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ARTICLE

An Event-Related Potential Study of Attention and Recognition Memory in Infants With Iron-Deficiency Anemia

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ABSTRACT

OBJECTIVES. The purpose of this work was to determine whether iron-deficiency anemia in infancy represents a risk factor for deficits in attention and memory development using event-related potentials.

METHODS. Artifact-free event-related potential data were obtained at 9 and/or 12 months from 15 infants with iron-deficiency anemia and 19 who were iron sufficient during a test of the infant's ability to discriminate a highly familiar stimulus, the mother's face, from a stranger's face.

RESULTS. A midlatency negative component associated with attention and a late-occurring positive slow wave associated with memory updating were identified at both ages in the iron-deficiency anemia and iron-sufficient groups. Consistent with the age-appropriate pattern of development at 9 months, the iron-sufficient group showed a greater attentional response (negative component) to the mother and a greater updating of memory for the stranger (positive slow wave). This pattern of responses was not evident in the iron-deficiency anemia group until 12 months, suggesting a delay in cognitive development.

CONCLUSIONS. These data suggest that iron-deficiency anemia adversely affects the allocation of neurophysiologic resources to attention and recognition memory during the processing of information about familiar and unfamiliar stimuli. This delay in cognitive development may reflect alterations in efficiency of central nervous system functions that seem related to early iron deficiency.

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Key Words
infant, iron-deficiency anemia, event-related potentials, attention, memory

Abbreviations
IDA—iron-deficiency anemia
ID—iron deficiency
IS—iron sufficiency
Hb—hemoglobin
ERP—event-related potential
NC—negative component
PSW—positive slow wave
EOG—electrooculogram

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IRON-DEFICIENCY ANEMIA (IDA) affects an estimated 1 to 2 billion people worldwide, primarily women and children.[1] Although the prevalence of IDA and iron deficiency (ID) has markedly declined in US infants in the last 30 years, poor, minority, and/or immigrant infants and toddlers remain at increased risk.[2] Infants with IDA or other indications of chronic, severe ID have shown lower cognitive test scores than infants with iron sufficiency (IS) in all but 1 of 14 studies from countries around the world.[3,4] All of the available follow-up studies, with intervals following iron therapy in infancy ranging up to young adulthood, report persisting lower scores (see review in ref 5). A recent meta-analysis estimated the long-term effects on intelligence quotient to be 1.7 points lower for each 10 g/L decrease in hemoglobin (Hb).[6] These lower scores on intelligence quotient tests, though consistently observed, give little indication of the neural mechanisms that underlie the cognitive deficits.

Assessing specific neurocognitive functions with brain-based measures in human infants is challenging. Event-related potentials (ERPs) provide a noninvasive means for measuring transient changes in the brain's electrical activity in response to stimuli, allowing the evaluation of attention and memory in very young infants. ERP studies informed by animal models of diet-induced ID have shown impaired recognition memory in human infants with prenatal ID because of maternal diabetes during pregnancy.[7–9] The study reported here examined infant recognition memory in relation to IDA during its period of peak postnatal prevalence (6–24 months). This study was part of an integrated cross-species program project on the brain and behavior effects of early ID in human infants, nonhuman primate infants, and developing rodents. As part of a hypothesis-driven neurodevelopmental approach, the hippocampus and/or related behaviors were assessed in all 3 species. Recognition memory was assessed using ERP in the human infant project.

We hypothesized that postnatal IDA would alter attention and recognition memory because of the effect of iron on hippocampal development and function. To examine this hypothesis, we recorded ERPs in a procedure specifically focused on the infant's ability to recognize a highly familiar stimulus, the mother's face, and to discriminate the mother's face from a stranger's face. Two ERP components of particular interest have been identified in studies of infant memory: a midlatency negative component (NC) associated with attention and a late-occurring positive slow wave (PSW) associated with memory updating. Previous research using this paradigm indicates that infants respond differentially to photographs of their mother versus a stranger, showing a larger NC to mother and a larger PSW to stranger at 6 months of age.[10] Developmental changes in NC and PSW responses continue over the course of infancy into early childhood and are often characterized by shifts in response patterns.[11,12] These changes are complex and nonlinear, presumably reflecting age-related changes in the allocation of attentional resources and interest.[13]

In this study, we compared NC and PSW in infants with IDA versus those who were IS at 9 and 12 months. We predicted that infants with IDA would show ERP responses that were less developmentally appropriate than those of IS infants.

