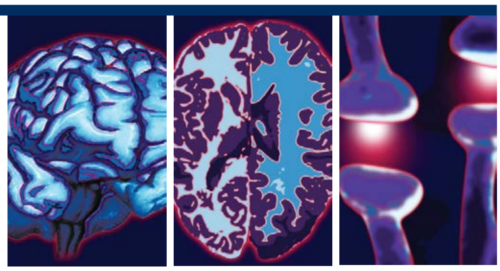
Research



Electroencephalogram Neurofeedback Treatment for Taiwanese Children with Attention Deficit Hyperactivity Disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder in children. Stimulant drugs treatment has been one of the major therapeutic options for children with ADHD. Roughly 34% of children are medication non-responders and many others are partial responders. Neurofeedback treatment is a promising alternative which is supported by western extensive peer-reviewed literature. However, there are limited empirical data of the effect of neurofeedback in Asian population. The purpose of the present study is to examine the effects of neurofeedback on the core symptoms and neuropsychological measures in Taiwanese children with ADHD who were partial responders to pharmacotherapy. Twenty-six children (7-12 years) with DSM-5 diagnosed ADHD entered this study. Subjects of neurofeedback group (N=13) received medication together with 20 sessions/ 8 weeks of neurofeedback training targeting on decreasing Theta brain wave of electroencephalogram. Control group children (N=13) received medication only. For the baseline and 8-week follow up assessments, all children received Continuous Performance test and their primary caregivers completed ADHD core symptoms rating scales. Significant improvements were noted on attention test and core ADHD symptoms measures for subjects who received add-on neurofeedback training as compared with the control group. The study supported the positive effect of neurofeedback training as add-on treatment for Taiwanese children with ADHD. Twenty sessions of neurofeedback can be beneficial in a short term follow up.

Keywords

Attention-deficit/hyperactivity disorder, Neuropsychiatric disorder, Children

Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common neuro-psychiatric disorder of children, affecting approximately 5% of the school-age population [1]. It is characterized by developmentally inappropriate deficits in attentional performance, impulsivity, and motor restlessness or hyperactivity [2]. ADHD typically starts in early childhood and is associated with functional impairment, including school dysfunction, problems with peer interaction, family conflict, poor occupational performance, injuries, antisocial behavior, traffic violations, and accidents [3]. Scientific effort has been directed at developing effective treatments, the vast majority of these studies have indicated that pharmacological treatment can exert a positive effect on the core symptoms of ADHD. Stimulants like methylphenidate has been

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demonstrated to improve core symptoms of ADHD in a multitude of well-controlled studies in large samples and across long periods of time [4]

Nevertheless, studies done worldwide showed that stimulants are effective in reducing the ADHD core symptoms in only 65-75% of individuals [4-6]. In many responders, there is still room for improvement. In addition, many parents voice concern about potential side effects of receiving prescription of controlled drugs (i.e. stimulants) to treat pediatric disorder and prefer the option of non-medical treatment. Although not yet approved by the FDA for use in adolescents, bupropion is a promising nonstimulant alternative with several reports of positive outcomes for treatment of ADHD in children and adolescents [5]. One of the promising alternatives to drug therapy for ADHD is electroencephalogram-neurofeedback (EEG-NF), which is supported by peer-reviewed literature, including large-scale controlled clinical trials [7-12].

The rationale for neurofeedback treatment is that patients with ADHD exhibit characteristic surface quantitative EEG disturbances when using computer applying techniques such as Fast-Fourier Transform to EEG data. Specifically, 85 to 90 percent of patients with ADHD display signs of cortical "hypoarousal," quantitatively described as elevated relative theta power, reduced relative alpha and beta power, and elevated theta/alpha and theta/beta power ratios. These patterns are typically observed over frontal and central midline brain regions [12-14]. A smaller subgroup of ADHD patients exhibits an EEG pattern suggestive of "hyperarousal," with greater relative beta activity, decreased relative alpha activity, and decreased theta/beta power ratios diffusely across multiple cortical recording sites [15-17]. EEG-NF training involves the learning to regulate ongoing neuronal oscillations (as recorded by EEG) in one or more frequency bands by visual or auditory feedback with the aim of gaining the ability to self-regulate brain activities.

