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The Effects of Individual Upper Alpha Neurofeedback in ADHD: An Open-Label Pilot Study

C. Escolano · M. Navarro-Gil · J. Garcia-Campayo · M. Congedo · J. Minguez

Abstract Standardized neurofeedback (NF) protocols have been extensively evaluated in attention-deficit/hyperactivity disorder (ADHD). However, such protocols do not account for the large EEG heterogeneity in ADHD. Thus, individualized approaches have been suggested to improve the clinical outcome. In this direction, an open-label pilot study was designed to evaluate a NF protocol of relative upper alpha power enhancement in fronto-central sites. Upper alpha band was individually determined using the alpha peak frequency as an anchor point. 20 ADHD children underwent 18 training sessions. Clinical and neurophysiological variables were measured pre- and post-training. EEG was recorded pre- and post-training, and pre- and post-training trials within each session, in both eyes closed resting state and eyes open task-related activity. A power EEG analysis assessed long-term and within-session effects, in the trained parameter and in all the sensors in the (1–30) Hz spectral range. Learning curves over sessions were assessed as well. Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity. Neurophysiological tests showed an improvement in working memory, concentration and impulsivity (decreased number of commission errors in a continuous performance test). Relative and absolute upper alpha power showed long-term enhancement in task-related activity, and a positive learning curve over sessions. The analysis of within-session effects showed a power decrease ("rebound" effect) in task-related activity, with no significant effects during training trials. We conclude that the enhancement of the individual upper alpha power is effective in improving several measures of clinical outcome and cognitive performance in ADHD. This is the first NF study evaluating such a protocol in ADHD. A controlled evaluation seems warranted due to the positive results obtained in the current study.

Keywords ADHD · Neurofeedback · Individual upper alpha · Cognitive performance · EEG

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by symptoms of inattention, impulsivity and hyperactivity according to DSM-IV (American Psychiatric Association 1994). This disorder is one of the most common psychiatric disorders of childhood, affecting up to 5 % of children worldwide (Polanczyk et al. 2007), presenting about 40–60 % persistence in adolescence and adulthood (Faraone et al. 2006). Deficits in executive functioning, working memory and response inhibition have been repeatedly reported (Barkley 1997; Martinussen et al. 2005; Castellanos and Tannock 2002).

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The most accepted treatments for ADHD are stimulant medication and behavior therapy (Barkley 1997). Stimulant medication has emerged as the primary treatment for the core symptoms of ADHD, however some children do not respond to medication or suffer from side effects such as headache, dizziness, insomnia, anxiety and gastroenterological problems (Graham et al. 2011). In addition to that, the long-lasting effects of both stimulant medication and behavior therapy are uncertain, with some studies reporting limited effects (Wang et al. 2013; Molina et al. 2009). Neurofeedback (NF) is a promising alternative treatment for ADHD (Arns et al. 2014; Loo and Makeig 2012).

NF provides the subjects with real-time feedback co-varying with their own brain activity, thus promoting the self-regulation of brain activity by means of an operant conditioning paradigm. The rationale behind NF training in ADHD is the electrophysiological evidence collected over the last decades of abnormal brain oscillations in comparison to normal controls (see Barry et al. 2003; Loo and Makeig 2012 for reviews). The most reliable EEG pattern in ADHD to date is an excess of theta activity (4–8 Hz) in fronto-central sites, measured in resting state (Barry et al. 2003; Snyder and Hall 2006; Clarke et al. 2001). Reduced alpha (8–13 Hz) and beta activity (13–30 Hz) have been commonly reported as well, thus theta/beta and theta/alpha ratios have been traditionally considered reliable measures to discriminate between ADHD and normal individuals (Barry et al. 2003; Snyder and Hall 2006). In this direction, NF studies have mostly used standardized protocols to "correct" the aforementioned abnormal EEG patterns. The most used protocol is theta suppression/beta enhancement, usually enhancing the sensorimotor rhythm (SMR) simultaneously (Loo and Makeig 2012; Monastra et al. 2006; Arns et al. 2009). The SMR term was coined to describe an EEG pattern measured over the somatosensory cortex in alert but motionless cats, in the (11–15) Hz range (Sterman 2000). The SMR enhancement throughout NF is suggested to improve hyperactive symptoms in ADHD since the pioneer work of Lubar and Shouse (1976).

An extensive evaluation of standardized NF protocols has been performed during the last 40 years in ADHD children, with recent reviews pointing out their effectiveness (Arns et al. 2014; Loo and Makeig 2012; Heinrich et al. 2007). Despite the positive results, these protocols may not be able to account for the large EEG heterogeneity in ADHD (Loo and Makeig 2012; Arns et al. 2008). In addition, recent findings challenge the theta/beta ratio as a marker for ADHD, which was found increased in only 20–30 % of ADHD individuals (Arns et al. 2013, 2012). This may be partially due to a subgroup of 10–15 % ADHD individuals showing increased (rather than decreased) beta activity (Clarke et al. 2013, 2001). Thus, individualized approaches may better cope with the EEG heterogeneity and improve the clinical outcome (Arns et al. 2014). Some recent NF studies are following this direction (Arns et al. 2012; Lansbergen et al. 2011b; Logemann et al. 2010).