METHODS

Participants

Black infants and caregivers were recruited for the study during routine 9-month visits to Children's Hospital of Michigan, between April 2002 and August 2005, during which a complete blood cell count was taken.[14] Because >90% of the clinic population was black, and the remaining population was of varying ethnic origins, recruitment was restricted to blacks. All of the methods and procedures for this study were approved by the Wayne State University and University of Michigan human investigation committees. Written informed consent was obtained from each infant's mother or primary caregiver. Based on hematologic measures from infants screened in the first year of the study, the prevalence of ID in this population ranged from 2.5% to 14.4%, depending on the criteria used.[14] Of 881 infants screened, 408 were not included because they met ≥1 of the following exclusionary criteria: ethnicity other than black (73); birth weight <2.5 kg (130); maternal diabetes or birth weight >4.0 kg (67); multiple birth (29); perinatal complications (85); hospitalization more than once or >5 days (108); chronic health problem (60); medicinal iron (22); in foster care (17); or mother <18 years old (43). The mothers of the qualified infants (n = 473) were asked to consider enrolling their infants in a study on the neurodevelopmental effects of ID to be conducted at the Child Development Research Laboratory, Wayne State University, at ages 9 and 12 months. For those willing to consider participation (n = 412), an extra tube of blood was drawn for additional iron-status analyses. Infants and their mothers were invited to participate in the study based on provisional criteria related to infant iron status (B.L., unpublished data, 2007). These criteria were considered provisional because not all of the ID indicators were available before the 9-month neurodevelopmental assessment. Among the 242 infants invited to participate at 9 months, 113 healthy, term black infants (47%) participated in the final neurodevelopmental assessment sample. Of these, 87 (77%) returned for 12-month neurodevelopmental testing. Iron supplements were provided to all of the infants in the study. However, the study cannot determine the effects of iron therapy on 12-month infant function because of uncertainty about the degree to

which the iron was actually administered to the infants and the relatively small number of infants for whom blood work was available at 12 months (58%) (B.L., unpublished data, 2007).

The analyses presented here compared infants with IDA to infants with IS. IDA was defined as Hb ≤105 g/L with abnormal scores on ≥2 measures of the following indicators of ID: mean corpuscular volume <74 fL, red cell distribution width >14%, zinc protoporphyrin/heme ratio >69 μmol/mol of heme, ferritin <12 μg/L, and transferrin saturation <12%. The comparison group of infants with IS had Hb ≥115 g/L and ≤1 abnormal iron indicator. One infant with IS and 3 infants with IDA were not assessed with ERP because of a refusal to wear the electrode cap or equipment malfunction. Artifact-free ERP data were obtained from more than half of the infants who were assessed, a proportion that compares favorably with other infant studies using this methodology.[15] Thirteen (48%) of 27 infants with IDA and 15 (60%) of 25 infants with IS provided artifact-free ERP data at 9 months ($\chi^2_1 = .73$; $P = .39$, not significant), and 9 (43%) of 21 with IDA and 11 (61%) of 18 with IS provided artifact-free data at 12 months ($\chi^2_1 = 1.28$; $P = .26$, not significant). Table 1 summarizes the Hb and iron indicators for the 2 groups. To consider the impact of IDA on development across this age period, we first report results for the 14 infants (7 IDA and 7 IS) who provided artifact-free ERP data at both the 9- and 12-month assessments. We then provide results for the larger number of infants at each age to corroborate the longitudinal findings.

Electroencephalogram Collection and Procedure

ERPs are recorded at the scalp and are time locked to a particular event (eg, a visual stimulus), reflecting summated postsynaptic potentials from synchronously firing neurons.[16] The amplitude of the ERP signal reflects the population of active neurons, and latency reflects the timing of that neuronal activation. Two of the most important components identified in ERP studies of infant memory are an NC occurring ~300 to 800 milliseconds after stimulus onset, which is characterized by a well-defined negative peak (millivolts) with maximum amplitude over frontocentral scalp and a PSW occurring ~1000 milliseconds after stimulus onset, which rises steadily over the course of several hundred milliseconds and is measured in arbitrary units based on voltage × time.[17,18] The NC has been characterized as an obligatory attentional response,[19–21] which differentiates between a familiar and unfamiliar stimulus.[10,22] PSW is believed to reflect the extent to which a stimulus is encoded and subsequently updated in memory.[10,22,23]

In this study, ERPs were recorded from 16 scalp electrodes mounted in a close-fitting cap (Electro-Cap International, Eaton, OH) using the 10–20 system.[24] The electrodes comprised midline (Fz, Cz, and Pz), frontal (F3 and F4), central (C3 and C4), temporal (T3, T4, T5, and T6), parietal (P3 and P4), and right occipital (O2)

TABLE 1 Background and Demographics for IS and IDA Groups With Artifact-Free ERP Data at Either Age