To the authors' best knowledge; there are limited empirical data of the effect of EEG-NF in Asian children. However, there are literatures supporting cultural implications in the diagnosis, treatment and perception of ADHD [18]. The purpose of the present study is to examine the effects of EEG-NF on the core symptoms and neuropsychological measures in Taiwanese children with ADHD. We also implemented a shorter treatment session tailored for our clinical context. We hypothesized that, for children with ADHD who are partial responders to preexisting stimulant treatment, participants who were treated with add-on EEG-NF training would have further improvements on behavioral and neuropsychological measures during post treatment evaluations.

Methods

■ Participants

Participants were twenty-six children recruited from the outpatient service of Department of Psychiatry, Kaohsiung Medical University Hospital, Taiwan. Inclusion criteria were 1) a primary diagnosis of ADHD based on semi structured interviews with parents and children using DSM-5 by child psychiatrists [2] 2) currently at the age of 8 to 12-year old 3) a Wechsler Intelligence [19] test of full scale intelligence quotient (FSIQ) score at least 80 4) on stable dosage of stimulants for more than four months but still with room for improvement. Room for improvement was defined as physician rated clinical global impression improvement scale as 3 or 4 [20]. Exclusion criteria were 1) currently receiving individual or group psychotherapy, 2) had substance use disorder, conduct disorder, mood disorder or anxiety disorder 3) had seizure disorder.

The preexisting stimulant medication was maintained at the same dose throughout the 8 weeks. A case-controlled between-subjects design was utilized. Children were allocated to one of the following two groups by their parents' time of convenience: EEG-NF group and waiting/control group. Informed consent was obtained from the subjects' parents according to the guidelines of the Institutional Committee on Clinical Investigation. Children themselves gave oral consents. Institutional review Board's approval of waiver for the control group was sought and granted.

■ Assessment

For children of the EEG-NF group, EEG was recorded via an electrocap with 19 electrodes according to the 10–20 electrode international system referenced to linked ear lobes during a 5-min eyes closed resting-state condition both before and after the treatment session. EEG data was filtered between of 0.5–50 Hz and digitized at a sampling rate was 256 Hz. Impedance was kept below 5 KΩ for all electrodes

All participating children underwent the following ADHD core symptoms and neuropsychological assessments twice, with 8-week interval in between.

1. ADHD core symptoms measure by parental report: Chinese version of the Swanson, Nolan and Pelham IV scales (SNAP): This behavior questionnaire is a reliable and validated instrument for rating ADHD-related symptoms of inattention, hyperactivity/impulsivity and oppositional defiant in both clinical and community settings. The psychometrics properties for Taiwanese children have been well established [21]. The primary caregiver of each participant was asked to fill in the forms.

2. Conners' Continuous Performance Test (CPT II) Version 5 for Windows® : This neuropsychological assessment is a computerized test which is widely used in research on attention for respondents aged 6 or older [22]. CPT II respondents are required to press the space bar whenever any letter except the letter 'X' appears on the computer screen. The inter-stimulus intervals (ISIs) are 1, 2 and 4 seconds with a display time of 250 milliseconds. The unique CPT paradigm is a test structure consisting of 6 blocks and 3 sub-blocks, each containing 20 trials (letter presentations). The presentation order of the different ISIs varies between blocks. The following types of measures are provided by the CPT II program: Response Times - Overall Hit Reaction Time (HRT), Overall HRT Standard Error (SE), Variability, HRT by Block, HRT SE by Block, HRT by ISI, HRT SE by ISI (the program classifies a reaction time less than 100 ms as a perseveration); Errors (omissions and commissions); by Block results; by ISI results (the change in reaction time and in consistency); and Signal Detection Theory Statistics T-scores and percentiles are available. In accordance with most of the ADHD clinical trials, the following five indexes were used for analysis this study: Overall Hit Reaction Time (HRT), Overall HRT Standard Error (SE), Variability and Errors (omissions and commissions).