The current study evaluates an individualized NF protocol for ADHD children. This NF protocol aims at enhancing the relative upper alpha power in fronto-central sites, individually determined for each child using the individual alpha frequency (IAF, Klimesch 1999) as an anchor point. On one hand, this protocol has the potential to decrease the excess of absolute theta power (most reliable EEG pattern in ADHD to date) and the excess of slow frequency oscillations in general. On the other hand, this protocol builds upon the positive results of alpha-based protocols in cognitive enhancement, mainly evaluated in healthy users (Gruzelier 2013). Positive results were obtained in working memory (Escolano et al. 2011; Nan et al. 2012), visuospatial rotation (Zoefel et al. 2011; Hanslmayr et al. 2005) and procedural learning (Ros et al. 2014). Thus, this NF protocol is meant to target the cognitive deficits of ADHD individuals. This paper reports an open-label pilot study with 20 ADHD children who underwent 18 NF sessions. Clinical and neurophysiological variables were measured pre- and post- training. EEG was recorded pre- and post- training, and pre- and post- the training trials within each session, in both eyes closed resting state and eyes open task-related activity. A power EEG analysis assessed long-term and within-session effects, in the trained parameter and in all the sensors in the (1-30) Hz spectral range. Learning curves over sessions were assessed as well.

Methods

Participants

20 Children with ADHD participated in the study. All children fulfilled DSM-IV[1] criteria for ADHD (American Psychiatric Association 1994). Diagnoses were based on a semi-structured interview with the parents using the Structured Developmental History of the BASC (Reynolds and Kamphaus 2004). WISC-IV (Wechsler 2003) was administered to estimate IQ. All children were drug-free and without concurring psychotherapy for at least 1 month before starting the NF training. Children with comorbid neurological or psychiatric disorders, or IQ $<$ 80 were excluded from the study. Three children did not complete the study, thus the final sample consisted of 17 children (mean $\pm$ SD age: 11.8 $\pm$ 2.2 years, one girl). Seven children were diagnosed with inattentive type, ten with

[1] DSM was recently updated to the fifth edition (DSM-5).

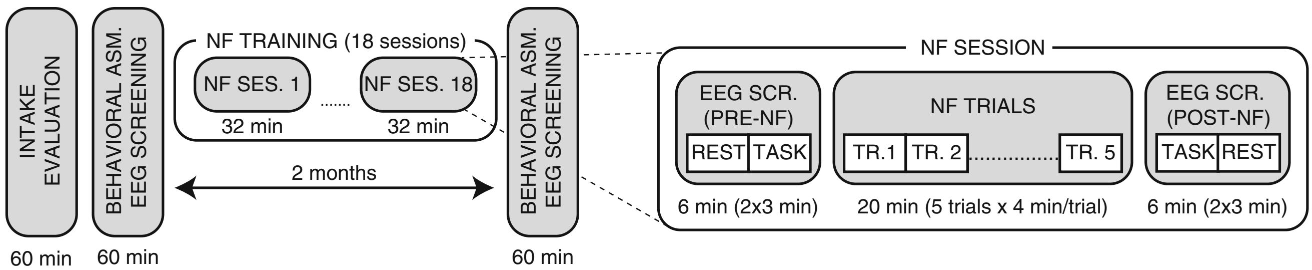

Fig. 1 Experimental design of the study. After an intake evaluation, the children carried out an initial and final behavioral assessment (clinical and neuropsychological tests) and EEG screening within a 2-months time interval. The NF training consisted of 18 sessions, which were composed of five training trials (four min each) and a pre- and post-EEG screening. The EEG screenings included eyes closed resting state activity (3 min) and eyes open task-related activity (3 min)

combined type. Families were informed about the study from local professionals in the city of Zaragoza (Spain). The experimental design was approved by the Ethical Review Board of the regional health authority and followed the Declaration of Helsinki. Parents and children signed informed consent.

Experimental Design

An open-label pilot study was designed (Fig. 1). After an intake evaluation, an initial and final behavioral assessment and EEG screening were carried out. The NF training was composed of 18 sessions, executed for 2 months (two or three sessions per week). Each session was composed of five trials of four min each for a total of 20 min of training, and a pre- and post- EEG screening. For each EEG screening we recorded three-min of eyes closed resting state activity and three-min of eyes open task-related activity. In the latter, children faced a computer screen showing a square that changed saturation color randomly from gray to red or blue (gradually). Children were instructed to count the number of saturation changes from gray to red as a cognitive challenge (Zoefel et al. 2011).

Behavioral Assessments

Parents rated the clinical conditions of the children pre- and post-training using the following scales: (*i*) Parent Rating Scales of the BASC (BASC-PRS, Reynolds and Kamphaus 2004), and (*ii*) Conners' Parent Rating Scales-Revised (CPRS-R, Conners et al. 1998). A battery of neuropsychological tests was administered to the children: (*i*) Two tests of the WISC-IV (Wechsler 2003) evaluated working memory. Digit span consisted of sequences of numbers that had to be repeated, either in same or reverse order. Letter-number sequencing consisted of sequences of letters and numbers that had to be repeated in both numerical and alphabetical order. The test scores were the number of correct responses. (*ii*) D2 test (Brickenkamp and Zillmer 1998) evaluated focussed and selective attention. Children crossed out target letters on a working sheet, working line by line with 20 s for finishing each line. The score was the concentration index. (*iii*) Conners' continuous performance test (CPT II, Conners and Staff 2000) is a computerized assessment of attention-related problems. The CPT displayed letters on a computer screen, and children had to press the space bar except when the letter "X" was displayed. The test scores were the number of omission and commission errors. Paired samples *t*-tests were performed for pre versus post comparisons.

