

Iron Deficiency in Infancy is Associated with Altered Neural Correlates of Recognition Memory at 10 Years

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Objective To determine the long-term effects of iron deficiency on the neural correlates of recognition memory.

Study design Non-anemic control participants ($n = 93$) and 116 otherwise healthy formerly iron-deficient anemic Chilean children were selected from a larger longitudinal study. Participants were identified at 6, 12, or 18 months as iron-deficient anemic or non-anemic and subsequently received oral iron treatment. This follow-up was conducted when participants were 10 years old. Behavioral measures and event-related potentials from 28 scalp electrodes were measured during a new/old word recognition memory task.

Results The new/old effect of the FN400 amplitude, in which new words are associated with greater amplitude than old words, was present within the control group only. The control group also showed faster FN400 latency than the formerly iron-deficient anemic group and larger mean amplitude for the P300 component.

Conclusions Although overall behavioral accuracy is comparable in groups, the results show that group differences in cognitive function have not been resolved 10 years after iron treatment. Long-lasting changes in myelination and energy metabolism, perhaps especially in the hippocampus, may account for these long-term effects on an important aspect of human cognitive development. (*J Pediatr* 2012;160:1027-33).

Iron deficiency in utero or early in postnatal life may effect brain development in several ways. It alters the development of oligodendrocytes, not only resulting in hypomyelination of white matter, but also may be linked to changes in startle response, auditory evoked potentials, and motor function in infants.^{1,2} Early iron deficiency also neurochemically alters the function of neurotransmitters.³ Many cognitive and behavioral tasks rely on proper functioning of the nigrostriatal dopaminergic and mesolimbic pathways, which are dependent on these neurotransmitters. Additionally, iron deficiency alters metabolism of cytochrome oxidase, which negatively effects the ability of the brain to generate and use metabolic energy, perhaps especially in the hippocampus.^{4,5} Iron deficiency also causes abnormal protein scaffolding during crucial periods of synaptogenesis, which has been shown to permanently alter the formation of dendritic structures and synapses within the hippocampus.⁵⁻⁷

This study focuses on a population of Chilean school-aged children. The children were identified as having iron deficient anemia (IDA) at 6, 12, or 18 months and then treated, with the control subjects, with oral iron. After treatment, all children reached normal iron status, and control subjects were monitored to ensure that normal iron status was maintained. At 4 years of age, analyses of auditory brainstem responses and visually evoked potentials revealed that the speed of transmission through the auditory and visual systems of the formerly iron-deficient anemic (FIDA) children was still not as fast as that of the control subjects.⁸ The findings suggest that early IDA, which has been shown to decrease neuronal metabolism and negatively affect neurotransmission processes, was still not corrected by the age of 4 years despite treatment. This study, in which the participants were approximately 10 years old, uses event-related potentials (ERPs) during a recognition memory task to explore the potential neurological effects of altered cell metabolism and morphology on brain regions involved in memory processes.

The link between recognition memory and the function of the hippocampus has been demonstrated in a number of studies.^{9,10} Because the hippocampus is involved in recognition memory processing that may be disproportionately affected by early iron deficiency, there is reason to believe that hippocampal differences may underlie any observed group differences in the two groups of children. On the basis of findings from an earlier study of IDA in infants with similar experimental design,¹¹ we predicted that potential hypomyelination as a result of early iron deficiency in FIDA children would be associated with impairments in recognition memory and reduced ERP amplitudes during a recognition memory task.

d'	Sensitivity index
EOG	Electrooculography
ERP	Event-related potential
FIDA	Formerly iron-deficient anemic
IDA	Iron deficient anemia

