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Iron supplementation brings up a lacking P300 in iron deficient children

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Abstract

Objective: A decrease in iron concentration is accompanied by alterations in catecholaminergic and GABAergic neurotransmission systems, important in learning, memory and attention. It was hypothesized that iron deficient children would present attention deficits. A visual-event related potentials (ERPs) study is presented using an oddball paradigm in order to determine the P300 in ID children.

Methods: After medical examination, blood was obtained from 201 children for a complete hematological study. Two groups were selected, iron deficient (ID) (serum iron <60 μg/dl) and control (C) (serum iron >60 μg/dl). In both groups ERPs were recorded while executing a continuous performance task (oddball paradigm). Afterwards iron levels were restored in ID children by iron supplementation (ID–IS group) and all tests reapplied.

Results: ID children almost lacked a P300 in central and parietal regions. After iron supplementation, P300 clearly became evident although its Pz amplitude remained smaller compared to C children.

Conclusions: A clear and strong correlation was found between ID and attention alterations in children. Iron supplementation nearly brings the P300 to normal levels although it is not known if the P300 difference in Pz is due to other nutritional/environmental deficits or to developmental psychomotor impairments in ID children.

Significance: It has been long known that iron deficient children have cognitive impairments but there is an insufficient number of electrophysiological works allowing to identify the source of this problem. In this work an attention deficit is demonstrated in ID children through a severely reduced P300, which recovers substantially after iron supplementation.

Keywords: Iron deficiency; Children; Psychomotor development; P300; ERPs; Attention

1. Introduction

Alterations in brain iron concentration have been associated with delays in psychomotor development and impairment of intellectual capabilities in children (Andrews, 1999; Beard, 2001; Beard et al., 2003; Desforges, 1993; Grantham-McGregor and Cornelius, 2001; Lozoff et al., 2000; Otero et al., 1999; Pless and Lipton, 1993; Pollitt, 1994; Walter, 1993). Cerebral iron homeostasis is necessary for its normal functioning and a decrease in iron concentration is accompanied by alterations in the conduction of cortical fibers and changes in dopaminergic, serotonergic and GABAergic neurotransmitter systems as well as in myelin formation (Beard, 2001; Beard and Connor, 2003; Beard et al., 1994; Ben-Shachar et al., 1993; Clarke et al., 1991; Connor and Menzies, 1996; Erikson et al., 2000; Erikson et al., 2001; Kwik-Uribe et al., 2000; Nelson et al., 1997).

Although a considerable number of works have studied the relationship between iron status and cognition/behaviour (Atkins and Pollitt, 1997; Beard et al., 2003; Clarke et al., 1991; Connor and Menzies, 1996; de Andraca et al., 1990; Desforges, 1993; Florencio, 1988; Grantham-McGregor and Cornelius, 2001; Hurtado et al., 1999; Logan, 1999;

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Lozoff et al., 1991; Lozoff et al., 2000; Pless and Lipton, 1993; Pollitt, 1994; Walter, 1993; Walker et al., 1998) the topic, however, remains controversial (Logan, 1999).

An association between iron deficiency (ID) anemia and poor cognitive and motor development with behavioral problems has been observed; significant concurrent associations between hemoglobin concentrations and measurements of cognitive development or school achievement (Atkins and Pollitt, 1997; Clarke et al., 1991; de Andraca et al., 1990; Florencio, 1988; Hurtado et al., 1999; Lozoff et al., 1991) have been established; longitudinal studies consistently indicate that children who have suffered anemia during infancy show poor cognition, school underachievement and behavioral problems into middle childhood (de Andraca et al., 1990; Hurtado et al., 1999; Lozoff et al., 1991; Lozoff et al., 2000; Wasserman et al., 1994).

In a previous work (Otero et al., 1999), 25 ID non-anemic children between the ages of 6 and 12 years showed worsened intellectual performance and also higher absolute power in slow bands of the EEG compared to their iron replete contemporaries. These results indicate that a strong relationship between ID and intelligence quotient in addition to learning capacity, as well as with changes in the EEG frequency spectrum exists. However, until now the mechanisms involved in conduct alterations and in intellectual disabilities related to ID remain to be answered.