EEG Recording and Neurofeedback Procedure

EEG data was recorded from 16 electrodes placed at FP1, FP2, AFz, F3, Fz, F4, FCz, C3, Cz, C4, P3, Pz, P4, O1, Oz and O2 (subset of the 10/10 system), with the ground and reference electrodes on FPz and on the left earlobe, respectively. EEG was amplified and digitized using a g.tec amplifier (Guger Technologies, Graz, Austria) at a sampling rate of 256 Hz, power-line notch-filtered at 50 Hz and (0.5–60) Hz band-pass filtered. EEG recording and the NF procedure were developed using software of *Bit&Brain Technologies, SL.*

The NF training focused on the increase of the relative upper alpha power, averaged over fronto-central sites (AFz, F3, Fz, F4, FCz and Cz, referred to as feedback electrodes). EEG power was calculated through a short-term FFT with 1 s hamming window, 30 ms of overlapping, and zero-padded to 1,024 points (0.25 Hz resolution). Relative power was computed in the (1–30) Hz range. For each session, the pre-NF EEG screening was recorded and then used to calibrate the training for each participant and session. In this calibration step, we automatically filtered out the blinking component from the task-related activity by Independent Component Analysis (ICA) using the FastICA algorithm (Hyvarinen 1999). Furthermore, we removed the epochs with amplitude larger than 200μV at any electrode. The IAF was computed for each electrode on the power spectra of the filtered EEG data as the frequency bin with the maximum power value in the (7–13) Hz alpha range (Klimesch 1999). Note that when no clear alpha peak was found, the IAF was computed on resting state EEG instead. The upper alpha band was then defined as (IAF, IAF+2) Hz (Klimesch 1999). The baseline was computed as the mean upper alpha power averaged across the feedback electrodes, and (5th–95th) percentiles established the lower and upper limits, respectively. After the calibration, the participants performed the training trials. During online training, EEG data was online filtered from blinking artifacts (through the aforementioned ICA filter) and a visual feedback was then displayed every 30 ms on a computer screen in the form of a square with changing saturation colors.

Offline EEG Pre-Processing

EEG data from the EEG screenings and training trials was filtered from artifacts using a semi-automatic method based on Riemannian geometry (Barachant et al. 2012, 2013). This method was separately applied to each recording session, applied on one hand to the resting state activity and on the other hand to the task-related activity and training trials. We first selected 15–20 artifact-free 1-s epochs by visual inspection. Covariances matrices were computed in each artifact-free epoch, and the geometric mean was computed. The remaining EEG data was then parsed into 1-s epochs using a sliding window algorithm with 30 ms overlapping. The distribution of the Riemannian distances between the geometric mean and the covariance matrix of each epoch was computed. Epochs with an absolute z-score higher than 2.5 were removed. A slight variation of this method was applied to the task-related activity and training trials to be more sensitive to non-blinking artifacts such as eyes and body movements. Initially, the extended infomax ICA (Lee et al. 1999) was applied to remove the eye blinking component and artifact-free epochs were selected by visual inspection in the sensor space. The semi-automatic method was then applied on the source space ($n-1$ components) and clean EEG data was projected to the sensor space.

EEG Analysis

Long-term effects assessed the power changes after the study, measured as the power comparison in the initial versus final EEG screening in both resting state and task-related activity. We performed a direct comparison in the trained parameter and an exploratory absolute/relative power spectral analysis in all the sensors in the ($\approx$ 1–30) Hz range (section "Cluster-Based Method for Power EEG Analysis").

Learning curves over sessions assessed the power changes as a function of the number of sessions, measured as the Spearman correlation between the power computed in the pre-NF EEG screening of each session (recorded before the training trials) versus the session number. We assessed the effects in resting state and task-related activity. We performed the analysis in the trained parameter and an exploratory analysis in absolute/relative power in the feedback sites and parieto-occipital sites (P3, Pz, P4, O1, Oz and O2) in the following bands: delta = (1, 3.5), theta = (IAF-6, IAF-4), lower alpha = (IAF-4, IAF), upper alpha = (IAF, IAF+2), beta1 = (IAF+2, IAF+8), beta2 = (IAF+8, IAF+14) and beta3 = (IAF+14, 30). A non-parametric randomization method using the r-max statistic was used to correct for the number of bands, i.e., to control the familywise type I error rate (FWER, Holmes et al. 1996). Following this method, the null distribution of the maximum absolute r-value across all bands was estimated by 5,000 random permutations. Then the absolute observed r-value for each band was tested against the $(1-\alpha)$th percentile of the null distribution. Bonferroni correction was further applied to control for the comparisons in absolute/relative power and the number of sensor clusters. The FWER was set at $\alpha = .05$.

Within-session effects assessed the power changes immediately after the training trials (in both resting state and task-related activity) and during training. First, the power values computed in the pre- and post-NF EEG screenings of each session were averaged across sessions. The power in the training trials were averaged across sessions as well, and further averaged across the five trials (averaged training power). Within-session effects in resting state and task-related activity were measured as the averaged pre- vs post-NF power comparison. We measured the effects during training as the averaged pre-NF power value in task-related activity (baseline) vs the averaged training power. We performed a direct comparison in the trained parameter and an exploratory absolute/relative power spectral analysis (section "Cluster-Based Method for Power EEG Analysis").

