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ABSTRACT

Neurofeedback (NFB) is an operant conditioning procedure, by which the subject learns to control his/her EEG activity. On one hand, Learning Disabled (LD) children have higher values of theta EEG absolute and relative power than normal children, and on the other hand, it has been shown that minimum alpha absolute power is necessary for adequate performance. Ten LD children were selected with higher than normal ratios of theta to alpha absolute power (theta/alpha). The Test Of Variables of Attention (TOVA) was applied. Children were divided into two groups in order to maintain similar IQ values, TOVA values, socioeconomical status, and gender for each group. In the experimental group, NFB was applied in the region with highest ratio, triggering a sound each time the ratio fell below a threshold value. Noncontingent reinforcement was given to the other group. Twenty half-hour sessions were applied, at a rate of 2 per week. At the end of the 20 sessions, TOVA, WISC and EEG were obtained. There was significant improvement in WISC performance in the experimental group that was not observed in the control group. EEG absolute power decreased in delta, theta, alpha and beta bands in the experimental group. Control children only showed a decrease in relative power in the delta band. All changes observed in the experimental group and not observed in the control group indicate better cognitive performance and the presence of greater EEG maturation in the experimental group, which suggests that changes were due not only to development but also to NFB treatment.

INTRODUCTION

Learning disorders (LD) are diagnosed when an individual's achievement on individually administered, standardized tests in reading, mathematics, or written expression is substantially below that expected for age, schooling, and level of intelligence. LD are classified as "specific" (reading disorder, mathematics disorder or disorder of written expression) or "learning disorder not otherwise specified," which might include problems in all three areas.[1] Children included in this study belonged to the latter group. At the present time there is not an efficient treatment for these children, and for this reason we decided to explore the effect of neurofeedback on a group of LD children and compare its effect with another group of placebo-controlled LD children. The ethical use of placebo controls in clinical research has been the subject of debate, but according to the Helsinki Declaration, placebo-controlled studies are ethically acceptable for those disorders for which no effective treatment is available.[2] Furthermore, placebo-controlled studies are necessary to satisfy criticisms that NFB lacks adequate scientific credibility.

Neurofeedback (NFB) is an operant conditioning procedure, whereby an individual can learn to modify the electrical activity of his or her own brain.[3] Although the exact physiological basis underlying it is not well understood, NFB has proven useful in the treatment of many psychiatric entities, such as attention deficit/hyperactivity disorder,[4-6] depression,[7] obsessive-compulsive disorder,[8] as well as the treatment of addictions, principally alcoholism,[9] and of epilepsy.[10-12]

For a long time, the norm has been to apply NFB in an *a priori* selected lead. For example, in children with AD/HD[1] NFB is generally used on the basis of frontal EEG activity.[5,13] This seems justified, since a hypofrontality has been noted in PET[14] and functional Magnetic Resonance Imaging (fMRI) studies[15] in AD/HD children. However, LD children did not show alterations in specific cerebral

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regions. The most frequently reported EEG abnormality in LD children is an increase in theta relative power according to their age. Harmony, et al.[16] reported higher theta relative power in LD children than in normal subjects at C3, P3, P4, O1, T5, F4, C4, O2, F8 and T3. Thatcher[3] proposed the use of normative databases in order to individualize the treatment. In the present paper NFB was applied at the lead with the highest abnormal theta/alpha ratio for the age of the subject.

Several studies have reported higher amounts of delta, and principally theta, and lower amounts of alpha in LD children compared to normal children of the same age.[16-18] An important percentage of LD children showed an EEG pattern more typical for younger children, which has been interpreted as a delay of EEG maturation.[16,17,19] Other groups of LD children showed paroxysmal EEG activity.[18,20-25]

In general, NFB is applied on the basis of EEG activity at rest. One might think it would be more appropriate to use NFB when the subject is performing some cognitive task. However, the normative databases that exist are based on recording the EEG at rest,[26-29] and to our knowledge EEG normative values have not been reported during mental tasks. On the other hand, it should be taken into account that EEG activity at rest underlies neural activity during task performance.[3]

It is well known that EEG absolute power decreases with age in all bands, most markedly in the delta and theta bands.[30,31] Delta and theta relative power also decrease with age, whereas alpha and beta bands increase.[32] Although alpha absolute power decreases with age, a minimum quantity of this activity at rest is necessary for the correct performance of mental tasks.[33,34] This activity should be present in those regions involved in the task, and for this reason NFB treatment was applied in order to reduce the theta/alpha ratio.