Considering the fact that the basal ganglia and particularly the caudate nucleus and dopaminergic systems are importantly involved in attention processes (Beard and Connor, 2003; Beard et al., 1994; Brozoski et al., 1979; Durstewitz and Seamans, 2002; Erikson et al., 2000; Erikson et al., 2001; Tanaka, 2002) and that the highest brain iron deposits are located precisely in basal ganglia, it was hypothesized that children with reduced iron stores would show attention alterations, measurable with psychological and electrophysiological tests. In our previous study (Otero et al., 1999) we found more delta activity in frontal leads of ID children, regions, which critically participate in attention processes (Coull, 1998; Polich, 1990). In order to assess possible alterations in attention, this paper presents an event-related study during a continuous performance task with a group of ID, non-anemic children.

2. Materials and methods

2.1. Sample

Before starting the study, permission was obtained from the local education authority (Secretaría de Educación, Cultura y Bienestar Social) and school directors to talk to parents of 8–10 years old children, subjects of this study, from seven primary, government-funded schools located in Toluca City, State of Mexico and surrounding suburbs. The parents were informed on the objectives, procedures and risks of this research and a written and signed approval for the participation of their children was requested.

The study was performed in two stages. In the first one a complete medical examination was carried out in an initial sample of 201 children from whom 10 ml of blood were obtained for a complete hematological study. Iron, transferrin, ferritin, transferrin iron saturation and soluble transferrin receptor (Stoltzfus et al., 1997) were determined and according to the results obtained, two groups were selected: iron deficient (ID) (serum iron <60 μg/dl) and control (serum iron >60 μg/dl). In the initial sample there were 28 ID and 173 control, iron-replete children (C group). All those children with any important pathological background or under medical supervision were excluded from the study and none of the children included in the study manifested serious illnesses or infections. Parasitism was an unlikely cause of malnutrition due to regular supervision and treatment by the local medical authority. The hematological results were handed out to parents and those children showing abnormal hematological indices or EEG anomalies ($n = 2$) were referred to a local hospital for clinical follow up. In the second stage, ID children were iron supplemented (ID–IS group) under medical supervision and after restoration of normal metal levels all tests were reapplied. Of 28 ID children, only ten (6 boys and 4 girls) finished the study and were matched with another 10 C children (5 boys and 5 girls) according to age and sociocultural status, determined this after applying a scale of psychosocial risk (Otero, 1997). The 10 ID children who finished the study were those who completed iron medication and their parents consented on repeating the hematological and ERPs studies. The rest either did not complete all tests or did not consent on repeating the studies.

The school performance of children was qualitatively assessed according to the grades obtained in mathematics and Spanish, considered the most difficult study subjects. C children obtained grades between 80–90% while ID children performed between 60–70%, with 60% considered the minimum acceptable. Although ID children are not failing these two subjects, their achievement is generally lower compared to C children.

2.2. Procedure

From each child of both groups, C and ID, visual events related potentials (ERPs) were EEG recorded while executing a continuous performance task using an oddball paradigm, generated this last one through the Mind Tracer system (Neuronics, México). In the oddball paradigm, color drawings of different animals were individually and sequentially presented in a computer's screen. The child was requested to press the right button of the mouse on the presentation of all images (frequent stimuli) except the crab (infrequent stimulus), situation in which the child was asked to press the left button of the mouse. Stimulus presentation lasted 300 ms; the interval between stimuli was of 2000 and 700 ms was the maximum time allowed for a response (Fig. 1). The task consisted of completing two blocks of 200 images each with a 20% presentation probability of the infrequent stimulus. Before starting each child had a short

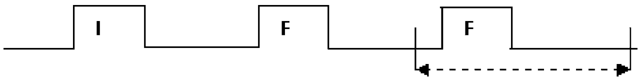

Fig. 1. Oddball paradigm design. Stimulus presentation, frequent (F) or infrequent (I) (20% probability of presentation), lasted for 300 ms. The interval between stimuli was of 2000 ms. The arrow heads (1000 ms span) indicate the window taken for analysis, starting at 100 ms pre-stimulus (Not in scale). See text for more details.