Cluster-Based Method for Power EEG Analysis

A cluster-based non-parametric randomization method (Nichols and Holmes 2002; Maris and Oostenveld 2007) was used to assess pre versus post power changes in all the sensors in the ($\approx$1–30) Hz range. This method is implemented in the Fieldtrip toolbox (FC Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands; see http://www.ru.nl/fcdonders/fieldtrip). First, the power spectra of each subject was centered to the IAF and the (IAF-8, IAF+18) Hz range was considered. Since mean $\pm$ SD IAF was 9.25 $\pm$ 1.22 Hz, the (1.25–27.25) Hz range

Table 1 Results of the clinical and neuropsychological tests pre- and post-training

	Pre training	Post training	*t*-stat	*p*-value	ES
Clinical scales					
BASC-PRS (T-scores)					
Externalizing problems	61.44 (2.94)	55.94 (2.01)	$t_{16} = 3.52$	**.003**	0.85
Internalizing problems	57.50 (2.92)	50.41 (2.23)	$t_{16} = 4.12$	**<.001**	1.00
Adaptive skills	41.12 (2.14)	41.53 (1.92)	$t_{16} = -0.21$	.833	0.05
CPRS-R (T-scores)					
Global index	68.38 (2.65)	60.62 (1.97)	$t_{16} = 4.86$	**<.001**	1.18
Inattention (DSM-IV)	$71.12 (1.99)	62.65 (1.82)	$t_{16} = 4.78$	**<.001**	1.16
Hyperactivity/impulsivity (DSM-IV)	73.88 (2.43)	64.32 (1.71)	$t_{16} = 4.74$	**<.001**	1.15
Total score (DSM-IV)	74.38 (1.91)	64.50 (1.57)	$t_{16} = 6.30$	**<.001**	1.53
Neuropsychological tests					
Digit span (WISC-IV)					
# Correct responses	13.53 (0.65)	15.76 (0.85)	$t_{16} = -5.16$	**<.001**	1.25
Letter-number sequencing (WISC-IV)					
# Correct responses	16.00 (0.65)	17.65 (0.66)	$t_{16} = -2.26$	**.038**	0.55
D2					
Concentration index	48.76 (6.44)	62.06 (5.66)	$t_{16} = -3.29$	**.005**	0.80
CPT					
# Omission errors	4.42 (0.94)	4.79 (0.98)	$t_{16} = -0.44$	.664	0.11
# Commission errors	58.57 (5.65)	45.10 (5.51)	$t_{16} = 2.68$	**.016**	0.65

Significant effects are marked bold ($p < .05$)

BASC Parent Rating Scales (BASC-PRS) with the composite scales. Conners' Parent Rating Scales (CPRS-R) with global index and DSM-IV items. Two tests of the WISC-IV evaluating working memory: digit span and letter-number sequencing, with the number of correct responses. D2 test with concentration index. Conners' Continuous Performance Test (CPT) with the number of omission and commission errors. *t*- and *p*-values for the paired samples *t*-tests are provided, as well as Cohen's *d* effect size (ES)

was covered on average. The clustering method computed the pre versus post difference by performing paired samples *t*-tests in the (sensor, frequency)-pairs. Those pairs exceeding a threshold ($q = .05$) were clustered on the basis of spatial and spectral adjacency, and cluster-level statistics were calculated as the sum of the *t*-values within every cluster. Finally, the significance probability at the cluster-level was estimated by a permutation method (Pesarin 2001). The null distribution of the cluster values was constructed by 5,000 random permutations. The observed values were then tested against the $(1 - \alpha)$th percentile of the null distribution. This method controls for the type I error rate and corrects for multiple comparisons across sensors and frequencies. The type I error at cluster-level was set to $\alpha = .05$.

Results

Behavioral Assessments

The scores of the clinical and neuropsychological variables are summarized in Table 1. Regarding the clinical variables, BASC-PRS showed a significant decrease in both the externalizing ($t_{16} = 3.52, p = .003$) and internalizing problems scores ($t_{16} = 4.12, p < .001$), showing large effect sizes ($d \geq .85$). No significant change appeared in adaptive skills. CPRS-R showed a significant decrease in the global index ($t_{16} = 4.86, p < .001$) and in the three DSM-IV items (inattention: $t_{16} = 4.78, p < .001$; hyperactivity/impulsivity: $t_{16} = 4.74, p < .001$; total score: $t_{16} = 6.30, p < .001$), showing large effect sizes ($d \geq 1.15$). Regarding the neuropsychological variables, a significant improvement in working memory performance appeared as measured by both the digit span test ($t_{16} = -5.16, p < .001$), showing a large effect size ($d = 1.25$), and by the letter-number sequencing test ($t_{16} = -2.26, p = .038$), which showed a medium effect size ($d = .55$). D2 test showed a significant increase in the concentration index ($t_{16} = -3.29, p = .005$), showing a large effect size ($d = .8$). The number of omission errors in the CPT test did not show a significant change. However, the number of commission errors decreased significantly ($t_{16} = 2.68, p = .016$), showing a medium-large effect size ($d = .65$).