Variable	IS		IDA		*t* or χ^2
	Mean (SD) or %	*n/N*	Mean (SD) or %	*n/N*	
Hb, g/dL	12.3 (0.5)	19	10.0 (0.4)	15	13.4[a]
MCV, fL	78.0 (2.8)	19	71.8 (5.6)	15	4.3[a]
RDW, %	13.0 (0.7)	19	14.6 (1.9)	15	3.4[b]
ZPP/H, μmol/mol	56.4 (8.0)	18	99.5 (30.4)	15	5.4[a]
Ferritin, μg/L	35.1 (27.4)	13	42.0 (31.9)	11	0.6
Transferrin saturation, %	25.6 (10.3)	13	20.0 (9.3)	11	1.4
Lead, μg/dL	2.3 (1.0)	19	2.3 (2.0)	15	0.1
Infant gender, % female	31.6	6/19	53.3	8/15	1.6
Infant age					
9-mo assessment	9.9 (0.2)	19	9.5 (0.4)	15	2.7[c]
12-mo assessment	12.8 (0.7)	15	12.5 (0.5)	13	1.0
Primary caregiver age, y	24.2 (5.2)	18	23.7 (5.0)	15	0.2
SES	28.6 (9.4)	19	28.4 (10.6)	14	0.1
HOME, total	30.9 (6.2)	15	30.4 (6.2)	13	0.2
Mother's education, highest grade	12.8 (1.4)	18	11.6 (1.4)	15	2.5[c]
Maternal PPVT-R, 9 mo	76.6 (17.2)	16	72.0 (18.1)	15	0.7
Maternal Raven, 12 mo	35.8 (12.2)	15	36.7 (9.7)	13	0.2
Maternal depression, BDI	4.6 (3.8)	18	10.3 (9.5)	15	2.2[c]
Infant breastfed, %	52.6	10/19	53.3	8/15	<0.1
Formula started, %	94.7	18/19	86.7	13/15	0.7

t values adjusted for unequal variances are reported when Levene's test for equality of variances was rejected at $P < .05$. SES indicates Hollingshead socioeconomic status; MCV, mean corpuscular volume; RDW, red cell distribution width; ZPP/H, zinc protoporphyrin/heme ratio; HOME, Home Observation for Measurement of the Environment; PPVT-R, Peabody Picture Vocabulary Test-Revised; Maternal Raven, Raven Standard Progressive Matrices; BDI, Beck Depression Inventory.

[a] $P < .001$; [b] $P < .01$; [c] $P < .05$.

scalp sites plus the left and right mastoids (M1 and M2) and a ground electrode. Cz was the reference lead during acquisition. Electrooculogram (EOG) was recorded from bipolar miniature electrodes placed vertically above and below the right eye for the purpose of artifact detection. Impedance for all of the scalp and EOG electrodes was kept below 10 kOhm. Electroencephalogram and EOG were acquired using a Model 15 Grass Neurodata Acquisition System (Grass Instruments, Quincy, MA) and amplified at a gain of 20 000 for scalp leads and 5000 for EOG. The bandpass was 0.1 to 30 Hz, and a 60-Hz notch filter was engaged. Data were sampled every 5 milliseconds (200 Hz). ERP data were digitized online and then edited by computer algorithm. Before averaging, trials with excessive artifact (ie, electroencephalogram more than ±125 mV) were rejected. Data were then rereferenced to an averaged mastoid reference, and eye movement-related artifact was corrected.[25] Using 100 milliseconds before stimulus onset as the baseline, individual trials were baseline corrected and then averaged for each participant within each stimulus type.

In the mother-stranger paradigm, the infant was presented with randomly alternating digital photographs repeated with equal probability of his/her mother's face and an unfamiliar stranger's face. The stranger was the mother of another infant participating in the study, with whom the infant was not familiar. The infant was seated on the mother's lap ~60 cm from a 13-in computer monitor; the faces on screen were 10-cm wide (visual angle: 9.5°) and 15-cm high (visual angle: 14°). Stimuli were presented for 500 milliseconds with randomly alternating intertrial intervals, ranging between 500 and 1000 milliseconds; ERP data were collected for 1500 milliseconds after stimulus onset for each trial. To maximize processing of as many stimuli as possible, an experimenter observed the infant from behind a screen and paused whenever the infant looked away from the screen, repeating trials as necessary. A maximum of 100 total trials was presented to the infant (50 trials for mother and 50 for stranger), with an equal number of trials for each stimulus (see Table 2 for more information).

The NC in this study occurred between 300 and 650 milliseconds after stimulus onset; the PSW, at 800 to 1500 milliseconds. The NC and PSW were most prominent over frontocentral electrodes (Fz, F3, F4, Cz, C3, and C4); thus, the analyses focused on overall frontocentral scalp activity. Data were included in the ERP analyses if they met all of the following criteria: (1) ≥10 good trials for each condition (ie, mother and stranger); (2) activity at mastoids not exceeding ±10 μV; (3) data did not appear contaminated by EOG or mastoids; and (4) activity at no channel exceeding ±125 μV (±250 μV for EOG). These criteria were designed to eliminate outliers and other questionable values and were applied in a review of individual ERP waveforms by investigators who were blind with respect to iron status. After removing trials not meeting these criteria, brain activity at each electrode was averaged over an equal number of trials for mother and stranger. If there was a discrepancy in the number of good trials between mother and stranger conditions, the excess trials from 1 condition were randomly removed by the computer program to equalize the number of trials between conditions.