In this study, we seek to show that LD children whose EEG is slower than the norm for their age learn to modify their EEG activity with NFB, and that this EEG modification is associated with behavioral improvement. As it has been suggested that improvement may be related to changes in attention and the care of parents and teachers, a placebo-controlled group was also studied.

METHODS

Subjects

Fifty-two children between 7 and 11 years of age (16 of them female) were studied in order to select children with primary learning disability, normal neurological exam, IQ greater than 70, mother with at least a third-grade elementary school education, per capita income greater than 50 percent of minimum wage, and at least one EEG lead with an abnormal value of the theta/alpha ratio. Twelve children satisfied these criteria, but only 10 of them (5 in each group) finished the NFB treatment. They had cranial Computed Tomography (CT) without important abnormalities. All children had an abnormal theta/alpha ratio at least in one lead when their ratio at rest with eyes closed was compared with a normative database.[27] All children were volunteers; parents' informed consent was obtained in all cases.

The Test Of Variables of Attention (TOVA)[35] in visual mode was applied to all children. TOVA is a computerized continuous performance test on which the subject has to respond to a target that is more frequent than the nontarget in the first half of the test, and less frequent in the second half.

Children were classified in two groups, without differences in averages of age, sex, IQ or ADHD score[35] from TOVA. One group received NFB training (experimental group), and another group received placebo training (control group). Results for these 10 children will be presented.

EEG recording

Subjects were seated in a comfortable chair in a dimly lit room. EEG was recorded from 19 leads of the International 10-20 System using linked ear lobes as reference. A1A2 reference was used in order to have the same conditions as in normative data. The amplifier bandwidth was set between 0.5 and 30Hz. EEG was sampled every 5 msec using a MEDICID 3E System and edited off-line. An expert electroencephalographer using visual editing selected 24 artifact-free segments of 2.56 sec, for quantitative analysis.

EEG analysis

Analysis was done off-line. The Fast Fourier Transform and the crosspectral matrices were calculated every 0.39 Hz, and the following measures were obtained for each referential lead: the absolute (AP) and relative (RP) powers in each of four frequency bands: delta (0.5-3.5 Hz), theta (3.6-7.5 Hz), alpha (7.6-12.5 Hz) and beta (12.6- 19 Hz). The ranges of these bands were selected according to normative data[27] provided by MEDICID 3E.

NFB and placebo treatment

Z values for the theta/alpha ratio were calculated in the following manner: absolute power in each band was computed for the average reference, and the geometric power[36] was subtracted from the crosspectral matrix. The value log(theta AP/alpha AP) was computed. Z values for this logarithm were calculated by means of

$$Z=(\log(\text{thetaAP}/\text{alphaAP})-\mu)/\sigma$$

where μ and σ are, respectively, the mean value and the standard deviation of the normative sample of the same age as the subject. Two or three EEG recordings were made from each child in order to select the lead where the most abnormal Z value of the theta/alpha ratio was found in two recordings. On the basis of the EEG activity at this lead, NFB or placebo treatment was applied, depending on the group to which the child belonged.

NFB was conducted using an NFB program adapted to the MEDICID IV recording system and software. EEG recordings were obtained from a monopolar lead, situated at the place with the most abnormal theta/alpha ratio, rela-

Table 1

Experimental group

Identity	Age	IQ	ADHD score from TOVA	Sex
W003	10.56	70	-1.44	M
W008	10.30	78	-4.72	F
W024	8.44	102	-0.98	M
W035	10.01	84	1.32	M
W048	7.26	72	-0.41	M
MEAN	9.3	81.2	-1.2	
SD	1.4	12.9	2.2	

Table 2

Control group

Identity	Age	IQ	ADHD score from TOVA	Sex
W005	10.81	75	0.6	M
W009	8.80	70	-2.59	M
W031	7.83	92	-0.95	M
W041	11.36	100	0.22	M
W052	9.77	80	-2.15	F
MEAN	9.7	83.4	-1.0	
SD	1.4	12.4	1.4	

tive to linked earlobes. Threshold level was selected every 3 minutes so that the subject obtained the reward (a 500 Hz tone) between 60% and 80% of the time. Throughout the recording, the ratio was computed for 20 msec every 5 msec and compared with the threshold. If the ratio was lower than the threshold, the reward was given. Subjects were told to maintain the tone as much as possible, because it meant that their brain was working well.