Long-Term Effects

Mean ± SD IAF was 9.25 ± 1.22 Hz at study entry. No significant change in IAF appeared after the NF training. Trained parameter (relative upper alpha power in fronto-central sites) showed a long-term increase in task-related activity (paired samples *t*-test: $t_{16} = -2.44, p = .026$), with an average increase of 13.4 %. Figure 2a displays the results of the exploratory analysis. Significant clusters were only found in task-related activity, both in relative and absolute power. A relative power increase appeared in

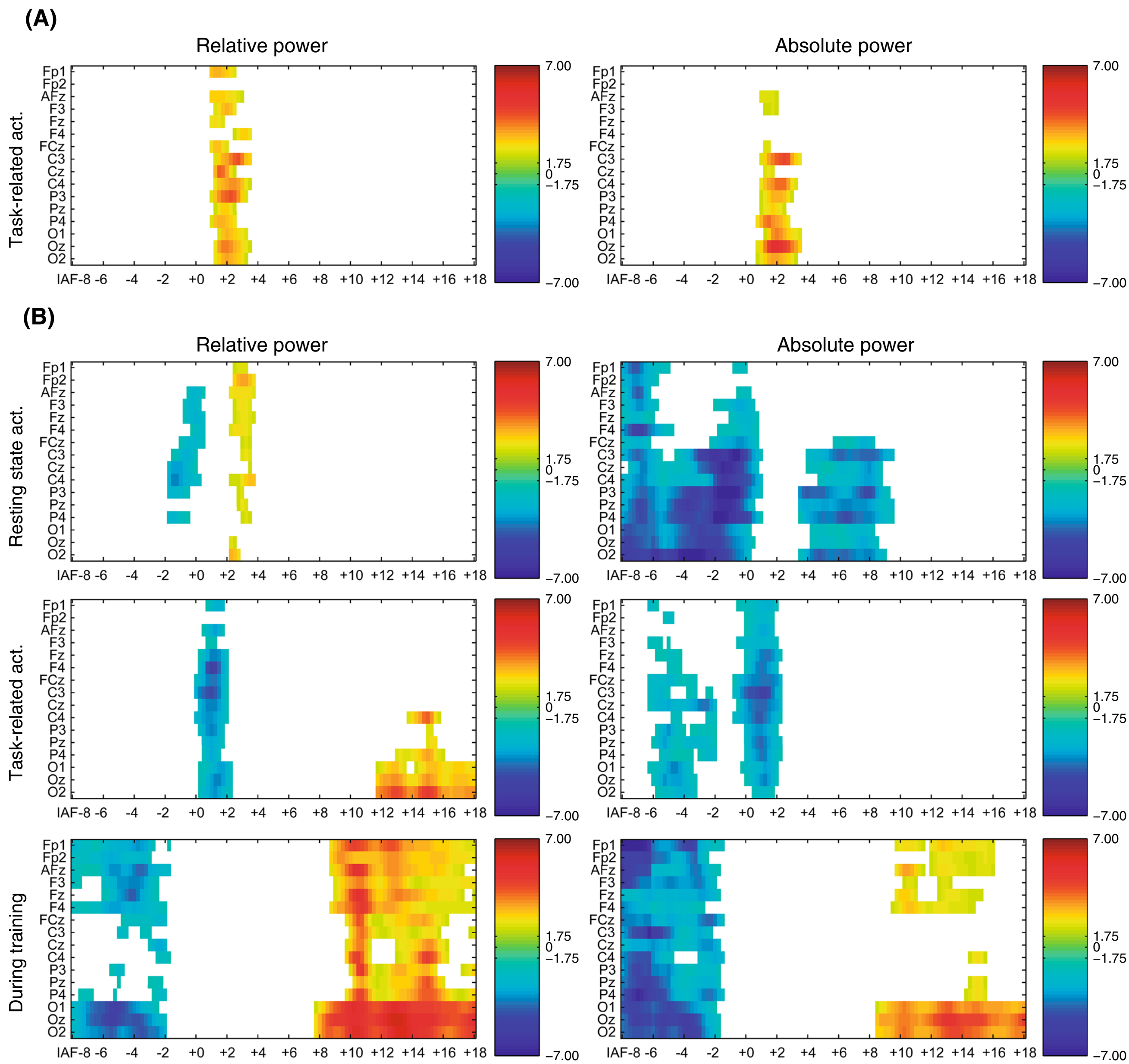

Fig. 2 Sensor × frequency maps displaying the (**a**) long-term effects and (**b**) within-session effects. Significant clusters (pre vs post power changes) are displayed. *Left figures* display the effects on relative power and right figures the effects on absolute power. Power spectra was centered per subject to the IAF. X axis shows the frequency bins in the (IAF−8, IAF+18) Hz range, whereas Y axis shows the sensor locations. *Color scale* represent *t*-values, with positive and negative values indicating a power increase or decrease, respectively

(IAF+1, IAF+3) Hz ($p = .039$), partially covering upper alpha and beta1. An absolute power increase was marginally significant in the same frequency range, apparent in central and parieto-occipital sites ($p = .07$). No significant effects were found in resting state.

Learning Curves Over Sessions

Children with less than 30 s of artifact-free data in a given EEG screening of a session (in either resting state or task-related activity) were excluded from the analysis of that session. The mean ± SD number of children per session was 13.8 ± 1.3. Trained parameter (relative upper alpha power in fronto-central sites) showed a positive learning curve over sessions in task-related activity ($r_{17} = 0.62, p = .008$), see Fig. 3. The exploratory analysis in relative power revealed a marginally significant negative learning curve in parieto-occipital sites for delta power, measured in task-related activity ($r = -0.65, p = .083$). Absolute power analysis revealed a positive learning curve in parieto-occipital sites for upper alpha power, measured in task-related activity ($r = 0.75, p = .01$). No significant