adaptation trial of the task assigned. Recording of ERPs was done in the EEG 10–20 derivations system with a monopolar montage and using linked ear lobes as reference. Twenty artifact-free EEG segments of 1000 ms each (100 ms pre-stimulus) (Fig. 1) were visually selected for averaging and only those windows corresponding to correct answers were taken into account. The Mind Tracer software allowed us to mark all windows corresponding to correct answers, both for infrequent and frequent stimuli. After marking these, between 20 and 25 artifact-free windows were selected and averaged separately for each stimuli (infrequent and frequent). The ERPs grand average was computed for each group and separately for frequent and infrequent stimuli. ID children were later supplemented with elemental iron (5 mg/kg/day) and clinical check ups carried out every 4 weeks for not more than 3 months. After iron supplementation a second hematological study was performed and all blood and ERPs tests repeated.

2.3. Statistical analysis

For the analysis of hematological variables a Mann-Whitney test was used to assess differences between groups and a Wilcoxon test applied for the analysis of within group differences. ERPs were analyzed using a multivariate non-parametric permutational test (Galán et al., 1997) to assess differences within groups (infrequent vs. frequent stimulus and ID vs. ID–IS) and between groups (C vs. ID; C vs. ID–IS). This last test was used because MANOVA and repeated measures ANOVA are limited in ERP studies analysis due to violations of their statistical assumptions: firstly, the presence of many variables and few subjects and, secondly, the non-observance of a normal distribution in the sample. The multivariate non-parametric permutational test proves one global null hypothesis and two marginal null hypotheses. The global null hypothesis tests the equality between ERPs recorded in two different conditions (for example, infrequent vs. frequent; control group vs. ID group) in all derivations and in all latencies. The marginal null hypothesis tests the equality of the ERP amplitude (1) at a particular latency in different derivations and (2) for different latencies for a given derivation (Galán et al., 1997).

3. Results

3.1. Hematological study

In Tables 1 and 2 are presented the hematological variables with statistically significant differences between C and ID children (Table 1) and between ID and ID–IS (Table 2). Hemoglobin, hematocrit and red blood cells values were significantly lower in ID than in C. In ID these values were actually slightly under reference values for Toluca City (2,600 m over sea level), however, almost all other iron related variables were abnormal, indicating that the ID group was in fact iron deficient but not anemic. It can be seen in Table 2 that after iron supplementation the hematological parameters of ID children reached normal values (ID–IS group).

3.2. Behavioural study

In Table 3 are presented the mean and standard deviation for the correct answers reaction times when either frequent or infrequent stimuli were presented. The number of correct answers for the infrequent stimuli for the three groups (C, ID and ID–IS) are also shown. In relation to reaction times we

Table 1
Hematological variables

	Controls				Iron deficients				
	Min	Max	Mean	SD	Min	Max	Mean	SD	$P<$
Hb (gr/dl)	14.4	15.5	14.9	0.49	11.9	12.9	12.4	0.26	0.001
Ht (%)	41.5	48.3	44.2	2.60	34.3	38.3	36.2	1.40	0.001
RBC (1×10^6/ml)	4.80	5.90	5.30	0.40	3.80	4.80	4.20	0.30	0.010
MCV (fl)	83.6	91.6	89.3	3.50	78.0	85.8	81.4	2.20	ns
Fe (μg/dl)	80.0	132.0	105.6	20.0	55.0	65.0	58.4	2.80	0.000
Ferr (μg/l)	72.0	146.0	116.0	28.3	13.4	92.0	36.4	15.3	0.002
STfR (nmol/l)	12.6	19.2	15.4	2.50	19.0	25.6	21.6	2.80	0.002
TfSat (%)	33.9	45.2	39.6	3.90	22.1	33.3	25.0	3.80	0.001

Mean, standard deviation, minimum and maximum values for Control and Iron Deficient groups ($n=10$ for each group) after applying a Mann Whitney U Test. Abbreviations: Hb, hemoglobin; HT, hematocrit; RBC, red blood cells; MCV, mean corpuscular volume; Fe, serum iron; Ferr, ferritin; STfR, soluble transferrin receptor; TrfSat, Transferrin percentage of iron saturation.