In placebo treatment, all conditions were exactly as in NFB, except that in this case the reward and its duration were random, noncontingent on EEG activity. After a period of noncontingent reinforcement, NFB treatment was applied to these children.

Each child received 20 sessions of training (each of which lasted 30 min) over a period of 10 to 12 weeks. At the beginning of each session, the child was told that if his/her performance was good, he/she would receive candies at the end of the session. At the beginning of the treatment, children were told that those who participated in all 20 sessions would receive a prize (a toy).

Immediately after 20 NFB sessions, TOVA and EEG were carried out again. Two months later a second EEG was recorded after NFB treatment. A second application of WISC was carried out 6 months after the first application, in accordance with WISC recommendations.

Statistical analysis

Sample sizes are very small and normal distribution is not warranted, so parametric analyses are not appropriate. The statistical significance of the differences between behavioral and EEG data before and after treatment was assessed by a multivariate nonparametric permutational test[37] for dependent variables. For EEG data, the global null hypothesis tested the equality between power spectra recorded before and after NFB treatment at all leads, and the marginal null hypothesis tested the equality of the power at a particular lead. We performed separate analyses for AP, RP in each band, and for the theta/alpha ratio. For TOVA data we performed two different analyses: one for ADHD score and another for percentage of omissions (%O), percentage of false alarms (%FA) and average of response time (RT). In WISC we performed 3 analyses: a) total IQ, b) verbal and performance scales, and c) the 10 items included in WISC. As in EEG, in all behavioral analyses, global null hypothesis tested the equality of all variables included in each analysis, and the marginal null hypothesis tested the equality of particular variables.

The EEG recordings before and after NFB were evaluated by visual inspection by two independent electroencephalographers, who did not know if the EEG was recorded before or after NFB, or if it corresponded to members of the control group or the experimental group. The design met the requirements of the "double blind." When the two electroencephalographers had different opinions about an EEG, the records were evaluated by a third electroencephalographer.

RESULTS

Tables 1 and 2 show the age, IQ, sex and ADHD score from TOVA before treatment for experimental and control groups, respectively.

Behavioral results

In each group, the scores before and after NFB treatment were compared. Results are shown in Figure 1. Table 3 shows the mean and standard deviation of IQ values before and after treatment in both groups. Total IQ (p=0.02), verbal (p=0.03) and performance (p=0.04) WISC scores increased significantly only in the experimental group. The global hypothesis for the analysis of the 10 items from WISC was not significant, but the marginal hypothesis produced a significant increase in the "ordering of pictures" item (p=0.03). Three out of 5 children in the experimental group improved their total IQ, while for 2 of them it remained the same. Significant increases in ADHD score from TOVA were observed in the experimental group. There were no important behavioral changes in the control group.

EEG results

In the experimental group, leads with the most abnormal theta/alpha ratio in each child were T3 (3 cases), P4 and F4. No significant differences were found between the EEG recorded before treatment and the EEG recorded immediately after treatment was finished. The following

Figure 1
WISC-R values before and after NFB treatment in experimental and control groups. Significant differences (*) were observed only in the experimental group. V= verbal scale, and P= performance scale.

Table 3
WISC-R scores before and after treatment

	EXPERIMENTAL GROUP		CONTROL GROUP	
	BEFORE	AFTER	BEFORE	AFTER
Verbal score	86.2±15.82	92.6±20.06	89.4±16.96	79.0±10.22
Performance score	77.2±13.00	85.6±14.93	78.4±10.64	80.6±2.97
WISC-R	81.2±12.85	88.4±17.90	83.4±12.36	78.0±6.89