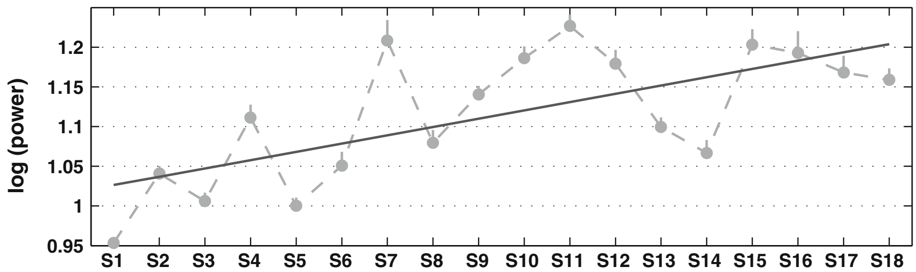

Fig. 3 Relative upper alpha power in fronto-central sites (trained parameter) over sessions, measured in task-related activity. *Dots* depict the mean ± SEM power value in each session, computed in the EEG screenings recorded immediately before the training trials. Data was normalized per subject to the power in the initial EEG screening

learning curves were found in resting state. Note that we are strictly controlling the FWER in the exploratory analysis by a randomization procedure plus Bonferroni correction.

Within-Session Effects

Trained parameter (relative upper alpha power in fronto-central sites) showed a within-session decrease in task-related activity (paired samples *t*-test: $t_{16} = 2.66, p = .017$), with an average decrease of 4.4 %. No significant effects in the trained parameter appeared either in resting state or during training. Figure 2b displays the results of the exploratory analysis. Regarding the resting state, a relative power decrease was found in lower alpha, (IAF-2, IAF) Hz, apparent in fronto-central and parietal sites ($p = .063$), and a power increase in beta1, (IAF+2, IAF+4) Hz ($p = .083$). An absolute power decrease was found in slow frequencies (delta and theta) and lower alpha, (IAF-8, IAF) Hz ($p < .001$), and a power decrease in beta1, (IAF+4, IAF+9) Hz, in central and parieto-occipital sites ($p = .003$). Regarding the task-related activity, a power decrease was found in upper alpha measured in relative ($p = .005$) and absolute power ($p = .001$). A relative power increase was found in beta3, (IAF+12, IAF+18) Hz, apparent in parieto-occipital sites ($p = .007$), and an absolute power decrease in theta and lower alpha, (IAF-6, IAF-2) Hz ($p = .005$). During training, slow frequencies and lower alpha, (IAF-8, IAF-2) Hz, showed a power decrease measured in relative ($p = .008$) and absolute power ($p < .001$). A power increase appeared in beta2 and beta3, (IAF+8, IAF+18) Hz, in relative ($p < .001$) and absolute power ($p = .01$).

Discussion

The current study evaluated an individualized NF protocol in children diagnosed with ADHD. Individualized approaches may better cope with the large EEG heterogeneity in ADHD and improve the clinical outcome (Arns et al. 2014). Recent NF studies have followed this direction (Arns et al. 2012; Lansbergen et al. 2011b; Logemann et al. 2010). Please note that in our study, "individualized NF approaches" refers to studies determining the EEG trained parameter according to the EEG activity of the individual rather than using a fixed EEG parameter for all the participants of the study. For instance, Arns et al. (2012) classified each individual into a set of EEG clusters by a comparison to a normative database, and performed a different protocol according to the cluster (e.g., theta/beta, alpha or beta suppression, SMR enhancement). Lansbergen et al. (2011b) and Logemann et al. (2010) performed a theta/beta protocol combined with SMR enhancement, in which the feedback sensors and range of frequency bands were determined by a comparison to a normative database.

The NF protocol herein proposed aimed at enhancing the relative upper alpha power in frontro-central sites, individually determined using the individual alpha frequency (IAF) as an anchor point. To the best of the authors knowledge, this is the first NF study evaluating such a protocol in ADHD individuals. In comparison to the aforementioned approaches, this NF protocol does not rely on a normative database comparison and it can address recent concerns of children with slow IAF. For example, Lansbergen et al. (2011a) found that children showing slow IAF may be clustered as an excess of theta activity. In addition to that, the use of an unique NF protocol makes possible to perform an homogenous group-level EEG analysis. On one hand, this protocol has the potential to deal with the excess of absolute theta power, which is the most reliable EEG pattern in ADHD to date (Barry et al. 2003; Snyder and Hall 2006). Due to the 1/*f* distribution of EEG power spectra, we hypothetized stronger effects in slow frequencies (power decrease) and upper alpha (power increase). On the other hand, this protocol builds upon the positive results of alpha-based protocols in cognitive performance, mainly evaluated in healthy users (see Gruzelier (2013) for a review on NF studies on cognitive enhancement). Thus, this NF protocol has the potential to alleviate the cognitive deficits of ADHD individuals. Note that deficits in executive functioning, including working memory, and response inhibition have been repeatedly reported (Barkley 1997; Martinussen et al. 2005; Castellanos and Tannock 2002).

EEG Analysis

An extensive power EEG analysis was conducted. We assessed long-term and within-session effects in all sensors in the (≈1–30) Hz frequency range by a cluster-based randomization method, obtaining sensor × frequency maps of the power changes. Furthermore, the learning curve over sessions was assessed in fronto-central and parieto-occipital sites for a set of frequency bands covering the (1–30) Hz range. We believe that the present analyses can offer a clearer insight of the electrophysiological effects rather than traditional analyses only in the trained parameter.