■ EEG-NF treatment protocol

EEG-NF treatment consisted of 20 sessions being conducted over a period of 8 weeks. Each session consisted of 40 min of visual and auditory feedback, interrupted for short breaks of 5 minutes. Training was administered to all participants by the same therapist (I-Ting Li) using the BrainMaster Avatar (BrainMaster Technologies, Inc., Bedford, Ohio) hardware and software. We adopted the Lubar [23] protocol with modification for young age subjects. Lubra proposed that the Theta/ Beta EEG ratio (TBR) as a target for neurofeedback, where children are taught to decrease the excess theta and increase beta EEG activity at fronto-central locations [24]. Because the average age of our participants was younger than most of Lubar's clients, we only trained our children to decrease the excess theta and we shortened the treatment session to 20 times in total.

The ongoing EEG was band-pass filtered in the following four frequency ranges: theta (4–7 Hz), sensorimotor rhythm (SMR, 12-15 Hz), beta 1 (15-18 Hz), and beta 2 (22-30 Hz). Our training paradigm targeted the inhibition of EEG theta wave at Cz location and the aim of neurofeedback training was to decrease the power in the theta band ("inhibit bands"). Information about the power in each of these frequency bands was monitored by the therapist throughout the session and fed back audiovisually to the children via a personal computer. During training, children were asked to sit as quietly as possible in a comfortable arm chair in front of a 19 inch computer screen. EEG data were obtained from the active electrode(s) placed on the scalp at the Cz referenced to A1 (sampling rate: 256 Hz). At the beginning of a training session, threshold level was determined for each participant from 5-min baseline amplitude measures of activity in the theta bands (with eyes closed). Reward criteria were set so that reward thresholds had to be in range below inhibited threshold in 50% of sampled events in a 500-ms period to receive a reward. When participants consistently achieved the defined goals (e.g. hit the gaming score above 800), their thresholds were made more difficult (i.e. the percent of sampled events achieving was between 30-65%). Visual feedback was provided by the Pacman-type game "mazes" in which an icon moved through a maze eating dots. When the reward criterion was attained, scores were indicated by an audio signal (a Doo-Doo sound with a counter increasing its value) and visual reward showing the icon moving through the maze eating dots.. When the icon reached the end of the maze, a bar chart appeared showing the performance and there was a short break before the next maze started.

■ Statistics

SPSS (V.22.0) was used for numerical data analysis. For ADHD core symptom and neuropsychological measure, we conducted Mann-Whitney U test to compare the difference between neurofeedback and control group; and we used Wilcoxon signed rank test to analyze the difference over 8 weeks in each group. For all statistical procedures, significance was assured if $p < 0.05$.

Results

■ Group characteristics

The subjects included for the final analysis consisted of 26 adolescents: 13 children receiving EEG-NF and medication treatment (the case group) and 13 children receive medication treatment only (as control group). The case group consisted of 9 males and 4 females, with an average age of 10±1.53 years and average FSIQ of 105±9.26. Their daily average dose of methylphenidate was 25±8.16 mg. The control group consisted of 10 males and 3 females, with an average age of 9±1.53 years and average FSIQ of 106±7.65. There were 8 children with combined presentation and 5 children with inattentive presentation in each of the case/control group. Their daily average dose of methylphenidate was 25.8 ± 8.68 mg. As reported in Table 1, there was no difference in gender, current age, ADHD presentation, daily average dose of methylphenidate and FSIQ noted between the case group and control group.