TABLE 2 **ERP Descriptive Statistics**

Variable	IS	IDA	t or χ^2
9 mo			
n	15	13	—
ERP total trials	89.0 (12.2)	86.0 (14.6)	0.6
ERP rereferenced trials	71.6 (14.9)	62.6 (22.5)	1.3
Cross-average minimum	27.9 (8.9)	23.5 (8.9)	1.3
Cross-average maximum	32.5 (8.0)	27.1 (10.1)	1.6
12 mo			
n	11	9	—
ERP total trials	80.4 (14.9)	80.8 (25.4)	< 0.1
ERP rereferenced trials	55.0 (18.9)	62.4 (25.5)	0.8
Cross-average minimum	22.0 (8.8)	25.3 (10.4)	0.8
Cross-average maximum	24.6 (9.6)	29.1 (12.6)	0.9

Data are presented as mean (SD) except where noted. *t* values adjusted for unequal variances are reported when Levene's test for equality of variances was rejected at $P < .05$. — indicates no data.

Control Variables

The IDA and IS groups were compared on the following sociodemographic variables (Table 1): infant gender and age; age of primary caregiver (mother); socioeconomic status assessed on the Hollingshead Scale (A.B. Hollingshead, PhD, Four-Factor Index of Social Status, unpublished manual, 1975); the Home Observation for Measurement of the Environment,[26] a semistructured interview that assesses quality of intellectual stimulation and emotional support provide by the caregivers; maternal education (highest grade); 2 measures of maternal intellectual competence, the Peabody Picture Vocabulary Test-Revised[27] and the nonverbal Raven Standard Progressive Matrices[28]; maternal depression assessed in the Beck Depression Inventory[29]; breastfeeding (present/absent); and whether the infant was taking formula at the time of study entry. Only 2 (5.9%) of the mothers (1 from each group) had begun to give their children cow's milk when asked at the 9-month assessment.

Data Analysis

Table 2 shows that the IS and IDA groups were very similar at both ages in number of ERP trials viewed, number of trials available for rereferencing, and number of trials cross-averaged by condition. Data for F4 were missing for 1 infant in the IDA group at 9 months because of failure of that electrode during the session. Because the other electrodes were all acceptable for that infant, data for F4 were imputed from Fz and F3

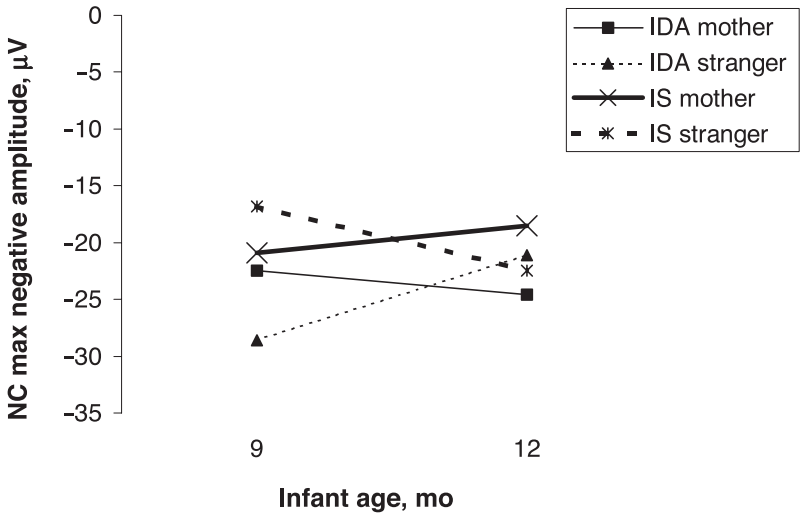

FIGURE 1
Mean NC maximum negative amplitude for repeated measures at 9 and 12 months for subgroups IDA ($n = 7$) and IS ($n = 7$).

based on the high proportion of variance accounted for by those electrodes in relation to F4 for both mother and stranger conditions for NC and PSW in the sample as a whole, (R^2 range: 0.65–0.85; all P values $< .0001$). Peak amplitude and corresponding latency of NC and area of PSW were analyzed by 2 × 2 × 2 × 6 repeated-measures analysis of variance. The between-subjects factor was group (IDA and IS), and the within-subjects factors were condition (mother and stranger), age (9 and 12 months), and electrode (Fz, F3, F4, Cz, C3, and C4).