Children showed long-term effects in the trained parameter: relative upper alpha power in fronto-central sites was significantly enhanced after the NF training, measured in task-related activity. An average increase of 13 % was found, as well a significant positive learning curve over sessions. In line with these results, Nan et al. (2012) performed a similar NF protocol of relative upper alpha enhancement in healthy users, obtaining a positive learning curve over sessions. We also found a significant absolute upper alpha power enhancement in parieto-occipital sites, and a learning curve over sessions. The increase of absolute upper alpha power in NF literature has been related to improvements (in healthy users) in working memory (Escolano et al. 2011) and visuospatial rotation (Zoefel et al. 2011; Hanslmayr et al. 2005). The long-term effects in task-related activity were mainly restricted to the upper alpha band, with no significant effects in resting state. The stronger effects in task-related activity illustrate the importance of recording EEG in several conditions to provide additional information of the underlying brain processes. This is in contrast to the common practice to study only the resting state, either eyes closed or eyes open. Note that a correlation analysis was conducted between the behavioral and EEG variables, both in the initial and change scores, but no significant results were found.

The within-session effects measured the immediate effects after training in resting state and task-related activity, and the effects during training. To do so, EEG data was collected over sessions, and we compared the EEG screenings recorded immediately before versus after the training trials, and the EEG screenings recorded before versus the EEG during the training trials. A significant decrease in absolute and relative upper alpha power appeared in task-related activity, instead of the expected increase. This may be explained by an alpha "rebound" effect. While that kind of effect had been previously reported in EEG literature mainly related to motor acts in alpha or beta activity (Pfurtscheller and Lopes da Silva 1999), a recent alpha-based NF study with post-traumatic stress disorder (PTSD) patients reported that effect in alpha activity immediately after a single session of training, pointing to homeostatic/compensatory brain mechanisms (Kluetsch et al. 2013). Regarding the resting state, an absolute power decrease was found in slow-frequency oscillations (delta and theta) and lower alpha, as well as a power decrease in lower part of beta. No significant effects in the trained parameter were found during training, however an absolute and relative power decrease appeared in slow-frequency oscillations and lower alpha, as well as an increase in upper part of beta. Thus, although the children were not able to increase the relative upper alpha during training, they showed a strong effect in slow frequencies (as hypothetized) and in upper part of beta to a lower extent. The latter effect was unexpected and should be further explored in future studies.

Behavioral Assessments

Parents reported a significant reduction in the clinical symptoms of the children after the NF training. The externalizing and internalizing problems scores in the BASC test showed a significant improvement, as well as the inattention and hyperactivity/impulsivity scores in the CPRS test. The effect sizes in inattention and hyperactivity/impulsivity were 1.16 and 1.15, respectively. Regarding the neurophysiological tests, children showed a significant improvement in working memory as measured by the digit span and letter-number sequencing tests of the WISC-IV. We found a significant improvement in concentration as assessed by the D2 test. The number of commission errors in the CPT test was significantly decreased, thus suggesting an improvement in impulsivity. No significant change in the number of omission errors was found.

Interesting, slightly superior effect sizes in hyperactivity/impulsivity ($d = 1.15$) were found in comparison to literature (see Arns et al. (2009) meta-analysis). In this direction, a large body of research has hypothetized that the neuronal substrates of inhibitory mechanisms are related to alpha oscillations (Sauseng et al. 2009; Freunberger et al. 2011; Klimesch et al. 2007). Although it should be interpreted with caution, the upper alpha power enhancement herein reported may target mechanisms of behavioral inhibition, thus leading to higher outcomes in hyperactivity/impulsivity symptoms. SMR enhancement also has been traditionally hypothetized to alleviate hyperactivity. Due to the similitudes between these two protocols, the aforementioned relation may account for the clinical improvements and cognitive enhancement in ADHD. It was already pointed out by Hanslmayr et al. (2005) that the results in cognitive enhancement obtained after SMR-based NF (in healthy users) might be in part influenced by upper alpha activity. However, certainly more research is needed to elucidate the mechanisms of action underlying this protocol.

Limitations

Due to the novelty of the NF protocol in ADHD individuals an open-label pilot study was designed. The number of NF sessions was small in comparison with ADHD literature (30 to 40 sessions are usually executed). Furthermore, non-specific effects of the treatment cannot be ruled out due to the lack of a control group. The positive results of this NF protocol suggest that it should be further explored in a randomized controlled trial with a higher number of sessions and a larger sample size. Note that diagnosis was based on DSM-IV (American Psychiatric Association 1994) since it was the more recent edition at the beginning of our study, however it was recently updated to the fifth edition (DSM-5, American Psychiatric Association 2013).

References

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

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, *7*(03), 421–438.

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.

Arns, M., Drinkenburg, W., & Kenemans, J. L. (2012). The effects of QEEG-informed neurofeedback in ADHD: An open-label pilot study. *Applied Psychophysiology and Biofeedback*, *37*(3), 171–180.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: A meta-analysis. *Journal of Attention Disorders*, *17*(5), 374–383.

Arns, M., Heinrich, H., & Strehl, U. (2014). Evaluation of neurofeedback in ADHD: The long and winding road. *Biological Psychology, 95*(0):108–115. (Society of Applied Neuroscience) Special issue on Neurofeedback.

Barachant, A., Bonnet, S., Congedo, M., & Jutten, C. (2012). Multiclass brain-computer interface classification by Riemannian geometry. *IEEE Transactions on Biomedical Engineering*, *59*(4), 920–928.