■ Core ADHD symptoms as reflected by parental rated SNAP scales

At the baseline, the two groups showed no difference in ADHD core symptoms severity as reflected in the scores of three subscales (inattentive, hyperactive-impulsive, oppositional-defiant) and the total score (Table 1). Table 2 reported the changes over 8 weeks of the two groups, in-group comparison and between-group comparison. In summary, the EEG-NF group showed improvement in all the three subscales and total score of the SNAP over 8 weeks, while the control group showed no significant change in core symptoms severity. Comparison of the two groups showed that the magnitude of change over 8 weeks was significantly larger in the EEG-NF group (i.e. more improved), especially over inattentive symptoms domain.

■ Neuropsychological measures

At the baseline, the two groups showed no difference in neuropsychological measures of CPT except in the index of variability of overall hit reaction time. Table 3 reported the changes over 8 weeks of the two groups, in-group comparison and between-group comparison. In summary, the EEG-NF group showed significant improvement in the index of error (omission, commission), reaction time standard error and variability, while the control group had no significant change over 8 weeks. Comparison of the two groups showed that the magnitude of change over 8 weeks was significantly larger in the EEG-NF group in commission error, reaction time standard error and variability (Table 3)

■ Brain wave analysis

The QEEG spectral power showed no statistically

Table 1: Demographics and baseline measurement of the neurofeedback (case) group and the waiting (control) group.

group	case (*n*=13)	control (*n*=13)	z/χ^2	*p*
Current age in years mean (S.D)	10(1.53)	9(1.53)	-1.34	.20
Gender (M/F)	9/4	10/3	.17	.68
ADHD presnetation (combined/inattentive)	8/5	8/5		
Full scale IQ mean (S.D)	105(9.26)	106(7.65)	-.18	.88
SNAP				.
Inattentive score	14.15(4.39)	11.92(2.873)	-1.59	11
Hyeractivity/impulsivity	10.77(4.64)	9.68(3.98)	-.55	.58
ODD score	8.38(5.81)	9.25(3.22)	-.91	.37
total score	33.31(11.32)	30.83(9.01)	-.63	.53
CPT-II				
Error of omission	20.38(12.17)	12.42(13.47)	-1.85	.06
Error of commission	24.23(8.41)	21.00(7.58)	-.98 -1.58	.33
Reaction time SE	14.29(4.95)	10.77(6.27)		.12
MPH daily dose in mg	25(8.16)	25.8(8.68)	-.345	.73

SNAP: Chinese version of the Swanson, Nolan and Pelham IV scales
CPT-II: Conners' Continuous Performance Test MPH: methylphenidate

Table 2: The parental reported SNAP of the case and control group over 8 weeks.

SNAP	Case Mean(SD)	Pre-post (case) z/p	Control mean(SD)	Pre-post (control) z/p	Group comparison of pre-post difference z/p
Inattentive					
pre	14.15(4.39)		11.92(2.873)		
post	9.23(4.38)	-3.82/.002**	11.25(3.14)	-.60/.06	-.15/.00**
Hyperactive/impulsivity					
pre	10.77(4.64)		9.68(3.98)		
post	7.00(3.53)	-2.17/.03*	10.33(4.03)	-.77/.44	-1.84/.07
Oppositional defiant					
pre	8.38(5.81)		9.25(3.22)		
post	5.54(4.81)	-2.21/.027*	8.92(5.11)	-.72/.47	-1.34/.18
Total score					
pre	33.31(11.32)		30.83(9.01)		-2.72/.01**
post	21.77(9.86)	-3.11/.002**	30.75(9.60)	.00/1.00	

SNAP: Chinese version of the Swanson, Nolan and Pelham IV scales

Table 3: The CPT performance of the case and control group over 8 weeks.