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Methods

The children in this study were involved in earlier research in Chile on the behavioral, developmental, and neurofunctional effects of IDA. All participants were healthy, full-term infants (≥ 3 kg) with no prenatal complications or acute or chronic illnesses. Anemia was defined as venous hemoglobin level ≤ 100 g/L at 6 months and < 110 g/L at 12 and 18 months. Iron deficiency was defined as two of 3 iron measures in the iron-deficient range (mean corpuscular cell volume < 70 fL, erythrocyte protoporphyrin > 100 μ g/dL red blood cells [1.77 nmol/L]), serum ferritin < 12 μ g/L), an increase in hemoglobin level ≥ 10 g/L after 6 months of iron therapy, or both.¹² Each time an infant with IDA was identified, the next infant without anemia of the same age was invited to join the control group. Those children identified as having IDA at 6 months of age were treated with 15 mg/d of elemental iron as oral ferrous sulfate for a period of 1 year. Those children identified at 12 or 18 months were treated with 30 mg/d of oral iron supplements for a minimum of 6 months. Of the infants with post-treatment measures of iron status, IDA was corrected in all except one. Because of the high prevalence of iron deficiency in Chile, infants from the control group also were treated with iron to ensure that they did not become iron-deficient. Detailed information on the children's background and the design of the earlier studies with this sample has been published previously.^{13,14}

Participants in this study were 209 children (93 control subjects, 116 FIDA children). Of these 209 participants, 54 (26%) were excluded from further analyses for low behavioral performance (<75% correct), 50 participants (24%) were excluded for excessive movement artifact, 8 participants (3%) were excluded for electrooculography (EOG) contamination, and 2 participants (1%) were excluded because of technical issues. Thus, the final sample consisted of 44 control subjects (23 female) and 51 FIDA children (19 female).

Stimuli and Task Procedure

Participants sat on a comfortable chair in a dimly lit room approximately 65 cm from the computer screen and were tested in a recognition memory task. The stimuli consisted of 176 pictures of Spanish words that were determined to be within the vocabulary of the average 10-year-old Chilean child. The word stimuli were presented as white letters on a black background in the center of a 19-inch computer monitor subtending a visual angle of 4° by 11°. The stimuli were divided in 4 blocks of 72 trials each, with 288 total trials available. For each of the 4 blocks, participants were presented with a word stimulus (new) followed by either another new word or one that had been presented previously (old). Each block of 72 trials had exactly 44 "new" words and 28 "old" words (ie, repeated "new" words) that were presented after a lag of 1, 2, 4, or 5 words. Some new words were never presented again as old words. The first and second blocks of trials consisted only of new, lag 1, and lag 4 words, and the third and fourth blocks of trials consisted only of new, lag 2, and

lag 5 words. To measure each subject's performance and attention, participants were asked to press one button for old words and one button for new words. Each trial consisted of a 100-ms baseline and a 500-ms stimulus presentation, followed by a 1600-ms post-stimulus recording. During the post-stimulus recording period, the computer monitor was blank. The inter-trial interval randomly varied from 500 to 1000 ms. All participants viewed the stimuli in the same order. However, not every subject completed all 4 blocks of trials.

Electrophysiological Recording and Processing

ERPs were recorded from 28 scalp electrodes with a modified 10-20 system. Participants wore a close-fitting lycra cap with sewn-in tin electrodes (Electro-Cap International, Eaton, Ohio). Scalp electrodes (Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, PO3, PO4, PO7, PO8, O1, O2, T3, T4, T5, and T6) were referenced to Cz during acquisition. Data were also recorded at the left (M1) and right (M2) mastoids. Bipolar vertical EOG was recorded from electrodes placed vertically above (Fp1) and below (Fp2) the right eye, bisecting the midline to record blinks and other eye movements. After cap placement, an abrasive gel was inserted into each electrode site, and the scalp under each site was gently abraded. After scalp abrasion, a small amount of electrode gel was inserted into each electrode site. Electrode impedances were considered acceptable at or below 10 KΩ. Electroencephalography and EOG signals were acquired with a Neurodata Acquisition System (Grass Instruments, West Warwick, Rhode Island) and amplified with Model 15 amplifiers with a gain of 50 000 for the scalp channels and 5000 for EOG. The amplifier filter settings were 0.1 to 30.0 Hz and a 60-Hz notch filter was applied. All channels were digitized at 200 Hz on the hard drive of a personal computer with a 12-bit A/D converter (National Instruments, Austin, Texas).