Table 2
Hematological variables

	Before medication				After medication				
	Min	Max	Mean	SD	Min	Max	Mean	SD	$P <$
Hb (gr/dl)	11.9	12.9	12.4	0.26	13.3	14.6	13.9	0.45	0.005
Ht (%)	34.3	38.3	36.2	1.40	39.1	45.6	42.8	2.06	0.005
RBC (1×10^6/ml)	3.80	4.80	4.20	0.30	4.60	5.20	4.90	0.23	0.010
MCV (fl)	78.0	85.8	81.4	2.20	80.0	90.0	85.9	3.31	0.037
Fe (μg/dl)	55.0	65.0	58.4	2.80	69.0	134.0	91.9	22.3	0.005
Ferr (μg/l)	13.4	92.0	36.4	15.3	104.7	317.4	204.8	91.5	0.001
STfR (nmol/l)	19.0	25.6	21.6	2.80	8.50	20.4	13.2	3.50	0.005
TfSat (%)	22.1	33.3	25.0	3.80	18.3	59.8	31.9	12.6	0.049

Mean, standard deviation, minimum and maximum values for Iron Deficient and Iron Supplemented group ($n = 10$ for each group) after applying a Wilcoxon test for paired samples. Abbreviations: Hb, hemoglobin; HT, hematocrit; MCV, mean corpuscular volume; Fe, serum iron; Ferr, ferritin; STfR, soluble transferrin receptor; TrfSat, Transferrin percentage of iron saturation.

found that the median gave the most adequate measure of these for which reason a median test (Mann-Whitney test) was applied to compare results between groups. No significant differences were found in relation to reaction times when C vs. ID, ID vs. ID–IS and C vs. ID–IS were compared. On the other hand, the number of correct answers was significantly higher in C than in ID, while no differences were found between C and ID–IS (Mann-Whitney test). The ID–IS group, similarly to the C group, showed a higher number of correct answers than ID (Wilcoxon test).

3.3. ERPs study

EEG recording was made according to the 10–20 system for the three study groups: C, ID, ID–IS. In Fig. 2 are shown the ERPs grand averages for the infrequent and frequent stimuli in C3, C4, P3, P4, Cz and Pz derivations which were the only ones obtained with statistically significant differences. It is noticeable how in the C group these derivations present a prominent P300, which comparatively is nearly absent in ID children. After iron supplementation, however, it is observed in the ID–IS group a prominent appearance of a P300, although of less amplitude than in C. In Table 4 mean amplitude and latency values as well as amplitude differences between infrequent and frequent stimuli for the three groups are shown.

Applying the multivariate non-parametric permutational test (Galán et al., 1997) it was found a significant global difference ($P < 0.001$) in the C group in derivations C3, C4, P3, P4, Cz and Pz in the latencies comprehended between 250 and 545 ms (Fig. 3A). In the ID group there were no global differences ($P < 0.53$) but only a slight significant difference observed at a latency of 175 ms in F8 (Fig. 3B). In the latter derivation, neither the regional localization nor the latency correspond to P300, for which reason we consider this an odd, non-significant result. After iron supplementation, a global difference ($P < 0.02$) between infrequent and frequent stimuli appeared in the latencies comprehended between 300 and 500 ms in C3, C4, P3, P4, Cz and Pz in the ID–IS group (Fig. 3C).

Finally, a comparison of ERPs to infrequent stimuli between groups was made. Comparing the ID and the ID–IS groups (Fig. 3D), a significant global difference ($P < 0.001$) was obtained in latencies at approximately 250 ms and between 400–550 ms, while comparing C and ID–IS no global differences ($P < 0.13$) between them were found except one significant difference ($P < 0.05$) in Pz at latencies between 250 and 500 ms (not shown).