The IDA and IS groups were similar in sociodemographic background, except that the infants with IDA were slightly younger at study entry, and their mothers had fewer years of education and were more depressed (see Table 1). For the 14 infants with artifact-free data at both ages in the longitudinal analyses, there was no difference in maternal education (mean: 12.1 vs 12.3 years for IDA versus IS, respectively; $t_{12} = 0.49$; $P = .80$). However, the age difference at study entry (ie, the 9-month assessment) showed a suggestive trend for these 14 infants (mean: 9.3 vs 9.8 months for IDA versus IS, respectively; $t_{12} = 2.07$; $P = .06$), and more maternal depression (Beck Depression Inventory total score) was evident in the IDA group (mean: 12.0 vs 2.4 for IDA versus IS, respectively; $t_{12} = 2.38$; $P = .035$). Further examination of these maternal depression data revealed that 3 of the 7 mothers in the IDA group had total scores ranging from 17 to 28, which is classified as "moderately depressed," whereas the next highest score from any mother from either group was only 5. Given the limited degrees of freedom available in this small longitudinal sample, the potential confounding effects of age at study entry and maternal depression were examined in separate repeated-measures analyses of covariance.

RESULTS

Longitudinal Analyses

NC

For NC amplitude across the 6 frontocentral electrodes, there was a significant 3-way interaction of age × iron group × condition ($F_{1,12} = 7.73$; $P = .017$; see Fig 1). Results were essentially the same in the analyses of covariance controlling for age at study entry ($F_{1,11} = 5.00$; $P = .047$) and for maternal depression ($F_{1,11} = 6.82$; $P = .024$). To better understand this 3-way interaction, condition × iron group effects were tested separately at 9 and 12 months. At 9 months, there was a significant condition × iron group interaction ($F_{1,12} = 6.61$, $P = .024$). The pattern at 9 months, as shown in Fig 1, was for a larger NC to mother in the IS group but larger NC to the stranger in the IDA group. A posthoc pairwise comparison test revealed that this mean difference in NC to the mother versus stranger was significant for the IS group (mean difference: 4.14 μV; SE: 1.23; $F_{1,6} = 11.36$; $P = .015$), though not for the IDA group, in which there was more within-group variability (mean difference: 6.07 μV; SE: 3.78; $F_{1,6} = 2.58$; $P = .159$). At 12 months, the response pattern was the reverse of that seen at 9 months; that is, the IDA group showed a larger NC to the mother at 12 months, and the IS group shifted to a larger NC to the stranger (see Fig 1). There were no main effects of age, iron group, or condition or other significant interactions among these variables. There were no effects for latency to NC by condition, iron group, or age.

PSW

There was also a significant 3-way interaction for age × iron group × condition for PSW area ($F_{1,12} = 45.01$; $P < .001$; see Fig 2). The same pattern of results was found in the analyses of covariance controlling for age at study

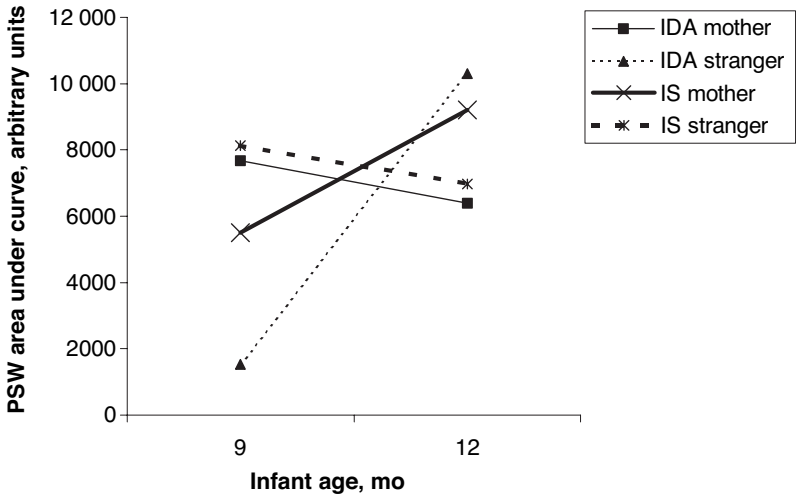

FIGURE 2
Mean PSW area under curve (arbitrary units) for repeated measures at 9 and 12 months for subgroups IDA ($n = 7$) and IS ($n = 7$).