ERP data were edited offline with the ERP32 analysis software package (New Boundary Technologies, Minneapolis, Minnesota). Scalp channels with excessive artifact ($> \pm 100$ μ V) were rejected; the entire trial was rejected when > 4 scalp channels exceeded this threshold. Data were re-referenced to an average mastoid configuration, and eye movement-related artifact was corrected.¹⁵ Only trials on which participants responded correctly were included in subsequent analyses. Individual subject averages were constructed for each stimulus type (correctly remembered "old" words and "new" words) with a 100-ms baseline period. Control participants contributed an average of 82 trials per condition, and FIDA participants contributed an average of 86 trials per condition. A separate grand mean was created for each condition by averaging together the individual subject averages.

Inspection of the grand averaged waveforms revealed a series of two well-defined components that were extracted and subsequently analyzed: frontal FN400 (F3, Fz, F4; 300–500ms) and midline P300 (Fz, Cz, Pz; 500–800ms). Electrode groupings and time windows were selected on the basis of

earlier reports of these components and through visual inspection of the grand-averaged and individual waveforms.

Statistical Analyses

Because hit and false alarm rates reflect response bias (the tendency to respond yes or no) and sensitivity (the degree of overlap between signal and noise distributions), signal-detection analyses were used for behavioral data.¹⁶ The sensitivity index (d') was calculated to measure the distance between the signal mean (proportion of repeated words that the subject correctly identified as "old") and the noise mean (proportion of new pictures that the subject incorrectly identified as "old"). d' is measured in SD units, in which a value of 0 indicates a participant's inability to differentiate signal from noise, and larger values indicate a greater signal compared with noise. Negative d' values can result from task confusion. Children who were unable to correctly identify at least 75% of old and new pictures ($d' = 1.25$) were rejected from further behavioral analyses.

Statistical analyses were conducted with SPSS software version 16.0.1 (SPSS Inc, Chicago, Illinois). Behavioral (d' scores, reaction time) and electrophysiological measures (peak amplitude and latency for FN400 and mean amplitude for P300) were analyzed by using repeated-measures ANOVA with Greenhouse-Geisser corrected degrees of freedom. Within-subjects factors were condition (new, old), and between-subjects factors were group (control, FIDA). For electrophysiological data, electrode was also examined as a within-subjects factor.

Sample characteristics that were considered as potential confounders can be found in the Table.¹⁷⁻²¹ Differences in mean scores between FIDA children and control subjects were explored with t tests or χ^2 . The following covariates were found to be significantly different in the two groups ($P < .10$) and were therefore considered in subsequent analyses as potential confounders: sex, gestational age, maternal depression, maternal education, home environment at 10 years, socioeconomic status at 10 years, and stress score at 10 years. The quality of the participant's home environment was measured with the Home Observation for Measurement of the Environment Inventory.²² Socioeconomic status was measured with a modified version of the Graffar method, which is designed to establish socioeconomic strata within a population.²³

All co-variates were initially entered into the general linear model. Non-significant covariates ($P > .10$) were eliminated from subsequent models until only significant covariates were included in the final model. When omnibus ANOVAs revealed significant main effects or interactions, post-hoc paired t tests were conducted using a Bonferroni correction for multiple comparisons.

Results

The Table shows background characteristics of the participants, including iron status in infancy and at 10

Table. Sample characteristics by iron status in infancy and at 10 years

Group	FIDA (n = 51)	Control (n = 44)
Child		
Age at test, years	10.2 (.22)	10.2 (.24)
Sex, % female (n)	37.3 (19)	52.3 (23)
Birth weight, g	3496.9 (391.7)	3617.3 (416.8)
Gestational age*	39.3 (1.0)	39.8 (1.2)
Height at 10 years, cm	139.5 (6.6)	138.1 (5.4)
Weight at 10 years, kg	38.8 (9.1)	37.6 (7.6)
Participant IQ	92.1 (10.5)	95.6 (11.1)
Iron status in infancy		
Hemoglobin, g/L†	103.0 (6.6)	124.3 (7.8)
Mean corpuscular volume, fl†	66.9 (4.7)	75.6 (3.4)
Free erythrocyte protoporphyrin, $\mu\text{g}/\text{dL}$ †	166.3 (68.8)	89.0 (21.4)
Ferritin, $\mu\text{g}/\text{L}$ †	7.2 (7.5)	16.1 (12.6)
Iron status at 10 years		
Hemoglobin, g/L*	132.4 (9.1)	136.4 (9.3)
Mean corpuscular volume, fl*	80.7 (3.8)	82.6 (3.5)
Free erythrocyte protoporphyrin, $\mu\text{g}/\text{dL}$	68.9 (14.2)	65.2 (15.4)
Ferritin, $\mu\text{g}/\text{L}$	23.6 (11.1)	27.5 (10.6)
Family		
Mother's education, years*	9.1 (3.0)	10.3 (2.7)
Mother's IQ‡	84.6 (10.1)	85.2 (11.9)
HOME score at 10 years§	34.5 (8.4)	39.0 (7.1)
Socioeconomic status at 10 years¶,	35.8 (7.3)	31.5 (7.2)
Maternal depressed mood at 10 years	23.7 (15.6)	13.5 (11.2)
Number of life stressors at 10 years , *	5.7 (2.7)	4.2 (2.3)