4. Discussion

ID is believed to affect up to 50% of the world's population, making it the most common global nutritional deficiency (WHO, 1998; Williams and Goldman-Rakic, 1995). Poverty, parasitism, congenital diseases and inadequate nutritional habits lead to ID, anemia or both, insuficiencies associated with a wide variety of adverse

Table 3
Behavioural results

		ICRT	IIRT	FCRT	FIRT	NCRI
C	Mean	518.6	490.1	537.1	711.4	76.0[a]
	SD	53.4	146.2	81.1	422.8	3.7
ID	Mean	578.3	587.6	504.2	616.1	48.2
	SD	49.8	103.8	65.0	83.4	18.5
ID–IS	Mean	600.7	441.4	483.9	788.6	69.8[b]
	SD	129.7	237.7	71.3	470.7	10.3

[a] Significant difference C vs. ID ($P < 0.019$).
[b] Significant difference ID vs. ID–IS ($P < 0.028$).

ICRT, Infrequent Correct Reaction Time: reaction time for correct responses to infrequent stimuli; IIRT, Infrequent Incorrect Reaction Time: reaction time for incorrect responses to infrequent stimuli; FCRT, Frequent Correct Reaction Time: reaction time for correct responses to frequent stimuli; FIRT, Frequent Incorrect Reaction Time: reaction time for incorrect responses to frequent stimuli; NCRI, Number of Correct Responses to the Infrequent stimuli.