Table 4
NFB effect on EEG variables

		Before > After		After > Before	
EEG parameter	Frequency band	Global Prob.	Leads p<0.05	Global Prob.	Leads p<0.05
EXPERIMENTAL GROUP					
Absolute Power	Delta	0.03*	Fp1, Fp2, F3, F4, C3, C4, P3, P4, F8, T4, T6, Fz, Cz, Pz	0.98	
	Theta	0.03*	Fp1, Fp2, F3, F4, C3, C4, P3, F7, F8, T4, T5, T6, Fz, Cz, Pz	0.91	
	Alpha	0.03*	P4, T4	0.69	
	Beta	0.01*	Fp1, Fp2, F3, F4, P4, F7, F8, T4, Fz	0.99	
Relative Power	Delta	0.1	C3, O1, T3, T5	0.97	
	Theta	0.19	T6	0.68	
	Alpha	0.93		0.13	T6
	Beta	0.63		0.25	
(AP theta/AP alpha) ratio		0.16		0.94	
CONTROL GROUP					
Absolute Power	Delta	0.16	F4, C3, O1, O2	0.97	
	Theta	0.10	O1, T6	0.88	
	Alpha	0.31	T5	0.66	
	Beta	0.013	O1, T5	0.54	
Relative Power	Delta	0.03*	Fp1, Fp2	0.79	
	Theta	0.10	T6	0.32	
	Alpha	0.64		0.32	T6
	Beta	0.97		0.10	
(AP theta/AP alpha) ratio		0.29	Cz	0.78	

* "Leads p<0.05" indicates those places that show significant differences in Marginal Hypothesis

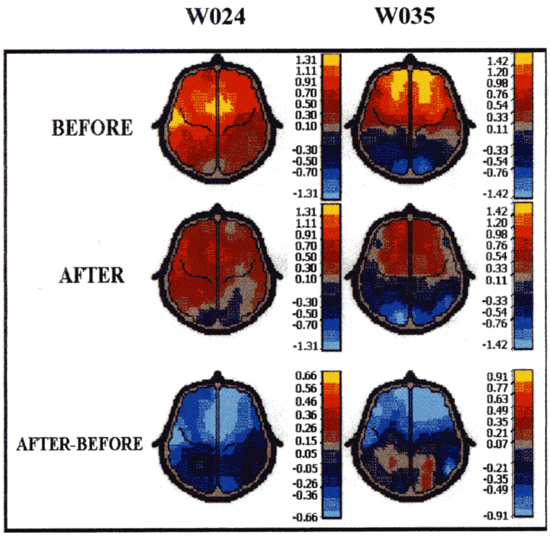

Figure 2:
Maps of the quotient (theta AP/alpha AP) in 2 children (W024 and W035) before and after two months of NFB treatment. Subjects W024 and W035 received NFB on the basis of T3 and F4 activity, respectively. At the bottom of the figure, the differences (after-before) treatment are shown. Note that T3 in W024 and F4 in W035 are included within the region of maximum quotient reduction.

Table 5

EEG interpretation by visual inspection

GROUP	IDEN	BEFORE	AFTER
EXPER.	W003	Brief general paroxysms of theta waves	Normal
	W008	Parietal paroxysmal activity (only in Laplacian montage)	Normal
	W024	Slight generalized paroxysmal activity	Normal
	W035	Slight anterior paroxysmal activity	Normal
	W048	Moderate generalized slow waves and Severe generalized paroxysms	Severe generalized paroxysms
CONTR.	W005	Slight generalized paroxysmal activity	Slight generalized paroxysmal activity
	W009	Moderate generalized paroxysmal activity	Severe generalized slow waves and Severe generalized paroxysms
	W031	Slight generalized paroxysmal activity Slight generalized slow waves	Slight generalized paroxysmal activity Slight generalized slow waves
	W041	Slight generalized slow waves	Normal
	W052	Slight generalized slow waves	Slight generalized paroxysmal activity

results, representing the comparison between EEG before and 2 months after NFB treatment.

After NFB, in the test of the global hypothesis, significant AP reduction in all bands was found in the experimental group ($p<0.05$), whereas in the control group only delta RP was significant ($p<0.05$). When marginal hypotheses were tested, significant changes ($p<0.05$) in many leads were observed (Table 4): in the experimental group, delta AP decreased in Fp1, Fp2, F3, F4, C3, C4, P3, P4, F8, T4, T6, Fz, Cz and Pz; theta AP, in Fp1, Fp2, F3, F4, C3, C4, P3, F7, F8, T4, T5, T6, Fz, Cz and Pz; alpha AP only in P4 and T4; beta AP decreased in Fp1, Fp2, F3, F4, P4, F7, F8, T4 and Fz; delta RP decreased in C3, O1, T3 and T5; theta RP and the theta /alpha ratio decreased in T6, while alpha RP increased in T6. In the control group, delta AP decreased in F4, C3, O1 and O2; theta AP, in O1 and T6; alpha AP in T5; beta AP in O1 and T5; delta RP in T6 and (Theta AP/Alpha AP) ratio in Cz.