HOME, Home Observation for Measurement of the Environment Inventory.

Values are means (SD) for continuous variables and percentages for categorical variables.

Statistical significance was determined with either t-tests or χ^2 .

* $P \leq .05$.

† $P \leq .01$.

‡Standardized norm = 100 ± 15 . IQs in the low 80s are often observed in mothers with this level of education.^{17,18}

§Mean score of children 6 to 10 years old in Little Rock, Arkansas, was 41.6 (9.0).¹⁹

¶Measured by the Graffar scale, designed to differentiate families at the lower end of the socioeconomic spectrum. Scores of 35.8 and 31.5 fall in the medium range of the lower class spectrum.

||Scores range from 0-60; ≥ 16 is considered indicative of depression. The high prevalence of depressed mood in the Chilean mothers is consistent with earlier research with Latin American mothers²⁰ and US mothers in economically stressed situations.²¹

*Of a total of 28.

years. The mean age at test was 10.2 years for both the FIDA and control groups (range, 9.7-11.0 years). All participants had normal or corrected-to-normal vision; two participants (both in the control group) were left-handed. Only one child had IDA at 10 years, defined with age-appropriate National Health and Nutrition Survey II and III cutoffs^{24,25} as hemoglobin level $< 112 \text{ g/L}$ and two or more abnormal iron measures (mean corpuscular volume $< 76 \text{ fl}$, erythrocyte protoporphyrin $> 70 \text{ } \mu\text{g}/\text{dL}$ red blood cells [1.24 nmol/L], and serum ferritin $< 10 \text{ } \mu\text{g}/\text{L}$), and 4 children had iron deficiency without anemia, resulting in $< 5\%$ overall prevalence of iron deficiency.

Behavioral Data

Because of the block design used in task administration, accuracy as indexed by d' was analyzed with a 2 condition (d' lag 1, d' lag 4, OR d' lag 2, d' lag 5) by 2 group (control, FIDA) repeated measures ANOVA. Not every subject had d' scores and relevant co-variate information for all 4 blocks

($n = 40$ for control and $n = 47$ for FIDA for the d' analysis of the first two blocks and control = 39 and FIDA = 48 for d' analysis of the last two blocks). After controlling for the background factors that met criteria for the inclusion in the model—maternal depression and socioeconomic status—analysis of the first two blocks of trials (d' lag 1, d' lag 4) revealed no significant effects. After controlling for stress, analysis of the second two blocks of trials (d' lag 2, d' lag 5) revealed a main effect of accuracy ($F(1,84) = 11.959$, $P = .001$), by which d' for lag 2 ($M = 2.66$, $SD = .87$) was significantly larger than d' for lag 5 ($M = 2.44$, $SD = .86$). There was no group by accuracy interaction for either set of trials, in which $F(1,83) = 0.926$, $P = .339$ for the first two blocks of trials and $F(1,84) = 2.151$, $P = .146$ for the second two blocks of trials.