entry ($F_{1,11} = 43.58$; $P < .001$) and for maternal depression ($F_{1,11} = 24.51$; $P < .001$). At 9 months, there was a significant condition × iron group effect ($F_{1,12} = 20.27$; $P = .001$), with the IS group showing a larger PSW to the stranger than to the mother compared with the IDA group, which showed the opposite pattern. A posthoc pairwise comparison test revealed that this mean difference in PSW fell short of statistical significance for the IS group (mean difference: 2628; SE: 1415; $P = .113$) but was significant for the IDA group (mean difference: 6145; SE: 1340; $P = .004$). At 12 months, there was a significant condition × iron group interaction ($F_{1,12} = 7.32$; $P = .019$), which revealed a pattern opposite to that seen at 9 months; that is, the IDA group showed a significantly larger PSW to the stranger than to the mother, and the IS group showed the reverse pattern (see Fig 2). A posthoc pairwise comparison at 12 months showed that this difference was significant for the IDA group (mean difference: 3909; SE: 1019; $F_{1,6} = 14.71$; $P = .009$) but not for the IS group (mean difference: 2226; SE: 2025; $F_{1,6} = 1.21$; $P = .314$).

Cross-sectional Analyses at Each Age

We also performed cross-sectional analyses including subjects with data available at only 1 age (ie, 13 IDA vs 15 IS at 9 months; 9 IDA vs 11 IS at 12 months). The effects seen with these larger numbers were similar to those presented in the longitudinal analyses above. The ERP waveforms for these data are shown at 9 months (Fig 3) and 12 months (Fig 4). For NC amplitude at 9 months, there was a suggestive trend for the condition × iron group interaction seen in the longitudinal subgroup at 9 months ($F_{1,26} = 3.2$; $P = .087$). As in the longitudinal subgroup, there were no effects for NC latency by condition or iron group. For PSW area at 9 months, the condition × iron group interaction ($F_{1,26} = 12.1$; $P = .002$) was similar to the one seen in the longitudinal subgroup. Posthoc tests revealed that the IDA group showed a larger PSW to the mother than to the stranger (mean: 6057 vs 1662; $F_{1,12} = 7.5$; $P = .018$), whereas there was a suggestive trend for the opposite pattern in the IS group (mean: 6437 vs 4702; $F_{1,14} = 4.0$; $P = .066$). There was also a main effect for differences by electrode ($F_{5,22} = 3.5$; $P = .017$), suggesting some random variability across the electrodes. Therefore, we conducted additional analyses comparing only frontal electrodes (Fz, F3, and F4) versus only central (Cz, C3, and C4) electrodes. The results showed that the condition × iron group interaction was evident both for frontal ($F_{1,26} = 11.6$; $P = .002$) and central electrodes ($F_{1,26} = 7.5$; $P = .011$), suggesting that collapsing across frontocentral electrodes to create a region of interest was valid despite some variability across these electrodes.

For NC amplitude at 12 months, there was a significant condition × iron group interaction ($F_{1,18} = 5.2$; $P = .035$), which resembled the pattern seen in the longitudinal subgroup at 12 months. For PSW area at 12 months, the condition × iron group interaction showed a suggestive trend ($F_{1,18} = 4.0$; $P = .060$), with results resembling the pattern seen in the longitudinal subgroup. A posthoc analysis for the IDA group revealed significantly less PSW to the mother than to the stranger at 12 months across frontocentral electrodes (mean: 4781 vs 8091; $F_{1,8} = 12.6$; $P = .008$), consistent with the longitudinal findings. No differences were found in this regard for the IS group. Thus, the pattern of effects emerging overall with the larger sample sizes at 9 and 12 months supports the longitudinal findings presented above.

DISCUSSION

A number of consistent patterns associated with normal development have emerged in the infant ERP literature. Seminal studies from de Haan and Nelson[10,22] have revealed a larger NC amplitude in response to the mother's face as compared with a stranger's face at 6 months of