Barachant, A., Andreev, A., & Congedo, M. (2013). The Riemannian Potato: An automatic and adaptive artifact detection method for online experiments using Riemannian geometry. In *Proceedings of TOBI workshop IV*, pp. 19–20.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65.

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*(2), 171–183.

Brickenkamp, R., & Zillmer, E. (1998). *The d2 test of attention*. Seattle, WA: Hogrefe & Huber Publishers.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience*, *3*(8), 617–628.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *112*(11), 2098–2105.

Clarke, A. R., Barry, R. J., Dupuy, F. E., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2013). Excess beta activity in the EEG of children with attention-deficit/hyperactivity disorder: A disorder of arousal? *International Journal of Psychophysiology*, *89*(3), 314–319.

Conners, C. K., & Staff, M. (2000). *Conners' continuous performance test II (CPT II V. 5)*. North Tonawanda, NY: Multi-Health Systems Inc.

Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, *26*(4), 257–268.

Escolano, C., Aguilar, M., & Minguez, J. (2011). EEG-based upper alpha neurofeedback training improves working memory performance. In: *International conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Boston (USA), pp. 2327–2330.

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159–166.

Freunberger, R., Werkle-Bergner, M., Griesmayr, B., Lindenberger, U., & Klimesch, W. (2011). Brain oscillatory correlates of working memory constraints. *Brain Research*, *1375*, 93–102.

Graham, J., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Dittmann, R., et al. (2011). European guidelines on managing adverse effects of medication for ADHD. *European Child & Adolescent Psychiatry*, *20*(1), 17–37.

Gruzelier, J. H. (2013). EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. *Neuroscience & Biobehavioral Reviews*, *44*, 124–141.

Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback*, *30*, 1–10.

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.

Holmes, A. P., Blair, R., Watson, G., & Ford, I. (1996). Nonparametric analysis of statistic images from functional mapping experiments. *Journal of Cerebral Blood Flow & Metabolism*, *16*(1), 7–22.

Hyvarinen, A. (1999). Fast and robust fixed-point algorithms for independent component analysis. *IEEE Transactions on Neural Networks*, *10*(3), 626–634.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2–3), 169–195.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain research reviews*, *53*(1), 63–88.

Kluetsch, R., Ros, T., Théberge, J., Frewen, P., Calhoun, V., Schmahl, C., et al. (2013). Plastic modulation of PTSD resting-state networks and subjective wellbeing by EEG neurofeedback. *Acta Psychiatrica Scandinavica*, *130*(2), 123–136.

Lansbergen, M. M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011a). The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(1), 47–52.

Lansbergen, M. M., van Dongen-Boomsma, M., Buitelaar, J. K., & Slaats-Willemse, D. (2011b). ADHD and EEG-neurofeedback: A double-blind randomized placebo-controlled feasibility study. *Journal of Neural Transmission*, *118*(2), 275–284.

Lee, T. W., Girolami, M., & Sejnowski, T. J. (1999). Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Computation*, *11*(2), 417–441.

Logemann, H. N., Lansbergen, M. M., Van Os, T. W., Böcker, 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., & Makeig, S. (2012). Clinical utility of EEG in attention-deficit/hyperactivity disorder: A research update. *Neurotherapeutics*, *9*(3), 569–587.

Lubar, J. F., & Shouse, M. N. (1976). EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR). *Biofeedback and Self-Regulation*, *1*(3), 293–306.

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, *164*(1), 177–190.

Martinussen, R., Hayden, J., Hogg-Johnson, S., & Tannock, R. (2005). A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(4), 377–384.

Molina, B. S., Hinshaw, S. P., Swanson, J. M., Arnold, L. E., Vitiello, B., Jensen, P. S., et al. (2009). The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(5), 484–500.

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & La Vaque, T. J. (2006). Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. *Journal of Neurotherapy*, *9*(4), 5–34.

Nan, W., Rodrigues, J. P., Ma, J., Qu, X., Wan, F., Mak, P. I., et al. (2012). Individual alpha neurofeedback training effect on short term memory. *International Journal of Psychophysiology*, *86*(1), 83–87.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human brain mapping*, *15*(1), 1–25.

Pesarin, F. (2001). *Multivariate permutation tests: With applications in biostatistics* (Vol. 240). New York, NY: Wiley.

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology*, *110*(11), 1842–1857.

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

Reynolds, C. R., & Kamphaus, R. W. (2004). *Behavior Assessment System for Children*. Circle Pines, MN: AGS Publishing.

Ros, T., Munneke, M., Parkinson, L., & Gruzelier, J. (2014). Neurofeedback facilitation of implicit motor learning. *Biological Psychology 95*(0):54–58. SAN (Society of Applied Neuroscience) Special issue on Neurofeedback.

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A., et al. (2009). Brain oscillatory substrates of visual short-term memory capacity. *Current Biology*, *19*(21), 1846–1852.

Snyder, S. M., & Hall, J. R. (2006). A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology*, *23*(5), 441–456.

Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical Electroencephalography*, *31*(1), 45–55.

Wang, G. J., Volkow, N. D., Wigal, T., Kollins, S. H., Newcorn, J. H., Telang, F., et al. (2013). Long-term stimulant treatment affects brain dopamine transporter level in patients with attention deficit hyperactive disorder. *PloS One*, *8*(5), e63,023.

Wechsler, D. (2003). *Wechsler intelligence scale for children-4th edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation.

Zoefel, B., Huster, R. J., & Herrmann, C. S. (2011). Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *NeuroImage*, *54*(2), 1427–1431.