For reaction time analysis, $n = 41$ for control and $n = 50$ for FIDA for the first two runs and control $n = 42$ and FIDA $n = 49$ for the analysis of the last two runs. Analysis of reaction time data for the first two blocks of trials (new words, lag 1, lag 4) revealed a main effect of group, $F(1,89) = 4.171$, $P = .044$, by which the control subjects ($M = 1003$ ms, $SD = 205$) showed significantly faster reaction times than the FIDA group ($M = 1085$ ms, $SD = 176$). Additionally, there was a main effect of condition, $F(2,88) = 18.355$, $P < .001$, by which reaction times for new words ($M = 998$ ms, $SD = 189$) were significantly faster than those for words presented after a lag of 1 ($M = 1076$, $SD = 206$) or a lag of 4 ($M = 1070$, $SD = 213$). Analysis of the second two blocks of trials (new, lag 2, lag 5) revealed no significant effects. There was no group X condition interaction in either block of trials, in which $F(2,89) = 0.463$, $P = .576$ for the first blocks and $F(2,86) = 0.636$, $P = .481$ for the second blocks of trials.

Electrophysiological Data

Preliminary analyses were conducted to determine whether there were any electrophysiological differences among lags 1, 2, 4, and 5. Participants were included in this initial set of analyses only when they contributed usable data for both lag 1, 4 and lag 2, 5 trials (25 control, 29 FIDA). Analyses of each ERP component revealed no significant differences in amplitude or latency in any of the lag conditions. However, old/new effects were evident. All subsequent analyses were collapsed across condition.

FN400

Participants who did not meet the minimum requirement of 10 trials for each of the 3 frontal electrodes (Fz, F3, and F4) were excluded from analysis of the FN400 component. Participants were also excluded when they had missing values for any co-variate that met inclusion criteria for a given analysis, therefore, control $n = 40$ and FIDA $n = 48$ for amplitude analyses and control $n = 40$ and FIDA $n = 49$ for latency analyses.

After controlling for the 3 background factors that met criteria for inclusion in the analysis—sex, socioeconomic status, and maternal depression—there was a main effect of electrode, $F(2,82) = 4.027$, $P = .024$, by which Fz ($M = -24.4$ μ V, $SD = 12.8$) showed more negative amplitudes than F3

($M = -22.4$ μ V, $SD = 11.9$) and F4 ($M = -19.8$ μ V, $SD = 12.2$). There was also a condition by group interaction for FN400 peak amplitude, $F(1,82) = 3.918$, $P = .051$. Post-hoc tests indicated that for control subjects only, new words ($M = -11.7$ μ V, $SD = 6.0$) elicited more negative overall amplitude than old words ($M = -10.2$ μ V, $SD = 6.6$; **Figure 1**).

Both the Home Observation for Measurement of the Environment Inventory score and maternal depression met criteria for inclusion in the analyses of FN400 latency. After controlling for these co-variates, there was a main effect of group, $F(1,85) = 9.652$, $P = .003$, by which control subjects ($M = 360.0$ ms, $SD = 31.2$) showed significantly faster overall latency than the FIDA group ($M = 383.7$ ms, $SD = 40.2$; **Figure 2**). In addition, there was a main effect of condition (**Figure 2**), $F(1,85) = 4.841$, $P = .031$, by which old words ($M = 368.8$ ms, $SD = 40.4$) elicited significantly faster FN400 latency than new words ($M = 378.1$ ms, $SD = 43.8$).

P300

Participants who did not meet the minimum requirement of 10 trials for each of the 3 midline electrodes (Fz, Cz, and Pz) were excluded from analysis of the P300 component; therefore, there were 42 control subjects and 50 children with FIDA. After controlling for maternal education and gestational age, there was a main effect of group for P300 mean amplitude, which was qualified by a group by electrode interaction, $F(2,87) = 4.878$, $P = .030$. With post hoc comparisons, control subjects showed larger P300 mean amplitudes than FIDA children at electrodes Fz and Cz (**Figure 3**).

Discussion

Both the FIDA and control groups performed the recognition memory task with equal accuracy throughout the study, which means that the children in the FIDA group were not behaviorally impaired in their ability to make a new/old distinction. This finding suggests that the memory processes necessary for the task were largely intact in both groups. However, despite comparable accuracy throughout the study, it is important to note that the control group's response times were significantly faster than the FIDA group's response times during the first block of the experiment (lag 1 and lag 4 manipulation). By the second block of the experiment, there were no statistically significant differences between the groups. On the basis of earlier work within this same population of children, we posit that the response time differences in the first block likely reflect a learning delay that is characteristic of the children in the FIDA group. The response time group differences, which may reflect differences in underlying processes on this relatively easy recognition memory task, could also have implications for the performance of the FIDA group on a more difficult or taxing memory-dependent task, a hypothesis that is not explored in this study.