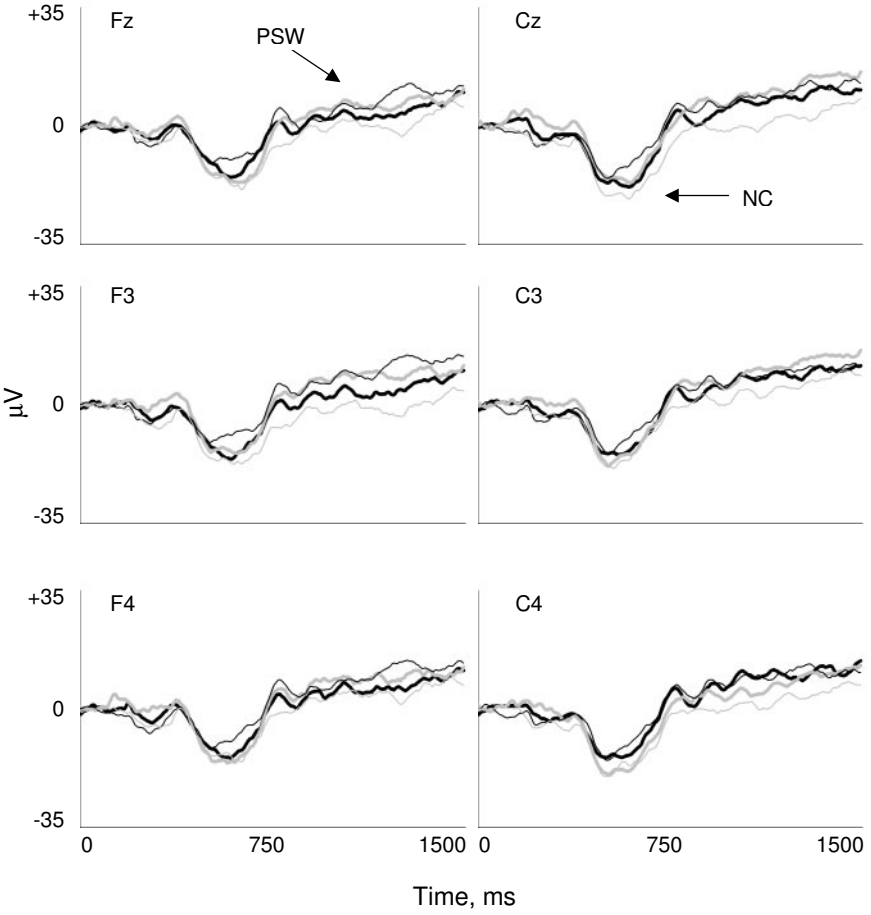

FIGURE 3
Grand means at 9 months for frontocentral electrodes for IDA (gray lines; $n = 13$) and IS (black lines; $n = 15$). Thick lines represent mother; thin lines represent stranger; 1500 millisecond recording, ± 35 μV.

age, indicating that around this age infants discriminate between faces and allocate relatively more attentional resources to the mother's face. This pattern was seen in the IS infants at 9 months, but the infants with IDA did not show the normal developmental response for young infants to attend more to the mother's face. At 12 months, there was a significant reversal of the NC amplitude pattern, with the NC of the IS group now larger to the stranger than to the mother and the IDA group showing the reverse pattern.

Although the explanation for this reversal is unclear, similar phenomena have been observed in ERP studies somewhat later in development, extending from infancy to 3 years of age.[12,30] Findings from Carver et al[12] suggest that the larger NC amplitude to mother at the younger age, as seen in our study, may reflect the greater salience or importance of the mother as an attachment figure at that point in development. The reversal seen in the IS group in our data at 12 months may reflect rapidly evolving infant interests and changes in attention, which could occur dramatically in response to emerging awareness, such as stranger and separation anxiety. The increased fear of strangers is likely to have an effect on the allocation of attentional resources when the infant is confronted with the face of a stranger, which could account for the increased NC amplitude in response to the stranger's photograph in the IS infants at 12 months. It is possible that IDA infants did not show the expected greater attentional response to the mother at the earlier age because of their tendency to be more wary, fearful, and hesitant in unfamiliar circumstances and/or with strangers.[31] It is also possible that infants with IDA showed a developmentally delayed response in focusing differentially on the mother, because they responded at 12 months much in the same manner as the infants with IS at 9 months.

A second important element of ERP associated with infant memory processes is the late-occurring PSW, which is believed to reflect processing of a partially encoded stimulus in memory.[23] Six-month-old infants typically show a larger PSW to the stranger's face in comparison with the mother's face, which likely reflects the updating of a memory trace for an unfamiliar stimulus.[22] Consistent with these findings, infants with IS showed the expected developmental pattern at 9 months, with a larger PSW to strangers. Infants with IDA did not show this pattern until 12 months, suggesting a delay in their cognitive development. Although we are aware of no other ERP study using a visual mother-stranger paradigm to assess effects of IDA, auditory recognition defi-