CPT index	Case (mean/SD)	Pre-post difference z/p	Control (mean/SD)	Pre-post difference z/p	Group comparison of pre-post difference z/p
Omission					
Error pre	20.38(12.17)	-2.36/.01*	12.42(13.47)	-7.47/.45	-.36/.72
post	10.85(10.78)		9.25(10.00)		
Commission					
Error pre	24.23(8.41)	-2.83/.00**	21.00(7.58)	-.49/.62	-2.80/.00**
post	17.15(7.34)		20.58(6.99)		
HRT					
pre	446.00(72.11)	-.66/.51	482.09(104.18)	-1.73/.08	-1.39/.17
post	453.65(95.42)		454.75(72.85)		
HRT SE					
pre	14.29(4.95)	-2.69/.00**	10.77(6.27)	0.00/1.00	-.239/.02*
post	9.19(4.09)		10.70(4.86)		
Variability					
pre	34.01(16.90)	-2.98/.00**	19.47(16.38)	-.16/.88	-2.98/.00**
post	12.53(5.73)		20.46(15.36)		

p<.05 * *p*<.01** HRT: Overall hit reaction time,
HRT SE :Overall hit reaction time Standard Error (SE),
Variability: variability of overall hit reaction time

significant change on theta activity and theta to beta power ratio (TBR) after the EEG-NF training in the case group (Table 4). However, detailed inspection of the brain wave data showed a decreasing pattern of theta amplitude and TBR. The post-treatment theta amplitude is 69% of the pre-treatment value at Cz position, while the post-treatment TBR is 62% of the pre-treatment value at Cz position.

Discussion

Our study supports effect of EEG-NF as add-on treatment for improving the core symptoms of ADHD and neuropsychological performance in Taiwanese children with ADHD who are partial responders to methylphenidate treatment. Our finding is consistent with previous western studies and adds support to the effects of this type of therapy [9,10,12]. Our study also demonstrates that EEG-NF helps the inattention domain of the core symptoms the most as reflected by the improvement of attention test scores. This finding also corroborates previous western studies [25,26].

This current study had several methodological limitations in need of further discussion. The most important ones were small sample size, non-randomized group assignment, and it was not a double-blind set up. However, the majority of western EEG-NF studies of ADHD also faced these limitations [25,26]. The majority of study treatment response was reported by an individual likely to be not blind to treatment, which was in most cases the parental assessment as we applied in this study. In contrast, in most clinical pharmacological trials testing treatment response, the assessment is preferably done by

Table 4: The brain wave analysis over 8 weeks of the case group.

Position	Pre Mean (Sd)	Post Mean (Sd)	Z	P
C3				
Theta amplitude	7.73(2.37)	7.36(2.48)	-1.01	0.31
Theta p to p	25.26 (7.91)	24.29 (88.45)	-0.66	0.51
Theta RP	22.06 (4.91)	22.32 (5.12)	-0.25	0.81
TBR	3.58 (1.78)	3.68 (2.51)	-0.18	0.86
C4				
Theta amplitude	7.90(2.39)	7.59(2.53)	-1.08	0.28
Theta p to p	25.86 (7.97)	25.10 (8.65)	-0.73	0.46
Theta RP	21.43 (4.26)	22.29 (4.41)	-0.73	0.46
TBR	3.69 (1.70)	3.74 (2.42)	-0.52	0.60
Cz				
Theta amplitude	8.55(2.30)	8.21(2.58)	-1.01	0.31
Theta p to p	28.07 (7.82)	27.23 (8.83)	-0.73	0.44
Theta RP	23.18 (5.41)	23.74 (4.64)	-0.38	0.70
TBR	4.58 (2.10)	4.53 (2.86)	-0.31	0.75

p to p to p peak to peak amplitude, in μV ; theta RP: theta relative power, power at theta/total (0.5-30 Hz) in percentage; TBR: Theta to beta ratio

individual blind to the treatment. A most recent meta-analysis of published randomized control trials has analyzed the treatment effectiveness of EEG-NF in children with ADHD. In this report, they found parental assessment(e.g. with an non-blinded assessment) reporting improvement in the overall ADHD score , the inattention score and the hyperactivity/impulsivity score in patients receiving EEG-NF compared to controls. On teacher assessment (probably blinded assessment), only the inattention score was significantly improved in patients receiving EEG-NF compared to controls [26].