To help elucidate the observed difference in response times between the FIDA and control groups on a subset of the task

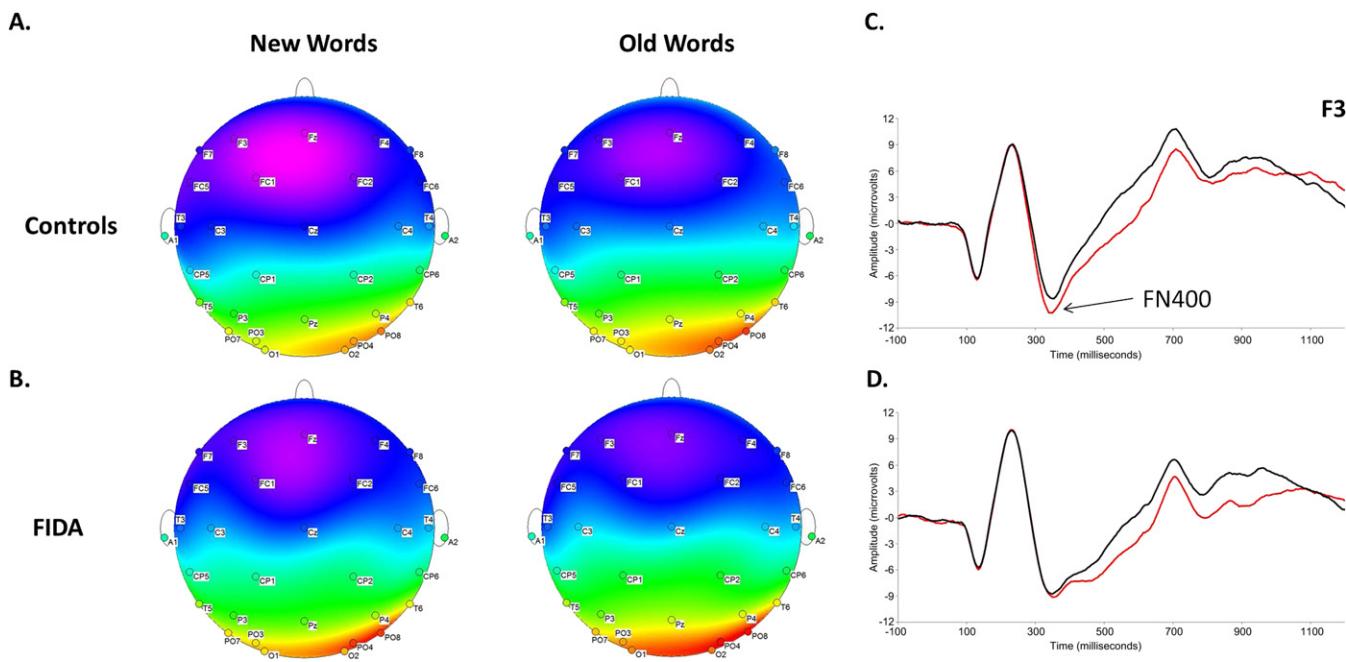


Figure 1. Topographic distribution of scalp potentials to new and old words for **A**, control subjects and **B**, FIDA children at 344 ms post-stimulus. Grand averaged ERP waveforms for **C**, control subjects and **D**, FIDA children over the left frontal electrode (F3).

and to explore other potential neurological effects of early iron deficiency, we next examined group differences in our ERP results. The robust main effect of group for the mean amplitude of the P300 component (**Figure 3**) suggests that early iron deficiency, which is known to reduce energy metabolism, may have affected the development of neural circuitry in the FIDA group. Deviation from typical development may reduce P300 amplitude, indicating impairments in neuronal processing of both new and old “target” words. Maximal P300 (or P3b) amplitudes are typically quantified primarily at parietal scalp locations because the signal becomes smaller and slower as it propagates toward central and frontal electrodes.¹⁰ To examine this characteristic pattern of propagation across the scalp, our analyses looked at all 3 midline electrodes (Pz, Cz, and Fz). The interaction of electrode and group for the P300 component revealed topographical differences in the distribution of the P300 in the two groups by which the signal was smaller for the FIDA group at the central and frontal midline electrodes. Despite this difference in magnitude, follow-up analyses did show the expected pattern of propagation across the scalp by which Pz > Cz > Fz for both the FIDA and control groups.