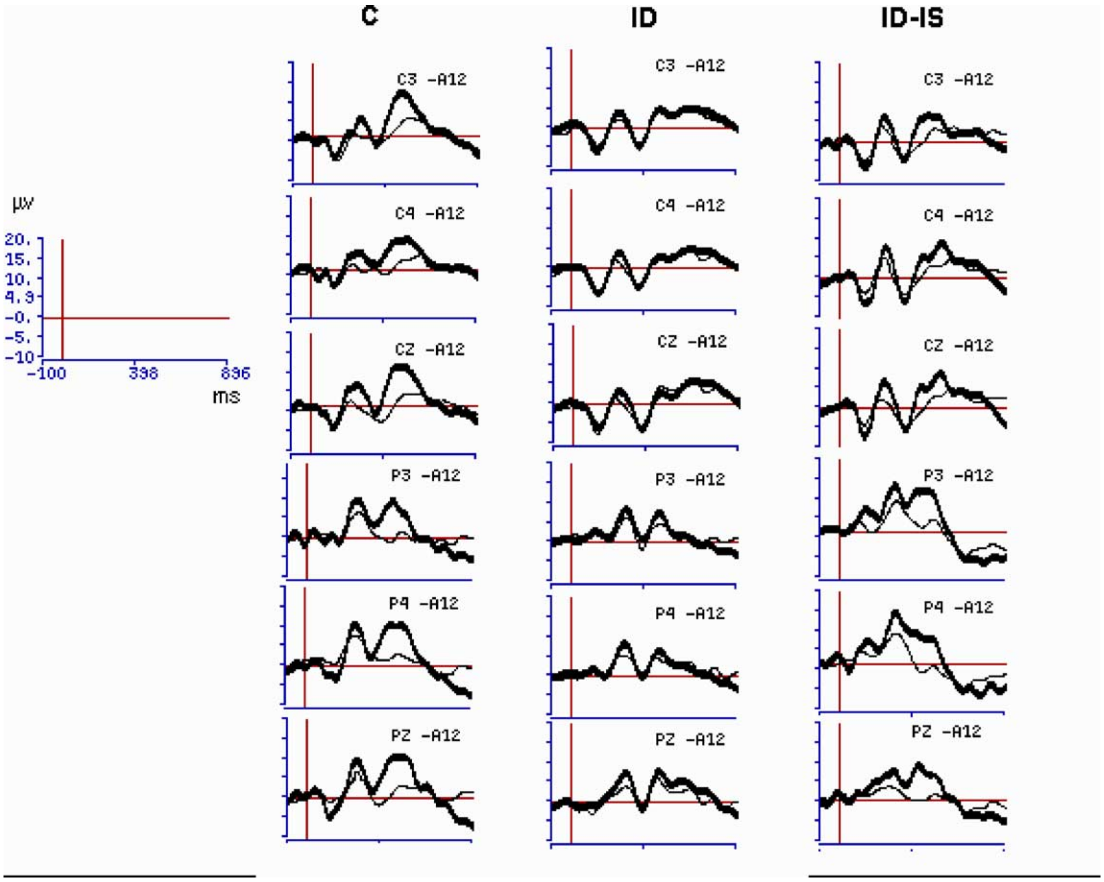

Fig. 2. Visual ERPs for frequent (thin trace) and infrequent (broad trace) stimuli. C, control group; ID, iron deficient group and; ID–IS, iron deficient-iron supplemented group. Note that in the ID group the thick and thin traces are almost overlapped. ms, miliseconds; µv, microvolts.

health outcomes. In children it includes delayed physical and cognitive development, lower IQ and poor school achievement (Atkins and Pollitt, 1997; de Andraca et al., 1990; Florencio, 1988; Hurtado et al., 1999; Logan, 1999; Lozoff et al., 2000; Lozoff et al., 1991; Walker et al., 1998). However, the biological source of lower test scores and behavioral changes in infancy and early school years is unclear.

The children who participated in the study were actually healthy. The sample was collected neither from a hospital nor from a medical clinical service but from local schools. Aproximately 15% (28 out 201) showed ID without anemia in whom the most probable cause of ID is likely to be nutritional. Legumes and corn are part of the basic staple diet and although the iron content of legumes is high the biodisponibility is poor due to the presence of phytates, an important inhibitor of iron absorption (Sandberg, 2002). Apart from ID, the children were healthy in every other aspect. Leukocytes counting was normal in all cases; our own paediatric supervision and the local medical

Table 4
Mean values of amplitude and latency of infrequent and frequent stimuli at P300 latencies

	C					ID					ID–IS				
	Infrequent		Frequent		I–F	Infrequent		Frequent		I–F	Infrequent		Frequent		I–F
	Amp	Lat	Amp	Lat		Amp	Lat	Amp	Lat		Amp	Lat	Amp	Lat	
C3	10.9	486	5.2	517	5.7	4.8	470	4.3	478	0.5	7.2	474	3.0	494	4.2
C4	7.5	494	2.9	529	4.6	2.8	470	2.8	462	0.0	6.8	537	3.4	548	3.4
Cz	10.1	486	4.5	548	5.6	4.0	470	2.8	470	1.2	7.7	540	3.9	540	3.6
P3	10.5	451	3.0	505	7.5	4.8	474	3.5	478	1.3	7.0	450	2.4	505	4.6
P4	12.1	521	3.4	310	8.7	4.9	455	3.2	470	1.7	8.0	521	2.8	501	5.2
Pz	12.0	431	4.6	505	7.4	7.3	470	6.4	466	0.9	8.8	494	3.8	509	5.0

Amp, mean amplitude; Lat, mean latency; I − F amplitude difference between infrequent and frequent stimuli.