In addition, an ideal control treatment should control for the non-specific factors embodied by the lengthy EEG-NF treatment sessions. These non-specific effects include the cognitive training given by the therapist to the child to let him focus on a computer screen for many sessions, verbal encouragement by the therapists, the amount of therapist-child interaction and total time committed. Hence, the best control group in EEG-NF study would receive placebo neurofeedback (sham) in which provided feedback is similar to EEG-NF, but not related to the child's brain activity. However, this kind of design is difficult to implement in a childhood disorder. We used a waiting list control group which was far from ideal, but it was not without precedence in this filed [27, 28].

Literature review of western studies found few studies exploring EEG-NF treatment effect with an intervention that controls for the nonspecific effects, these include study designs using semi-active control (i.e. cognitive remediation of eletromyographic biofeedback) and sham-neurofeedback group (i.e. the feedback is not related to brain activity) [29]. Meta-analysis [26] suggests the persistence of EEG-NF efficacy only for the inattention dimension of ADHD when considering recent well-controlled studies that include semi-active and sham-neurofeedback controls [30-33]. These study designs are considered the future trend for rigorous scientific exploration because they can afford more reliable and valid assessments than probably blinded teacher assessments to evaluate the efficacy of EEG-NF, However, a recent neurofeedback treatment design feasibility study shows that a double-blind design may not be feasible since using automatic adjusted reward thresholds may not work as effective as manually adjusted reward thresholds by the therapist [34]. Hence the perfect design for the control condition of neurofeedback study is still uncertain

In our study, the QEEG spectral power showed no statistically significant change on theta activity and theta to beta power ratio (TBR) when the case group had received EEG-NF training. Changes in trained EEG oscillations after neurofeedback training had only been demonstrated in two previous groups [35, 36], and the changes in resting EEG were found to be not necessarily corresponding to the applied neurofeedback protocol [30,37]. These findings had led researchers to conclude that change in EEG pattern to the training aim is not a necessary condition for clinical improvement. It has been speculated that a reorganization of EEG activities rather than changes in local activity at trained electrode site underlies the clinical effect [38]. The clinical improvement after neurofeedback training may not be due to the correction of a neural dysfuction, but to train the child to build a compensatory mechanism of a focused, attentive and relaxed state so that the underlying network can be strengthened.

The usual western EEG-NF treatment for ADHD children usually requires 30-40 sessions and implicates a substantial amount of client-therapist interaction and parental investment of time and energy. We adapted the program to be only with 20 sessions due to the practical limitations in our treatment context and we were happy to see that the results turned out to be just as positive as the usual 30-40 sessions. In addition, we used standardized EEG-NF training protocol (i.e. theta suppression) for every subject in this study. Theoretically, not all children with ADHD have increased theta activity [17, 39] and it has been proposed that increased theta in ADHD may be partly due to slow alpha oscillations rather than real enhanced theta activity [40]. Hence, in the clinical practice reported by western colleagues, therapists usually applied individualized EEG-NF training for ADHD children (i.e. training protocol is adjustable by the child's brain activity). We also want to acknowledge that our subjects were predominately male and of the mixed presentation by DSM-5. DSM-5 has changed the wording of "subtype" used in DSM-IV to "presentation". It is still a matter of debate whether the three ADHD presentations are in fact facets of the same condition, especially since the initial subtype differences in inattention symptoms often diminish as children progress from preschool to elementary years [41]. Furthermore, there are important differences in symptomatology between boys and girls with ADHD [42,43]. I. It is still undetermined whether the ADHD presentation or patient's gender has any implication in the application of neuro feedback as treatment.

In conclusion, this study supports effect of EEG-NF training as add-on treatment for improving the core symptoms and attention in Taiwanese children with ADHD. In addition, 20 sessions of EEG-NF can be beneficial in a short term follow up. This study is meaningful in providing empirical evidence for clinical consideration. However, the present study does not directly address the question of whether patients will be able to sustain clinical improvements following EEG-NF. Systematic, long-term follow-up studies examining the relationship between EEG-NF and stimulant dosing patterns are required.

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