In the experimental group, in 4 out of 5 children the quantitative EEG showed changes compatible with maturational improvement (AP decrease mainly in delta and theta bands, decrease of delta and theta RP and increase of alpha RP, decrease of theta/alpha AP ratio). In the control group, 2 children showed a maturational improvement, another 2 showed no changes, and 1 child showed an increase in the theta /alpha ratio. Four out of 5 children in the experimental group presented changes in the EEG, and in these 4 the changes were diffuse, but only in 2 of them was the location where the treatment was given involved in the area of maximum change (Figure 2)

In Table 5 the results of EEG interpretation by visual inspection are shown. In 17 out of 20, the two electroencephalographers' opinions coincided. All the children had some abnormality in the EEG before NFB treatment. In the control group, only 1 out of 5 showed a normal EEG after NFB, whereas in the experimental group after NFB 4 out of 5 children had a normal EEG. The child in the experimental group who continued to have severe generalized paroxysms was the one who showed no improvement in either quantitative EEG or WISC.

Computed tomography results

No important alterations were observed.

DISCUSSION

There are two reasons to apply NFB with eyes closed: a) normative data at rest with eyes closed has been validated in several studies,[38-40] and b) this condition facilitates alpha reinforcement.[41]

The theta AP/alpha AP ratio has been demonstrated to be a useful means of characterizing EEG abnormalities in children.[30] It shows several advantages: on the one hand, this quotient eliminates the major artifact sources in EEG recordings, eye movements and muscular activity. On the other hand, the use of this quotient and any other AP quotient eliminates approximately 40% of interindividual variability of EEG AP.[42,43]

In clinical practice, most NFB treatments include 40-60 sessions. Rossiter and LaVaque[44] demonstrated that 20 sessions of an NFB program significantly reduces the cognitive and behavioral symptoms of AD/HD. In this paper, it is shown that 20 sessions produced positive results in LD children with abnormal theta/alpha EEG ratio.

In four out of five children of the experimental group, NFB treatment was effective both behaviorally and electroencephalographically. This is consistent with results previously reported, which show that in 20% of the subjects NFB treatment did not have the expected effect[6]; this might be due to structural abnormalities. For this reason, Computed Tomographies were performed on the children, since brain lesions have been found in some LD children with EEG abnormalities.[45] However, in this study no important Computed Tomography alterations were observed.

Improvement in TOVA scores and WISC-R performance after NFB treatment support previous reports including subjects with AD/HD and LD.[5,13,46,47] Changes in WISC-R and TOVA performance, and no changes in EEG immediately after the NFB treatment are difficult to explain, as we primarily expected changes in EEG, and as a consequence behavioral changes. The same result has been reported by Lubar et al.[5] in AD/HD, and by Sterman[48] in epilepsy. Lubar et al.[5] reported behavioral improvement without EEG changes in a group of subjects, although a better behavioral improvement was observed in those subjects that showed positive EEG changes. However, Sterman[48] reported that not all patients who reduced seizure rate showed expected EEG changes, and a few patients who showed EEG changes experienced little clinical improvement. One possible explanation is that NFB modifies the function of deep brain structures, which are reflected in behavior, but not in the postsynaptic cortical activity. According to Thatcher et al.[49] and Nunez,[50] 97% of the cerebral activity that we record as EEG originates within the cortex.

There are, however, groups of cells in the thalamus that modulate cortical activity.[51] Lubar[52] considered that although thalamic pacemakers produce different brain rhythms, depending on which cortical loops they activate, changes in the cortical loops as a result of learning, emotion, motivation or neurofeedback can change the firing rate of thalamic pacemakers and hence change their intrinsic firing pattern. These functional changes may later modify the EEG by modulation of thalamo-cortical circuits. As behavioral changes were related to attention, we may suppose that noradrenergic brainstem nuclei and their projections to frontal lobes may be the locus for the immediate changes. This explanation is supported by the fact that NFB is an indication for attentional disorders.

All EEG changes observed 2 months after treatment in both groups are compatible with age increase; however, the experimental group showed a greater number of regions with significant changes, and these changes were greater in magnitude. These results suggest that NFB of (theta AP/alpha AP) ratio produce an important spurt in EEG maturation, and as a consequence, behavioral improvement.

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