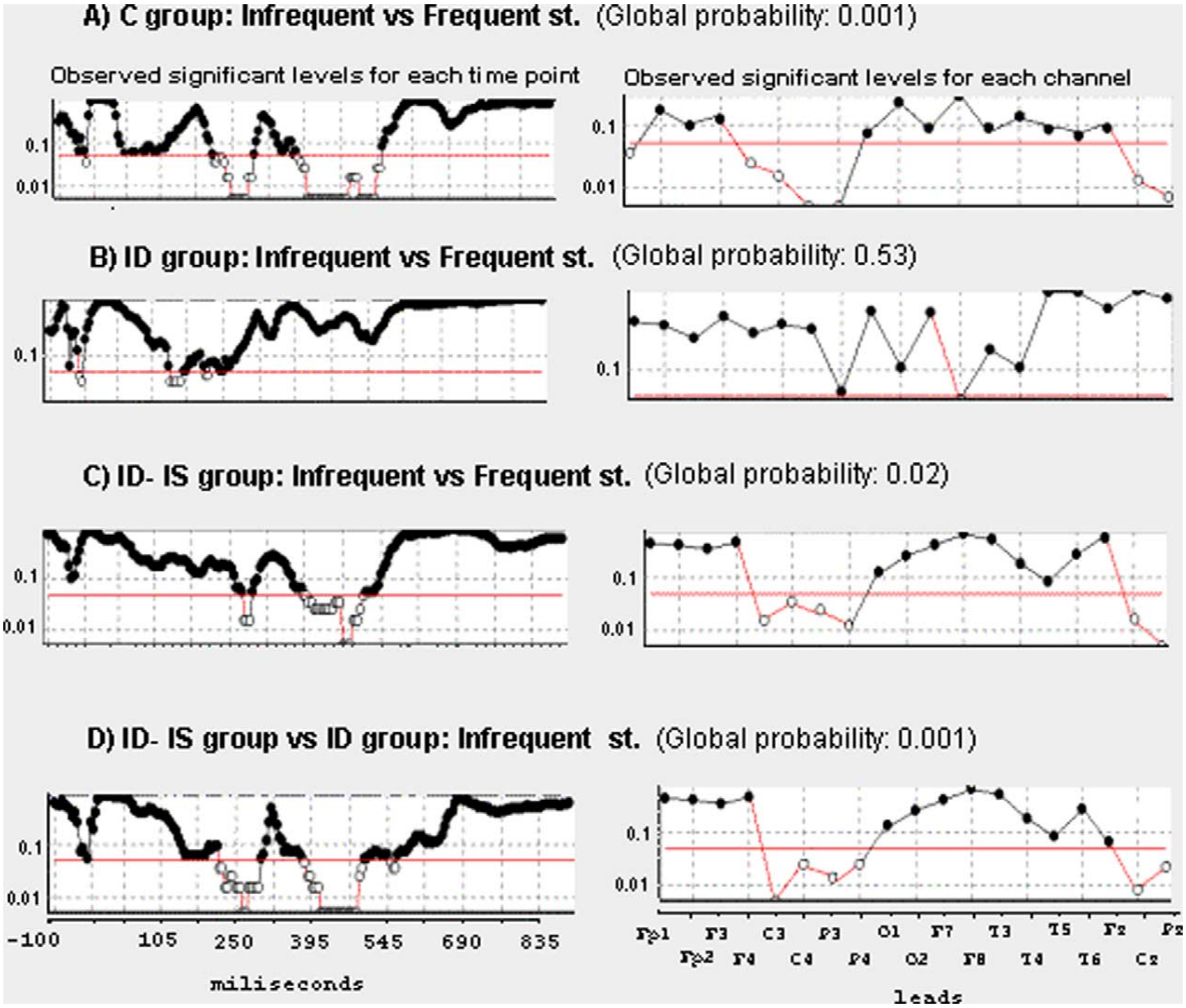

Fig. 3. Multivariate analysis of non-parametric permutations. Comparison between frequent and infrequent stimuli (st.). (A) control group; (B) iron deficient group; (C) iron deficient-iron supplemented group and; (D) iron deficient-iron supplemented group vs. iron deficient group. The significant levels for each time point (latencies) and for each channel (derivation) are shown. The empty circles in the plots show significant differences, while the horizontal line marks the alpha value, equal to 0.05.

supervision, which includes routine treatment against parasitic infections, indicated that no other diseases would confound our findings: no infectious, neurological or congenital problems were detected.

A close relationship between the electrophysiological and behavioural results was found in this work. There were no significant differences in reaction times between C and ID and between C and ID–IS groups, neither there were differences between the P300 latencies. It is well known that reaction times and P300 latency increase with the difficulty of the task (Coull, 1998; Picton, 1992; Polich, 1990). In our study the task was simple which could explain why there were no differences in reaction times nor in P300 latencies between groups. On the other hand, C children had more correct answers compared to ID and this is related to differences in P300 amplitude. Since the higher number of mistakes in the continuous performance task was made by the ID group, this is an evidence indicating that this children cannot sustain attention continuously. This also shows that the ERPs constitute an electrophysiological evidence of an attentional deficit in the ID group.