Analysis of FN400 latency revealed a main effect of group by which the control group had significantly shorter latency than the FIDA group. In a recognition memory task such as the one used, it is believed that both amplitude and latency of the FN400 may reflect memory searching.²⁶ Therefore, longer latency in the FIDA group may suggest a delay in crucial memory searching processes.

We also report a somewhat surprising interaction of group and condition for FN400 amplitude. In addition to general memory searching processes as aforementioned, there are several theories as to what the FN400 component represents. Some argue that the FN400 reflects a simple familiarity effect by which new words have larger negative amplitude than old words.²⁷ One more recent theory is that the amplitude of the

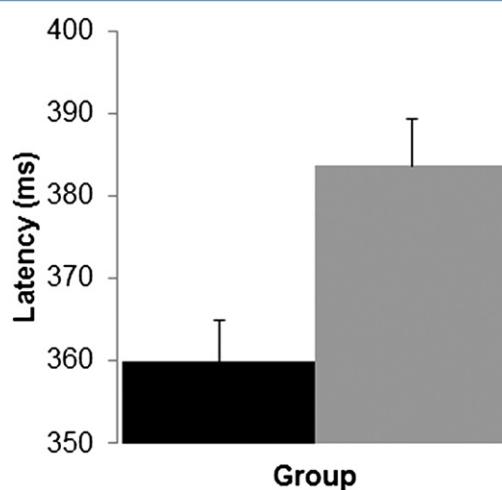


Figure 2. Mean latency to peak amplitude of the FN400 component, collapsed across condition. Black bar represents control and gray bar represents FIDA. Error bars represent + 1 SEM.