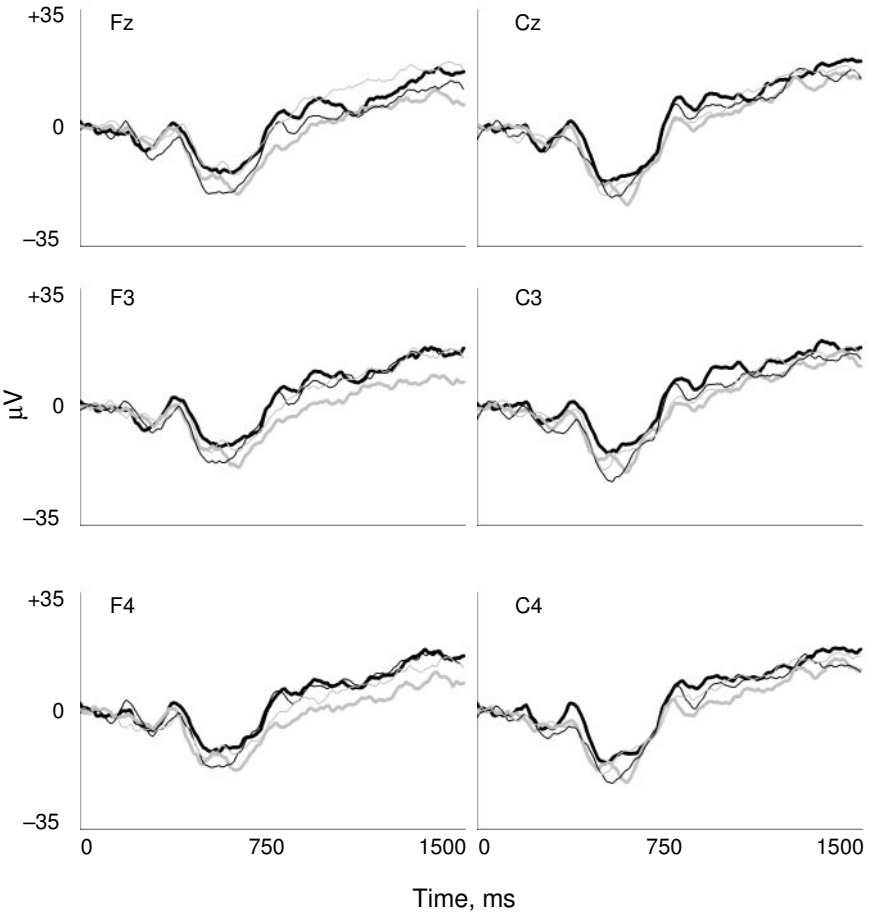

FIGURE 4
Grand means at 12 months for frontocentral electrodes for IDA (gray lines; $n = 9$) and IS (black lines; $n = 11$). Thick lines represent mother; thin lines represent stranger; 1500-millisecond recording, ± 35 μV.

cits have been found in studies of infants of diabetic mothers at high risk for prenatal brain ID.[32,33] For example, using an auditory ERP paradigm to assess recognition of the mother's versus a stranger's voice, Siddappa et al[32] found that infants of diabetic mothers who were presumed to have brain IS displayed a negative slow wave to the stranger's voice, whereas those who were presumed to have brain ID did not discriminate between the mother's and stranger's voices. In our study, infants in both groups seemed capable of discriminating between the stimuli, but the patterns of ERP activity in response to the mother and stranger suggested a delay in cognitive development in the infants with IDA. In light of findings from previous studies showing recognition memory in infancy to be predictive of cognitive and language deficits in childhood,[34,35] the developmental delay in recognition memory seen here may be an early indicator of later cognitive problems. Such a finding would be consistent with previous research relating IDA in infancy to poorer neurobehavioral function in childhood.[5]

The mechanisms underlying this delay in cognitive development associated with IDA are not clear, but there is an increasing body of relevant research in animal models. Several important developing central nervous system processes, such as myelination, dendritogenesis, synaptogenesis, and neurotransmission, are highly dependent on iron-containing enzymes and hemoproteins.[36] Recent studies on ID and brain development have demonstrated short- and long-term effects on myelination, neuroanatomy, neurotransmitter function, and neurometabolism, especially in the striatum and the hippocampus.[5] The hippocampus is of particular interest given its role in the discrimination of novel from familiar stimuli in recognition memory,[37] the domain found here to be affected in infants with IDA. Moreover, studies in rodent models of gestational and/or lactational ID provide evidence of reduced neuronal metabolism (as indexed by cytochrome c oxidase activity[38]) and altered dendritic structure in the hippocampus,[39] with associated poorer performance on spatial memory tasks[40,41] and on highly specific dorsal hippocampal tasks, such as trace conditioning.[42]

One strength of ERP is its capacity to reveal subtle developmental differences in neurophysiologic processes underlying cognition that would not be detected by behavioral observation. Thus, the results of this study suggest a delay in cognitive development among infants

with IDA in processing information about mother and stranger that was not clearly evident in their overt behavior. Given that the same pattern of findings was seen after controlling for infant age at study entry and maternal depression (ie, the sociodemographic variables on which the IDA and IS groups differed), we infer that the delay in cognitive development associated with IDA is more likely attributable to biological insult than to environmental factors, though this inference is necessarily tentative given the small sample size. Another limitation to this study is our inability to assess the effectiveness of iron treatment for infants with IDA because of incomplete hematologic data at the 12-month assessment resulting from attrition and/or compliance problems. Additional studies are needed to address these issues and to assess the degree to which this delay in cognitive development may presage adverse effects on subsequent cognitive and behavioral development in children with IDA in infancy.

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