It is well known that P300 has a broad centroparietal scalp distribution, typically elicited by oddball stimuli (Bernal-Hernández, 1994; Harmony, 1989; Silva-Pereyra et al., 2001). The results of this study present a very strong proof that in ID children the P300 is almost non-existent. However, iron supplementation and restoration of hematological normal values brings up the appearance of a considerable P300 with an amplitude very near to that of iron replete children, although still smaller in Pz ($P < 0.05$).

The oddball task was not repeated in C group because parents did not consent on it, for which reason we cannot completely rule out the effect of repetition on these results. However, recording in all derivations of the 10–20 system, significant changes appeared exclusively in those derivations and latencies corresponding to P300 after iron medication. These results strongly suggest that recovery of iron stores is the most likely factor bringing up the P300 in the ID–IS group. Equally, the appearance of P300 occurs in parallel to the improvement of the ID–IS group in the performance task.

Considering the role of iron in many and varied cerebral metabolic activities, from mitochondrial respiration to neurotransmitter synthesis and myelination, in this work is shown a strong correlation between ID and attention alterations. This was determined by the amplitude of the P300 when ERPs were recorded in 8–10 years old children executing a continuous performance task. It is known that the amplitude of the P300 is directly related to the novelty of the stimulus while its latency appears to be related to the assessment of the stimulus and of working memory adjustment to it. Thus the P300 has been used as a means to determine attentional function. The detection of an infrequent stimulus in an oddball paradigm is associated with a parietocentral component of an event related potential (P300). Its amplitude increases when the infrequent stimuli probability is low and with higher interstimuli intervals, while the latency depends on the difficulty of the task (Coull, 1998; Picton, 1992; Polich, 1990). Importantly, in this work is shown that iron supplementation is capable of bringing back this complex function.

ID in humans and experimental rats has been consistently associated to a known display of abnormal behaviors: decreased physical activity and play in the young, lethargy and fatigue, lessened work capacity, etc. The lactation period is foreseen as a critical nutritional stage for optimal psychomotor and cognitive development with evidences suggesting that hypomyelination and alterations in dopaminergic neurotransmission could be long lasting. It is known that dopaminergic systems play an important role in learning, memory and attention processes (Brozoski et al., 1979; Costa et al., 2003; Durstewitz and Seamans, 2002; Tanaka, 2002; Williams and Goldman-Rakic, 1995), with the latter requiring a high degree of executive control. Dopaminergic neurotransmission is profoundly affected in ID newborn rats in which the *striatum* and *nucleus accumbens* are particularly susceptible depending on the post-natal time of iron deprivation. Density reductions of dopamine receptors type 1 and 2 and in dopamine transporter are reported, as well as increased concentration of extracellular dopamine (Beard, 2001; Beard and Connor, 2003; Beard et al., 2003; Erikson et al., 2000; Erikson et al., 2001; Kwik-Uribe et al., 2000).

In this study iron supplementation was capable of bringing up considerably an almost non-existent P300 in a group of ID children, although insufficiently to reach the Pz amplitude observed in the C group.

The differences between C and ID–IS groups might well not be attributable to ID itself but to other associated, unidentified factors such as micronutrient deficiencies which were not explored here. We don't know the previous nutritional history of these children, if they suffered ID in earlier developmental stages or since when they presented the ID detected here. Some authors have found that the dopaminergic function might be irreversibly affected if ID is present during the lactation period (Beard et al., 2003). It is for these reasons that now we are investigating the psychomotor development of ID infants from birth up to 12 months of age and determining critical psychomotor developmental stages in relation to ID and psychosocial risk. Although all children studied here were matched according to sociocultural status, there could be important individual differences in relation to early environmental stimulation (Otero et al., 2003). Nevertheless the correlation between blood tests results, serum iron status, response to iron medication by ID children with the electrophysiological analysis strongly suggests that ID is the main cause of altered attention in ID children. Importantly we show in this work that an attention deficit resulting from ID can be substantially corrected after iron supplementation.

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