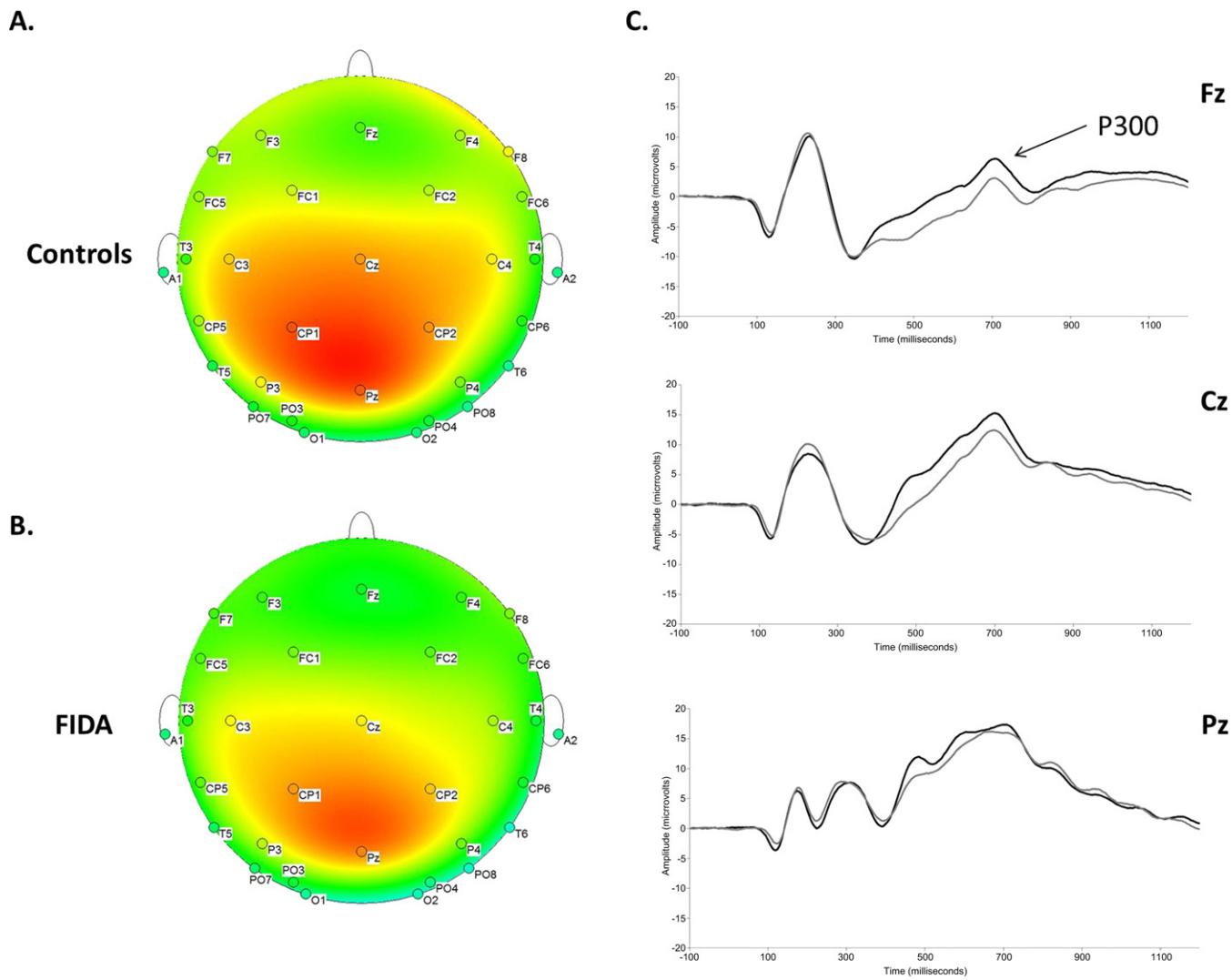


Figure 3. Topographic distribution of scalp potentials collapsed across memory condition for **A**, control subjects and **B**, FIDA children at 699 ms poststimulus. **C**, Grand averaged ERP waveforms for the mean amplitude of the P300 component collapsed across condition.

FN400 is related to activation of explicit semantic memory processes only for stimuli that carry meaningful associations.²⁸ In other words, it may be the case that the FN400 component shows a new/old effect for word stimuli that are conceptually familiar to the participant. Because of the simple level of vocabulary of our word stimuli and the age of the participants, it is reasonable to argue that differences in semantic memory updating might be a potential explanation for these data. In this study, the control group showed the expected new/old effect but the FIDA group did not. Thus, it appears as though iron deficiency might impact the development of crucial neural processes involved in accessing semantic memory for conceptually familiar words. This interpretation would benefit from study replication.

Overall, our data suggests that early iron deficiency status is associated with slower and smaller neurological and behavioral responses in the FIDA group as compared

with the control group. Our electrophysiological findings were more robust than our behavioral findings which speaks to the differential sensitivity of these two classes of measures. We argue that ERPs are a sensitive and therefore more accurate measure for detecting the early-onset differences that persisted throughout development.

Myelin dysfunction as a result of iron deficiency could be a mechanism for explaining the between-group differences in ERP latency and amplitude and differences in reaction times. The formation of myelin is an ongoing process that can take months or in some regions of the brain, years to complete,^{29,30} suggesting that a perturbation to brain development in the formative years of development could have long-lasting effects. More specifically, any significant change in iron homeostasis during rapid periods of neuronal development can produce alterations in myelin composition and related behaviors that are long-lasting and difficult to reverse.

despite subsequent treatment. Thus, hypomyelination and its effects on neurotransmission could help to explain some of the ERP differences observed in this recognition memory study.

An ongoing question in the current field of research is whether there is a specific window of time or sensitive period early in development during which brain development is disproportionately affected by iron deficiency or other nutrient deficiencies. In this sample, most children received iron supplementation at the age of 12 months ($n = 36$), and the groups that received supplementation at 6 and 18 months of age were much smaller ($n = 8$ for 6-month-old children and $n = 7$ for 18-month-old children). Because of these small sample sizes and because the prenatal iron status of participants was unknown, this study cannot separate out the timing effects of iron deficiency or timing effects of the treatment, although work is currently underway in China that may help us address this very vital question.

Nutrient deficiencies during periods of rapid cognitive development can cause long-lasting changes in the brain. Despite the receipt of adequate treatment after their iron deficiency, the FIDA children continued to show differences in cognitive processing and neuronal timing as compared with control subjects. All reported differences were significant after controlling for a comprehensive set of background factors. ■

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