, T. L., Newcorn, J. H., Telang, F., et al. (2009). Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA, 302*, 1084-1091.

Wangler, S., Gevensleben, H., Albrecht, B., Studer, P., Rothenberger, A., Moll, G. H., et al. (2011). Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial. *Clinical Neurophysiology,* 122, 942-950.

Wernicke, J. F., Faries, D., Girod, D., Brown, J., Gao, H., Kelsey, D., et al. (2003). Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Safety, 26*(10), 729-740.

Wigal, S. B. (2009). Efficacy and safety limitations of attention-deficit hyperactivity disorder pharmacotherapy in children and adults. *CNS Drugs, 23, Suppl 1*, 21-31.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biological Psychiatry, 57*(11), 1336-1346.

Willis, W. G., & Weiler, M. D. (2005). Neural substrates of childhood attention-deficit/hyperactivity disorder: electroencephalographic and magnetic resonance imaging evidence. *Developmental Neuropsychology, 27*(1), 135-182.

Woerner, W., Becker, A., & Rothenberger, A. (2004). Normative data and scale properties of the German parent SDQ. *European Child and Adolescent Psychiatry, 13, Suppl 2*, II3-10.

Zuvekas, S. H., Vitiello, B., & Norquist, G. S. (2006). Recent trends in stimulant medication use among U.S. children. *American Journal of Psychiatry, 163*(4), 579-585.